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Predictive Role of Activated Leukocyte Cell Adhesion Molecule in Colon Cancer

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Abstract

Aim: Colon cancer is one of the most common and deadly cancers worldwide. Activated Leukocyte Cell Adhesion Molecule (ALCAM) has been found to be associated with various malignancies. We investigated the expression of ALCAM in colon cancer patients, as well as its association with tumor size.

Materials and Methods: A total of 90 people, 50 patients with stage II colon cancer and 40 healthy controls were included in the study. Serum ALCAM and Carcinoembryonic Antigen (CEA) levels were measured in both groups. Tumor size was evaluated in the patient group.

Results: Circulating ALCAM levels were higher in patients with colon cancer than in the control group. Serum ALCAM levels were especially elevated in patients with larger tumor size.

Conclusion: ALCAM is overexpressed in colon cancer, and these results suggest that serum ALCAM levels may have a predictive role in the prognosis of this disease.

Keywords: Activated leucocyte cell adhesion molecule; ALCAM; CD166; Colon cancer; Prognosis

Introduction

Colon cancer is one of the leading causes of cancer-related deaths worldwide [1]. Systematic methods for diagnosing pathological markers might lead to earlier detection of patients at early stages of colon cancer, ensuring a decline in mortality rates. Advancements in diagnosis with screening methods as fecal occult blood test and flexible sigmoidoscopy have already reduced colon cancer mortality [2,3]. However, these techniques have limitations; such as low sensitivity of the fecal occult blood test, and invasiveness of flexible sigmoidoscopy. Carbohydrate Antigen 19-9 (CA19-9) and Carcinoembryonic Antigen (CEA) have been frequently used as tumor markers for identification of several types of cancer, including colon, liver, pancreatic, and gastric. Nonetheless, the sensitivity of these markers for colon cancer identification is low, especially in the early stages of the disease [4]. Therefore, there is a considerable need for colon cancer-specific diagnostic markers to achieve non-invasive, sensitive and specific screening of colon cancer.

Currently, such a molecule has been declared as a new potential molecular marker: Activated Leukocyte Cell Adhesion Molecule (ALCAM/CD166). It is a highly conserved, 110 kDa, multi-domain, transmembrane type 1 glycoprotein of the immunoglobulin superfamily, and it mediates homotypic and heterotypic interactions between endothelial cells and tumor cells [5,6]. ALCAM contributes to the development of various tissues during embryogenesis with its role in dynamic growth and migration [7]. It is also found in several malignant lesions, such as malignant melanoma, breast cancer, ovarian cancer, and pancreatic cancer. Its expression is related to multifarious outcomes in distinct tumors [8-11].

The main objective of the present study was to analyze whether ALCAM could be a novel cell marker for detecting and grading colon cancer.

Materials and Methods

The subjects gave their oral and written informed consent before their inclusion in the study, allowing the use of their blinded clinical data for research purposes. The study followed the principles of the Declaration of Helsinki Principles as revised in 2008 [12].

Patient selection

Fifty patients (male/female: 30/20) with a mean age of 57.4 ± 5.71 years (range 38 to 72 years)

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who visited the Department of General Surgery of Acıbadem Aile Hospital (Istanbul, Turkey) between 2016-2020 were enrolled in the study. All prediagnoses were pathologically confirmed by pre-operative colonoscopy and biopsy, and post-operative histopathologic examination. The control group consisted of 40 healthy volunteers (male/female: 22/18) with a mean age of 57.9 ± 4.62 years (range 40 to 71 years) who underwent check-up colonoscopy at our institute.

Collection of serum samples

Approximately 3 mL of peripheral venous blood was drawn from all patients in both groups early in the morning, after 6 h of fasting. Serum of each patient was collected in a Becton Dickinson vacutainer and kept at ambient temperature (20°C to 25°C) before centrifugation. They were centrifuged at 1500 rpm at room temperature (20°C to 25°C) within 45 min after blood collection, separated within 2 h, and immediately stored at -80°C.

Measurement of ALCAM and CEA in serum

The concentration of ALCAM in serum was measured by using a highly sensitive and specific non-competitive 'sandwich-type' Enzyme-Linked Immunosorbent Assay (ELISA) kits. The assay was based on mouse monoclonal antibody capture and biotinylated mouse monoclonal detection antibody (Human ALCAM ELISA kit (code: ab113317), ABCAM Systems, USA). The assay had a minimum detection limit of 15 pg/mL (range 20.48 to 5000 pg/mL). The concentration of CEA in serum was measured by using a commercially available automated ELISA kit (CEA Immunoassay, Roche Diagnostics, USA). The assay had an upper limit of normal as 5 ng/mL.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 21.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were described using mean, Standard Deviation (SD), median, minimum, maximum, and frequency, and were given as a percentage. All variables were normally distributed based on Shapiro-Wilk normality test, and histogram with Q-Q plot was drawn. Independent variables of the two groups were analyzed by t-test (Independent Samples T-Test). Gender variables of two groups were compared using Pearson's chi-square test with Yates's continuity correction. A p value of <0.05 was considered significant.

Results

Table I provides the demographic variables. Two groups did not differ in age (p=0.81) or gender (p=0.79). Table II provides the serum levels of CEA and ALCAM for both healthy controls and stage II colon cancer patients. The mean serum ALCAM level was significantly higher in the patient group (943.92 ± 470.69 pg/mL) compared to the control group (21.1 ± 1.66 pg/mL) (p<0.01) (Table II and Figure I). Similarly, mean serum CEA level was higher among stage II colon cancer patients (5.1 ± 1.1 pg/mL) than in healthy controls (1.37 ± 1.07 pg/mL) (p<0.01).

Tumor size was not shown to have statistically significant effect on serum CEA levels, regarding a cut point size of 3 cm. In contrast,

Table 1: Demographic variables of healthy controls and stage II colon cancer patients.

	Controls (n=40)	Stage II Patients (n=50)	p
Mean Age	57.9 ± 4.62	57.4 ± 5.71	0.81
Gender (M/F)	22/18	30/20	0.79

*p<0.05, **p<0.01, ***p<0.001

Table 2: Serum levels of CEA and ALCAM of healthy controls and stage II colon cancer patients.

	Controls (n=40)	Stage II Patients (n=50)	p
Mean CEA (ng/mL)	1.37 ± 1.07	5.1 ± 1.1	<0.01**
Mean ALCAM (pg/mL)	21.1 ± 1.66	943.92 ± 470.69	<0.01**

*p<0.05, **p<0.01, ***p<0.001

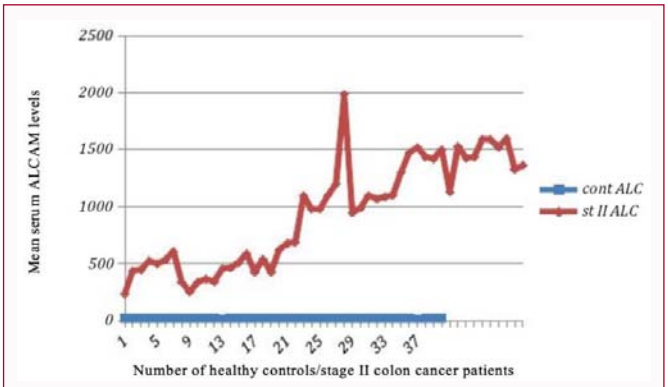

Figure 1: The histogram for mean serum ALCAM levels of healthy controls and stage II colon cancer patients.

serum ALCAM levels were shown to be affected by the tumor size, as patients with a tumor size over 3 cm had increased ALCAM expression compared to the patients with a tumor smaller than 3 cm (p<0.001). Mean serum ALCAM levels showed no statistically significant correlation with serum CEA levels, regarding the tumor size (p=0.82).

Discussion

The results of this study indicate that circulating ALCAM was significantly increased in stage II colon cancer patients compared to healthy controls. Moreover, the level of ALCAM expression in stage II colon cancer correlates with tumor size. Hence, ALCAM over expression might be a marker for colon cancer.

ALCAM is involved in neurogenesis, angiogenesis, hematopoiesis, and leukocyte trafficking [13-16]. It functions as a cell surface sensor for cell density, and controls the transition from local cell proliferation to tissue invasion [17]. The soluble isoform of ALCAM (sALCAM) was isolated as an alternative short ALCAM transcript comprehending only the first 3 exons. Since sALCAM protein possesses the immunoglobulin domain D1, which is necessary for homophilic ALCAM binding, and deteriorates cell-to-cell interaction through this binding. These steps provide the coordination of local tumor growth, invasion, and metastasis [7,18].

In literature, there are several studies which evaluate the relationship between this novel molecule and various types of cancers, and they have conflicting results. Some studies demonstrated that increased ALCAM expression were associated with poor prognosis for pancreatic cancer [10], and breast cancer [19]. On the other hand, there are some findings that support that higher ALCAM levels were indicating a favorable prognostic factor for epithelial ovarian cancer [9], prostate cancer [20], and breast cancer [8,21]. These controversial results may be due the variable functions of ALCAM depending on the tissue type and microenvironment surrounding tumor cells.

Our findings support that ALCAM is potent nominee as a marker for patients with (stage II) colon cancer. ALCAM plays a fundamental role in invasiveness and motility in colon cancer, and mechanistic

data that will increase the understand of why ALCAM up and down regulation might explain its different roles in different cancer types. Our data demonstrated a relation between ALCAM and colon cancer, as higher serum levels were observed in patients with stage II colon cancer than in healthy controls we were also able to show a positive correlation between tumor size and ALCAM levels. However, future studies are necessary to clarify this relationship. As the present study suggests, high sALCAM expression in colon cancer patients are caused by ALCAM shedding from the tumor and thus, sALCAM may be a biomarker in stage II colon cancer patients. Furthermore, they support the emerging concept that the release of soluble adhesion molecules may functionally contribute to the cancer progression [22]. The feasible use of sALCAM as biomarker in colon cancer is still needs to be investigated by comparisons with other colonic diseases.

Our study found ALCAM over expression in stage II colon cancer. Moreover, higher circulating ALCAM was associated with tumor size over 3 cm. Further studies are needed to investigate ALCAM's role in prognosis of colon cancer, and to identify it as an accredited marker.

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