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• *BRIEF REPORTS* •

Clinical evaluation of serum concentrations of intercellular adhesion molecule-1 in patients with colorectal 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 colorectal cancer.

METHODS: A total of 56 patients (mean age 57.3 years) having transitional cell carcinoma of the colorectal and 25 control patients (mean age 42.6 years) were enrolled in the study. The serum samples of the patients were obtained on the day before surgery. Sera were obtained by centrifugation, and stored at -80 ℃ until assay. Serum concentrations of ICAM-1 were measured with enzyme-linked immunoassay. Differences between the two groups were analyzed by Student's *t*-test.

RESULTS: No significant increase of serum sICAM-1 could be demonstrated in the Dukes A_1 patients (352.63±61.82 μg/L) compared to the control group (345.72±49.81 μg/L, $P>0.05$), Dukes A_1 patients (352.63±61.82 μg/L) compared to Dukes $A_{2,3}$ patients (491.17±86.36 μg/L, $P<0.05$). Furthermore, the patients with Dukes B had significantly higher serum concentrations of sICAM-1 than those of the control group (496.82±93.04 μg/L *vs* 345.72±49.81 μg/L, $P<0.01$). Compared with Dukes $A_{2,3}$, B colorectal cancer patients, patients with more advanced clinical stage (Dukes C and D) had higher levels of sICAM-1 (743.68±113.74 μg/L *vs* 491.17±86.36 μg/L and 496.82±93.04 μg/L, $P<0.001$). The difference was statistically significant in sICAM-1 levels between patients with positive lymph node status and those without lymph node involvement (756.25±125.57 μg/L *vs* 445.62±69.18 μg/L, $P<0.001$). Patients with poorly differentiated colorectal cancer had a higher level of sICAM-1 than those with differentiated and highly differentiated cancer (736.49±121.97 μg/L *vs* 410.23±67.47 μg/L, $P<0.001$).

CONCLUSION: In this study, serum ICAM-1 levels were found to be related to tumor presence, clinical stages, and grade. Increased ICAM-1 in patients with colorectal cancer which should be considered when the diagnostic and/or prognostic usefulness of soluble ICAM-1 is to be evaluated. sICAM-1 should prove useful for monitoring malignant disease stage and for evaluating the effectiveness of various therapeutic approaches for colorectal carcinomas.

Key words: sICAM-1; Colorectal cancer; Tumor metastasis; Clinicopathological factors

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INTRODUCTION

Colorectal cancer is the third most common malignant neoplasm worldwide[1] and has a higher incidence rate in Guangdong, Shanghai, Jiangsu, and Zhejiang Province. Moreover, with the development of economy, diets are high in total fat, protein, calories, alcohol, and meat (both red and white) and low in calcium and folate, which incline to increased incidence of colorectal cancer. The prevalence of colorectal cancer increased gradually in recent years. Efforts to identify causes and to develop effective preventive measures have led scientists pay much attention to it.

Intercellular adhesion molecule-1 (ICAM-1) is a monomeric, transmembrane molecule of the immunoglobulin superfamily with a molecular weight of 95-110 ku. Two ligands, the lymphocyte function-associated antigen-1 and the membrane adhesion complex-1, mediate adhesion and transvascular migration[2]. This protein mediates adhesion and transmigration of leukocytes through the endothelium. Surface expressed ICAM-1 is apparently shed from the cells and then circulates as soluble ICAM-1 (sICAM-1). Although the source of sICAM-1 has not been fully elucidated, it can be released by cancer cells and also by mononuclear blood, endothelial, and fibroblastic cells[3]. 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[4,5]. A soluble form of ICAM-1 (sICAM-1) lacking cytoplasmic tail and transmembrane region has also been found[5]. 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 escape from immune surveillance[6,7]. Shedding of ICAM-1 by circulating tumor cells may allow their escape from surveillance by cytotoxic T cell and natural killer cells and thus promote metastasis[8]. In our research, we have found that some anticancer gene and proto-ontogene have different expression in colorectal cancer[9,10]. In this study, we investigate the clinical significance of serum adhesion molecule levels at the time of diagnosis in patients with colorectal carcinoma and to evaluate the usefulness of these assays in terms of prognosis and survival.

MATERIALS AND METHODS

Patients and specimens

Serum samples were taken from 56 patients (32 men, 24 women, average age 57.3 years) with colorectal cancer admitted to the Affiliated Hospital of Guangdong Medical College from 2001 to 2002. In all patients the diagnosis was proven by histology. Staging was performed according to the criteria of Dukes system (Table 1).The reference group consisted of 25 others with non-malignant diseases (9 women and 16 men, average age 42.6 years). Blood samples were obtained from patients before the initial treatment. All blood samples were processed immediately for centrifugation. All sera were stored at -80 ℃ until assayed and determined not taking clinical information into account.

Table 1 Colorectal cancer patients and disease characteristics

Stage	*n*	%
Dukes A_1	3	5.36
Dukes $A_{2,3}$	6	10.71
Dukes B	21	37.50
Dukes C and D	26	46.43
Histologic differentiation		
Highly	22	39.29
Moderate	24	42.86
Poorly	10	17.85
Localization		
Right colon	17	30.36
Left colon	21	37.50
Rectum	18	32.14

Measurement of sICAM-1

The serum levels of soluble receptors were determined quantitatively by specific enzyme-linked immunosorbent assay (ELISA). The serum samples were diluted 10 times according to the manufacturer's instructions (R&D Systems), and as described previously[11]. Soluble receptor concentrations were calculated from standard curves generated by standard dilutions of known concentrations. The mean intra-assay CV, determined by assaying the sICAM-1 concentration in three serum samples in replicates of 10, is reported to be 4.4%. The mean inter-assay CV, determined by assaying three serum samples in duplicate in 18 separate assays by four operators, has been determined to be 7.4%. The cut-off values were calculated as the mean±SD were 860 ng/mL for sICAM-1. The reported sensitivity of the ELISA is less than 0.35 ng/mL.

Statistical analysis

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

RESULTS

We studied the correlation between the sICAM-1 levels and clinicopathological factors, Table 1 shows the relationships between the concentration of sICAM-1 antigen in the sera and various clinicopathologic features of the patients. No significant increase of serum sICAM-1 could be demonstrated in the Dukes A1 patients (352.63±61.82 μg/L) compared to a control group (345.72±49.81 μg/L, $P>0.05$). There is a significant statistic difference when Dukes A_1 patients (352.63±61.82 μg/L) compared to Dukes $A_{2,3}$ patients (491.17±86.36 μg/L, $P<0.05$). Furthermore, serum sICAM-1 levels were significantly higher in patients with Dukes B when compared to the control group (496.82±93.04 μg/L *vs* 345.72±49.81 μg/L, $P<0.01$). Among patient groups, while there was no significant difference between Dukes $A_{2,3}$ and Dukes B, a significant difference was found between Dukes B and Dukes C and D. Compared with Dukes $A_{2,3}$, B colorectal cancer patients, the patients with more advanced clinical stage Dukes C and D, had higher levels of sICAM-1 (743.68±113.74 μg/L *vs* 491.17±86.36 μg/L and 496.82±93.04 μg/L, $P<0.001$). Difference was statistically significant in sICAM-1 levels between patients with positive lymph node status and those without lymph node involvement (756.25±125.57 μg/L *vs* 445.62±69.18 μg/L, $P<0.001$). Poor differentiation was observed to have a higher level of sICAM-1 than moderated and highly differentiated patients $P<0.001$.The positive rates of each group were calculated with mean±SD of normal control sICAM-1 as a limit. The results are shown in Table 2.

Table 2 Correlation between soluble ICAM-1 concentrations and clinicopathologic factors in colorectal cancer

Factors	*n*	ICAM-1 (mean±SD, μg/L)	χ^2	*P*
Clinical staging				
Dukes A_1	3	352.63±61.82[a]		
Dukes $A_{2,3}$	6	491.17±86.36	2.88	<0.05
Dukes B	21	496.82±93.04[d]	0.18	>0.05
Dukes C and D	26	743.68±113.74	12.38	<0.001
Grade of differentiation				
Highly differentiated	22	410.23±67.47[b]		
Differentiated	24	486.53±103.64[d]	4.08	<0.01
Poorly differentiated	10	736.49±121.967	10.48	<0.001
Metastasis				
Liver	3	769.19±127.32		
Lymph node positive	23	756.25±125.57[d]	0.32	>0.05
Lymph node negative	30	445.62±69.18	16.98	<0.001

[a]$P<0.05$, Dukes A_1 *vs* Dukes $A_{2,3}$; [b]$P<0.01$, highly differentiated *vs* differentiated; [d]$P<0.001$, Dukes B *vs* Dukes C and D; Differentiated *vs* poorly differentiated; lymph node positive *vs* lymph node negative.

DISCUSSION

Soluble forms of cell adhesion molecules have been identified in the circulation and may be monitored as markers of inflammation and endothelial dysfunction[4]. Neoplastic transformation and the evolution to metastatic disease are characterized by a dramatic aberration in cellular cohesive interactions. The adhesion molecules have also been shown to facilitate tumor cell motility, adhesion of tumor cells to endothelium, neovascularization at the metastatic sites, and host inflammatory response to cancer. Evaluation of sICAM-1 has shown important clinical implications in many types of cancer. In particular, the measurement of serum concentrations of ICAM-1 might provide important prognostic values independent of conventional pathologic factors in cancer patients[12-14].

In the present study of colorectal cancer, revealed that serum sICAM-1 levels were elevated in patients with colorectal cancer. These parameters were elevated in both local and metastatic disease and significant correlations between the parameters and stage of disease were seen. The data of the present study are in agreement with those previously reported which described an increase in the sICAM-1 content of serum in colorectal carcinoma[15,16]. We have also demonstrated that concentrations of sICAM-1 are increased in colorectal cancer, particularly in patients with distant metastasis. Our study also showed that sICAM-1 levels were correlated with both clinical staging and lymph node during liver metastasis involvement. Basoglu[17] reported that the concentrations of sICAM-1 and TSA were significantly higher in patients with Dukes C and D, and they presume that sICAM-1 and TSA are the best of the tested markers. These markers should prove useful for monitoring malignant disease stage and for evaluating the effectiveness of various therapeutic approaches for colorectal carcinomas. In contrast to our study, it was demonstrated that the expression of sICAM-1 was inversely correlated with lymph node metastasis[18].

With regard to prognosis, Liu reported in gastric cancer that serum sICAM-1 concentration may be a valuable parameter for predicting the prognosis and degree of the gastric cancer. Liu[19] measured the circulating ICAM-1 in the sera of nasopharyngeal, oral, and laryngeal cancer cases and indicated that the circulating ICAM-1 was not elevated in the sera of oral and laryngeal cancer patients, but increased in nasopharyngeal cancer patients. They speculated that the discrepancy in the level of ICAM-1 among these three groups of patients with head and neck carcinoma might be attributed to either the different immunological reaction profiles or a cell-specific response. The cellular source and the mechanisms for releasing the soluble components of these endothelial adhesion molecules, although not well known, could involve either shedding or enzymatic cleavage from endothelial cells, leukocyte surfaces or tumor cells[20]. Some mechanisms have been proposed concerning the elevation of sICAM-1 in serum, such as enzymatic cleavage of cell surface adhesion molecules or secretion of alternatively spliced forms lacking the transmembrane domain. Additionally, that sICAM-1 has been described on malignant epithelial tissue may be the source of at least some of the sICAM-1 present in sera of cancer patients[21]. It is widely accepted that histological stage is a powerful prognostic factor in colorectal cancer. In this study, it was revealed that ICAM-1 status has prognostic value coincide with histological stage. Therefore, these results suggested that it may be possible to add ICAM-1 status to conventional clinicopathological factors to predict recurrence.

In conclusion, our study demonstrates that ICAM-1 expression may be a useful indicator of prognosis in patients with colorectal cancer. Patients with lymph node, liver invasion, and advanced clinical stage of tumors had significantly higher serum concentrations of sICAM-1. Invasion status and clinical stage are significant prognostic indicators. Though serum level of sICAM-1 cannot be served as a specific parameter for colorectal cancer, it is no doubt that the measurement of the ICAM-1 level may provide a convenient means to obtain a general indication of colorectal cancer. Therefore, sICAM-1 may be a valuable predictor for colorectal cancer clinically.

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