Serum Soluble Intercellular Adhesion Molecule-1 in Lung Cancer: Utility in Early Diagnosis and Detecting Metastatic Disease

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Abstract

The aim of this study is to determine the diagnostic value of soluble intercellular adhesion molecule 1 (sICAM-1) in patients with bronchial carcinoma.

In our study, sICAM-1 level in serum was measured in patients with bronchial carcinoma (n= 48, mean age=54.7±1.8), and compared with the levels in the patients with pulmonary tuberculosis (n=42, mean age=39.9±1.9) and the healthy controls (n=20, mean age=40.5±1.3 years). All of the subjects were male. The analysis was performed by enzyme-linked immunosorbent assay (ELISA).

The highest serum levels of sICAM-1 were measured in the group of lung cancer (1543.7±86.8 ng/ml) but the difference between lung cancer and tuberculosis groups (1586.2±147 ng/ml) was not statistically significant ($p<0.13$). Control subjects had significantly lower serum levels 372±33.04 ng/ml ($p<0.0001$). There was a significant difference between the levels of sICAM-1 in small-cell lung cancer (1921.2±151.7 ng/ml) and those in non-small-cell lung cancer groups (1372.1±92.6 ng/ml) ($p<0.002$). Among nonsmall cell lung cancer patients, sICAM-1 levels were significantly increased in those with distant metastasis (1827.6±130.8 ng/ml vs 1144.4±90.2 ng/ml; $p<0.0001$).

We concluded that sICAM-1 is not useful as a diagnostic tool in lung cancer, but high levels of sICAM-1 can be an indicator for distant metastasis in nonsmall-cell lung cancer patients, and can differentiate nonsmall-from small-cell lung cancers.

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Introduction

Adhesion molecules provide the binding of cells to each other and to extracellular matrix, appearing on the cellular surface by some stimuli (1,2). They play important roles nearly in every stage of embryogenesis, wound healing, immunologic and inflammatory response (3,4,5).

Adhesion molecules are comprised of four groups: integrins, cadherins, selectines and immunoglobulin super family. Intercellular adhesion molecule-1 (ICAM-1), the main subject of our study, is a transmembranous protein from the immunoglobulin super family. And it includes five immunoglobulin-like structures in the extracellular part of the molecule (6,7). It is first described by Rothlein in 1986. Its presence has been shown in many cells like endothelial cells, macrophages, T and B lymphocytes and thymic epithelial cells (8). They play

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Table 1. Clinical characteristics of patients

	Tuberculosis	Small-cell cancer	Squamous cell cancer	Adenocarcinom	Large-cell cancer	Controls
Patients (n)	42	15	20	10	3	20
Mean age, year	39.9	52.8	52.5	62.3	54.6	40.5
Metastasis (n)	—	—	7	3	0	—
sICAM-1 levels (ng/ml)	1586.2±147	1921±151.7	1329.6±92.5	1586.0±121.2	943.3±32.4	372±33.0

*All of the subjects were male
n= number of patients

important roles in inflammatory events and in immune system with T cell mediator.

Initially, it was found by Rothlein in 1991 that when lymphocytes are sprinkled in *in vitro* culture, they secrete a soluble form of ICAM-1. Then, by immunoblotting technique and ELISA, the presence of soluble ICAM-1 (sICAM–1) in the serum of normal individuals was shown (9,10,11). Yet, as in cellular membrane, no other resource with the same structure (mRNA) can be shown, it is declared that ICAM-1 is the same molecule as sICAM-1. Soluble forms originate from spilling or separation from the cell and different blood levels are due to the differences in separation (9,12).

In this study, the sICAM-1 levels in the sera of patients with tuberculosis and malignancy, and in those of the healthy subjects were measured by ELISA method to investigate its diagnostic value in bronchial carcinomas and in determining metastases.

Materials and Methods

In our study, 110 subjects, all examined in our hospital, were included. Of these, 48 were with bronchial carcinoma, 42 were with pulmonary tuberculosis, and 20 were healthy controls. All subjects were male.

Patients with bronchial carcinoma were 54 to 76 years old and the mean age was 54.7±1.7 years. While 33 patients (68.7%) had small-cell lung cancer, 15 (31.2%) had nonsmall-cell lung cancer. Patients with nonsmall-cell lung cancer have passed radiological, bronchoscopic and surgical staging; 20 (41.6%) had squamous cell carcinoma, 10 (20.8%) had adenocarcinoma, 15 (31.2%) had small-cell carcinoma, and 3 (6.2%) had large-cell carcinoma.

Tuberculosis patients were 16 to 73 years old and the mean age was 39.8±1.9 years. Acid-fast bacilli in the sputum smear of all these patients, and growth on tuberculous culture media were required for the diagnosis of tuberculosis.

20 healthy volunteers included as control subjects were 28 to 45 years old and the mean age was 40.5±1.3 years.

For better localization of the lesion, thoracic computerized tomography scans were obtained. According to the localization of the lesion, the diagnosis was made by transthoracic or bronchoscopic biopsy. Before the specific treatment (chemoterapy, radiotherapy or operation), 5 ml of venose blood was taken, the level of sICAM-1 in this serum sample was measured by ELISA method.

Statistical analyses of this study were made by Windows Release 5.0.1 SPSS Inc. 1992 Computer Program. A value of $p<0.05$ was considered significant. For comparisons, Student-t test, one way ANOVA, Post Hoc Tukey test, Chi Square test were used. The sICAM –1 values were given as mean standard deviation (SD).

Results

In our study, three groups of subjects were evaluated: 48 patients with lung cancer, 42 with pulmonary tuberculosis, and 20 healthy controls. The clinical characteristics of the patients are given in Table I.

The group of lung cancer patients was divided into two subgroups as small-cell and nonsmall-cell cancer. Nonsmall-cell cancer group was also divided into groups of squamous cell, adeno and large-cell cancer. The mean level of sICAM-1 in all the cancer patients was 1543.7±86.8 ng/mL, and in nonsmall-cell cancer patients 1372.1±92.6 ng/mL (1329.6±92.5 ng/mL in squamous cell, 943.3±32.4 ng/mL in large-cell, 1586.0±121.2 ng/mL in adeno and 1921.2±151.7 ng/mL in small-cell cancer groups). The difference between the levels of sICAM-1 in nonsmall- and small-cell cancers was considerable ($p<0.002$) (Figure 1).

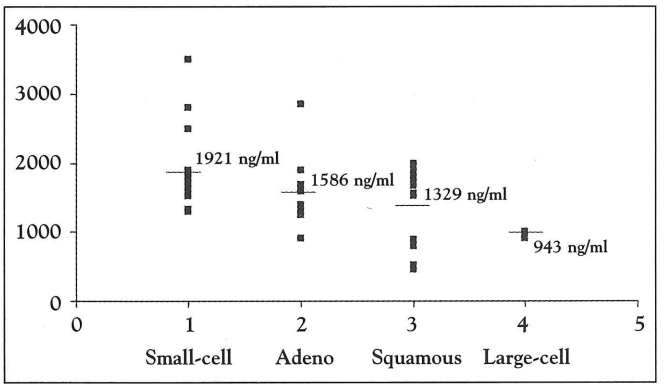

Figure 1: *sICAM-1 levels by cell type of cancer*

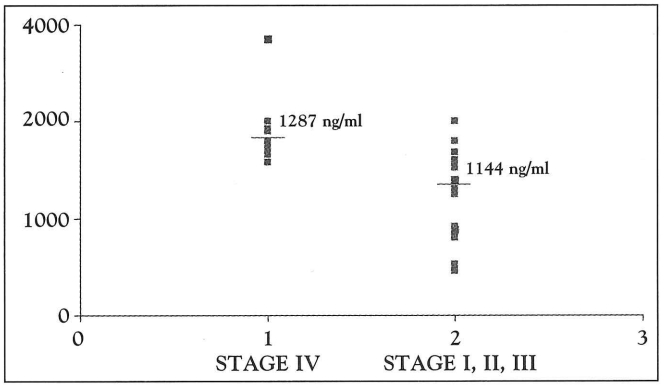

Figure 2: *sICAM-1 levels of NSCLC petients by stage*

The mean sICAM –1 level in nonsmall-cell cancer without metastasis was 1144.4±90.2 ng/ml, and in those with metastasis it was 1827.6±130.8 ng/ml, and the difference was statisticaly significant (p<0,0001) (Figure 2).

The mean sICAM-1 level in tuberculosis was measured as 1586±147.0 ng/ml. The difference between sICAM-1 levels in carcinoma and tuberculosis (1543.7±86.8 ng/ml, 1586.1±147.0 ng/ml, respectively) was not significant (p<0.13). The difference between the sICAM level of both groups (carcinoma and tuberculosis) and the sICAM level (372±33.04 ng/ml) of healthy group was found to be significant (p<0.0001) (Figure 3).

When the cut-off serum ICAM-1 value was taken as 400 ng/ml in distinguishing healthy controls from the carcinoma groups, the sensitivity was 100%, the specifity was 60%, the positive predictive value was 86%, and the negative predictive value was 100%. When the cut-off was taken as 1570 ng/ml, in differentiating the stage IV from the other stages, the sensitivity was 91%, the specifity was 82%, the positive predictive value was 71% and the negative predictive value was 95%.

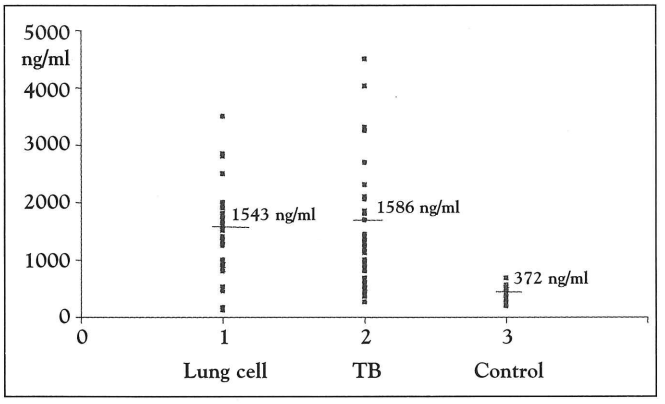

Figure 3: *Serum levels of sICAM-1 in lung cancer, tuberculosis and controls*

Discussion

ICAM-1 level on the surface of the cell rises as a response to cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), interferon (IFN). Parallel to this rise, the soluble form (sICAM-1) in blood also rises. sICAM-1 forms an important extracellular part of ICAM-1 attached to membrane and then attached to lymphocyte function-associated antigen-1 (LFA-1). Thus, sICAM-1 competes with ICAM-1 that is attached to membrane and prevents its function by bonding to the region where it is bound (10,12). We thought that, it is more advantageous working with the soluble form that reflects cellular ICAM-1 expression by considering the difficulties in obtaining the tissues and working immunohistochemically. Thus, we investigated the sICAM-1 levels in lung cancer, pulmonary tuberculosis, and healthy subjects. In our study, the sICAM-1 level in blood of the patients with carcinoma and tuberculosis was higher than in the blood of the healthy people.

The interrelation of the cells and adhesion molecules has great importance in the development and continuation of the immune response. Two main mechanisms arrange the interrelation of the cells. The first one is the production of the soluble cytokines such as interleukin, TNF and interferons. The second one is surface molecules which provide the relation between leucocyte and potential target. These molecules are known as adhesion molecules. Adhesion molecules, besides providing the interrelation of the cells essential for immunologic reactions, are required for patient defense against pathogens and carcinogenic cells (3). The bonding of T-cell receptor (TCR) that exists on T-cells and antigen- MHC complex that is on the antigen presenting cell, activate receptors like CD2 and LFA-1 found on the surface of lymphocytes (13). Following the bonding of TCR with antigen MHC complex, LFA-1/ICAM-1 adhesion power rises. Activated ICAM-1/LFA-1, functions as one of the cosimilators for TCR in the acti-

vation period of T-cells. In the defense against tuberculosis, there is a relation between T-lymphocyte and macrophage. Therefore, the effect of ICAM-1 on this relation is important. It is declared that LFA-1/ ICAM-1 adhesion plays the basic role in the sticking of T-cells to endothelial cells. All these indicate the importance of ICAM-1 molecule in the cellular immune response.

In our study, significantly higher levels of sICAM-1 in stage IV compared with those in the other stages in nonsmall-cell lung cancer patients, led us to consider the possibility of sICAM-1 level being an indicator of metastasis. This comment is concordant with the literature (3,14-16). If the cut-off value is taken as 1570 ng/ml, only one case is under the cut-off value and four without metastasis are above the limit. Sensitivity was found as 91%, specifity as 82%.

Osaki et al., compared sICAM-1 level of nonsmall-cell lung cancer patients with that of healthy people and reported that serum sICAM-1 level in 80% of nonsmall-lung cancer patients is higher than 306 ng/ml (17). Rothlein, et al., determined that in normal serum, sICAM –1 value was between 100 and 400 ng/ml. In our study, sICAM-1 values of healthy people were found to be concordant with the related literature, Rothlein et al., also reported that in malignancy, serum sICAM-1 levels were high (10). Tsujisaki et al., investigated sICAM-1 levels in the tumours of bladder, stomach, esophagus and pancreas, and also in the serum of patients that have cholecystitis and pancreatitis. They found that sICAM-1 level is generally higher in the tumour group (12). It has been also reported that sICAM-1 level in the serum samples of patients with melanoma increases and that this incline is parallel with the tumor stage, progression of the disease and metastasis. It has also been told that melanoma can be followed by blood sICAM-1 value, and it can be used in the early diagnosis of metastasis, especially liver metastasis (12,18). In the current study, the small-cell lung cancer was shown to present with significantly higher levels of sICAM-1 than nonsmall-cell type.

Some cytokines play important roles in the expression of adhesion molecules. It is known that cytokines such as IFN gamma, TFN alpha and IL-1 increase the expression of ICAM-1 in tumor cells. Azima et al., reported that when 10 u/ml of IFN is given to the small-cell lung cancer patients, ICAM-1 expression increases in 16 hours. 16 hours after IFN is given to Lu 135 cells that do not express ICAM-1, ICAM-1 was expressed by these cells (16).

Besides these, it is indicated that the tumor cells produce adhesion molecules and their soluble forms. In this case, they prevent effective immune defense by blocking LFA-1 receptors on NK and cytotoxic T-lymphocytes, which cause the annihilation of sICAM-1 producing the tumor cells. This can be a mechanism of the tumor cells to escape from immune control (19,20).

While many of the publications showed a relation between ICAM-1 expression and tumor metastasis, Smith and his colleagues indicated that ICAM-1 and LFA-1 expressions decrease on the surface of malignant cells of Hodgkin's disease and Burkitt's lymphosarcoma, and this is considered as another aspect of this issue. In this respect, it is declared that the decrease in adhesion molecules is a way for escaping from immune control, as it is difficult for tumor cells that don't have LFA-1 and ICAM-1 on their surface to be recognised by natural killer cells and cytotoxic T-lymphocytes (21).

The response of T-lymphocyte plays an important role in the pathogenesis and clinical course of tuberculosis. Specific cellular immune response is executed by sensitive T cells and cytotoxins secreted by them. Lymphocytes relate with macrophage, endothelial and epithelial cells by expressing adhesion molecules. By this method, they also bond tumor cells and result in cytotoxicity (22). Any important difference was not found between the sICAM-1 levels in tuberculosis and lung cancer in the present study.

In conclusion, measurement of sICAM-1 levels can not differentiate lung cancer from pulmonary tuberculosis, but can be used to determine metastatic disease in nonsmall-cell lung cancer, and also to differentiate small-cell lung cancer from nonsmall-cell lung cancer.

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