

A clinical evaluation of serum concentrations of intercellular adhesion molecule-1 in patients with gastric cancer

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Abstract

AIM To investigate the correlation between the serum soluble intercellular adhesion molecule-1 (sICAM-1) and the clinicopathologic features and to evaluate the possible prognostic significance of sICAM-1 concentration in gastric cancer.

METHODS Thirty-four patients with gastric cancer were prospectively included and evaluated. Venous blood samples were collected before the surgery. Sera were obtained by centrifugation, and store at -30°C until assay. The control group consisted of 20 healthy volunteers. Serum concentrations of ICAM-1 were measured with the quantitative sandwich enzyme immunoassay technic. Differences between the two groups were analyzed by Student's *t* test. $\bar{x}+2s$ of normal control sICAM-1 was taken as upper limit to calculate the positive rates.

RESULTS The mean value of serum ICAM-1 in patients with gastric cancer was $367.7 \mu\text{g/L} \pm 104.7 \mu\text{g/L}$ and that of control group was $236.9 \mu\text{g/L} \pm 74.3 \mu\text{g/L}$, and the difference was significant ($P < 0.001$). The patients with tumor size of $\geq 5\text{cm}$ had significantly higher serum concentrations of sICAM-1 than those with smaller ones ($406.7 \mu\text{g/L} \pm 90.2 \mu\text{g/L}$ vs $319.9 \mu\text{g/L} \pm 105.3 \mu\text{g/L}$, $P < 0.01$). Compared with stages I-II gastric cancer patients, patients with more advanced clinical stage (III-IV) had higher levels of sICAM-1 ($397.1 \mu\text{g/L} \pm 102.4 \mu\text{g/L}$ vs $306.0 \mu\text{g/L} \pm 82.3 \mu\text{g/L}$, $P < 0.05$). Difference was significant

statistically in sICAM-1 levels between patients with positive lymph node status and those without lymph node involvement ($403.6 \mu\text{g/L} \pm 99.7 \mu\text{g/L}$ vs $302.7 \mu\text{g/L} \pm 81.4 \mu\text{g/L}$, $P < 0.01$). No relation was observed between the level of sICAM-1 and grade of histological differentiation in the patients with gastric cancer.

CONCLUSION Serum sICAM-1 concentration may be a valuable parameter for predicting the prognosis and degree of the gastric cancer.

INTRODUCTION

Cell adhesion is essential for establishing and maintaining a normal immune defense system. Intercellular adhesion molecule-1 (ICAM-1; CD54), a 80-110KD cell surface glycoprotein and a member of the immunoglobulin supergene family, functions as a ligand for the leucocyte integrin adhesion receptors CD11a/CD18 (LFA-1) and CD11b/CD18 (mac-1). ICAM-1 expresses in various cell types and plays an important role in immunemediated mechanisms, especially in the process of antigen presentation and recognition, lymphocyte cytotoxicity, lymphocyte recruitment and targeting. It has been reported that the upregulated expression of ICAM-1 on cell surfaces occurred in a variety of diseases, including autoimmune diseases, endocrine diseases, and some cancers^[1,2]. A soluble form of ICAM-1 (sICAM-1) lacking cytoplasmic tail and transmembrane region has also been found^[2]. sICAM-1 can compete with membranous ICAM-1 to bind LFA-1, so that it can block leukocyte LFA-1 and prevent effective recognition and lysis of target cells by effector leukocyte. This phenomenon represents an important mechanism for tumor escaped from immune surveillance^[3,4]. The sICAM-1 levels and its prognostic significance for various malignant diseases have been evaluated^[5-8]. In this study, we determined the concentrations of sICAM-1 antigen in the sera of patients with gastric cancer to reveal the possible relationship between sICAM-1 and clinical pathological parameters such as histologic type, size of tumors and so on.

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MATERIAL AND METHODS

Patients and specimens

A group of 34 patients (24 men and 10 women) with gastric cancer were investigated. Their ages ranged from 35 to 74 years with a mean of 54. Eleven patients were in stages I and II, and 23 in stages III and IV. Blood samples were obtained from patients before the initial treatment. Samples collected from 20 healthy volunteers served as controls. All blood samples were processed immediately for centrifugation, and the sera were stored at -30°C until the sICAM-1 assay.

Measurement of sICAM-1

Serum sICAM-1 concentrations were determined with sICAM-1 ELISA (Biosource International, USA). Briefly, serum samples were diluted at 1:100 and applied to prepared polystyrene microcells precoated with mouse monoclonal antibody to human ICAM-1, a horseradish peroxidase conjugated anti-ICAM-1 was then added. Test wells are incubated to allow any ICAM-1 to be bound by antibodies on the microtiter plate. The walls were then washed and stabilized chromogen was added to the walls producing a blue color in the presence of peroxidase enzyme. The color reaction was then stopped by the addition of 1mol/L H_2SO_4 and changed from blue to yellow. Absorbances for samples and sICAM-1 standards were determined on a spectrophotometer using 450nm. Average absorbance values for each set of duplicate samples or standards were within 15% of the mean. sICAM-1 concentrations in serum sample were determined by comparing the mean absorbance of duplicate samples with the standard curve for each assay.

Statistical analysis

The Student's *t* test was used for statistical significance of differences between groups. $P<0.05$ was considered to be significant.

RESULT

The mean serum sICAM-1 levels in healthy volunteers and patients with gastric cancer were $236.9\ \mu\text{g/L}\pm 74.3\ \mu\text{g/L}$, $367.7\ \mu\text{g/L}\pm 104.7\ \mu\text{g/L}$, respectively; and serum sICAM-1 levels in 58.8% of patients exceeded $385.5\ \mu\text{g/L}$ ($\bar{x}+2s$ of normal controls), the difference being significant between patients with gastric cancer and healthy controls.

The relationship between serum sICAM-1 levels and clinicopathological features of gastric cancer patients was also observed. Patients with tumor size $\geq 5\text{cm}$ showed remarkable elevated levels of sICAM-1 than those with tumor size $<5\text{cm}$ ($P<$

0.01). Patients with advanced gastric cancer (stage III-IV) had higher serum levels of sICAM-1 ($P<0.05$) than early-stage gastric cancer patients (stage I-II). sICAM-1 levels in patients with lymph node metastasis were significantly higher than in those without lymph node invasion ($P<0.01$). No correlation was found between sICAM-1 levels and grade of differentiation in the observed gastric cancer patients. The positive rates of each group were calculated with $\bar{x}+2s$ of normal control sICAM-1 as a limit. The results are shown in Table 1.

Table 1 Correlation between soluble ICAM-1 concentrations and clinical histopathology in gastric cancer

Factors	<i>n</i>	ICAM-1 ($\bar{x}\pm s$, $\mu\text{g/L}$)	Positive rate %(<i>n</i>)
Tumor size			
$\geq 5\text{cm}$	19	406.7 ± 90.2^a	73.3 (14/19)
$<5\text{cm}$	15	319.9 ± 105.3	40.0 (6/15)
Lymph node invasion			
Positive	21	403.6 ± 99.7^a	71.4 (15/21)
Negative	13	302.7 ± 81.4	38.5 (5/13)
Grade of differentiation			
Differentiated	12	320.5 ± 93.2	33.3 (4/12)
Poorly differentiated	22	393.9 ± 103.1	72.7 (16/22)
Clinical staging			
I-II	11	306.0 ± 82.3	36.4 (4/11)
III-IV	23	397.1 ± 102.4^b	69.6 (16/23)

^a $P<0.01$, ^b $P<0.05$, vs the control.

DISCUSSION

A previous studies indicated that ICAM-1 was expressed on tumor cells in 12 of 28 cases of gastric carcinoma^[9]. Expression of ICAM-1 by tumor cells facilitated immune recognition and cytotoxicity^[10,11]. However, ICAM-1 also represents an escape mechanism in certain cancers. sICAM-1, after shedding from tumor cells or originating from other cells especially mononuclear cells, may block the attachment of cytotoxic T lymphocyte (CTL) cells and/or NK cells to tumor cells, since LFA-1 on immune cells could be blocked with sICAM-1^[3]. Recently, Becker *et al* found that cytolysis of melanoma cells mediated by CTL in an MHC-restricted manner, could be completely blocked in the presence of sICAM-1, the concentration of sICAM-1 for blocking cytotoxicity was $950\ \mu\text{g/L}$ ^[4]. Because the serum sICAM-1 concentration may reflect the level of sICAM-1 in tumor microenvironment in vivo, an increase in the circulating level of ICAM-1 may reflect unfavourable prognosis. It has been found that patients with malignant melanoma, having high levels of sICAM-1, had a statistically significantly shorter time to first relapse and lower overall survival^[7]. In this study, we have found that serum

sICAM-1 levels were significantly increased in patients with gastric cancer, which were above the normal range in 20 of 34 gastric cancer patients. It is entirely possible that concentration of sICAM-1 in gastric tumor microenvironment may be high enough to block the cytotoxicity mediated by immune effector cells. To further confirm this hypothesis, we will establish a method to assess the sICAM-1 level in gastric carcinoma tissues.

In this study, we observed the correlation between the level of sICAM-1 and the clinical parameters in patients with gastric carcinoma. Patients with tumor size of ≥ 5 cm had higher level of sICAM-1 than those with small ones. This results indicated that tumor load may be correlated with the level of sICAM-1. In other words, the gastric tumor cells were probably the major source of sICAM-1. This was confirmed by the study of Hyodo *et al.* They found that the elevated serum levels of sICAM-1 in a patient with hepatocellular carcinoma decreased after treatment with transcatheter arterial embolization (TAE) in a same pattern of change with the AFP levels. As AFP is produced and shed by hepatocellular carcinoma cells, it could be interpreted that sICAM-1 in HCC patients is released from tumor cells^[8]. Our study also showed that sICAM-1 levels were correlated with both clinical staging and lymph node involvement. Patients with lymph node invasion and advanced clinical stage of tumors had significantly higher serum concentrations of sICAM-1. Lymph node status, tumor size and clinical stage are significant prognostic indicators, therefore,

sICAM-1 may be a valuable predictor for gastric cancer clinically.

In summary, elevated levels of sICAM-1 exist in gastric cancer as in some other types of tumors. Though serum level of sICAM-1 can not be served as a specific parameter for gastric cancer, it is no doubt that the measurement of the ICAM-1 level may provide a convenient means to obtain a general indication of gastric cancer.

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