

## Soluble intracellular adhesion molecules (sICAM-1, sVCAM-1) in peripheral blood of patients with thyroid cancer\*

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The growth of a neoplasm and its ability to form metastases is a multistep process dependent on angiogenesis and immunological reactions of the organism. In this process adhesive factors are also involved. The aim of this work was estimation of the concentration of soluble intercellular adhesion molecules (sICAM-1) and vascular cellular adhesion molecules (sVCAM-1) in the serum of peripheral blood of patients with thyroid cancer before operation. The study comprised 48 patients (38 women and 10 men) aged from 18 to 87 years, in whom thin needle aspiration biopsy revealed cancer of the thyroid. Postoperative histopathological examination showed papillary cancer in 35 patients, oxyphilic cancer in 5 patients, anaplastic cancer in 4 and medullary cancer in 4 patients. In those patients, using the immunoenzymatic method ELISA, the concentration of sICAM-1 and sVCAM-1 in the serum of peripheral blood was determined. The control group comprised 26 healthy persons. We found statistically significant increase of sICAM-1 concentration in serum in all forms of cancer, in comparison with the control group. Mean concentrations of sICAM-1 were as follows: in papillary cancer patients  $455.23 \pm 28.66$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; in oxyphilic cancer  $455.60 \pm 95.21$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; in anaplastic cancer  $570.00 \pm 170.89$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; and in medullary cancer  $512.00 \pm 11.46$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ . The mean concentration of sVCAM-1 in serum was statistically significantly higher than in the control group only in case of anaplastic cancer ( $1033.75 \pm 86.30$  vs.  $644.58 \pm 27.30$  ng/ml;  $p < 0.05$ ).

We evaluated the correlation coefficient between the concentration of sICAM-1 and sVCAM-1 in the serum of patients with thyroid cancer. Positive correlation was observed between the concentration of sICAM-1 and sVCAM-1. The obtained results confirm essential role of the investigated adhesive factors in the process of thyroid cancer growth.

*Key words: thyroid cancer, adhesive factors, angiogenesis*

Thyroid gland oncogenesis is an abnormal process involving mutations of genes encoding signal transduction molecules, neoangiogenesis and the overexpression of cytokines involved in tumor invasion and metastatic potential. This multistep phenomenon of vascular cell invasion, migration, proliferation and differentiation not only depends on extracellular matrix enzymes activity, growth factor and their receptors expression, but is also mediated by cell adhesion

molecules [13, 21]. In particular, cellular adhesion mechanisms have been implicated in the pathogenesis of certain solid tumors and distant metastases formation. The term cellular adhesive molecules (CAM) denotes superficial receptors of cells and their ligands allowing the contact and communication between a cell and extracellular matrix, and between cells. The family of adhesive molecules consists of five basic groups of these molecules (selectins, integrins, cadherins, immunoglobulin-like molecules and isoforms of particle CD 44). Adhesive molecules participate in the differentiation of cells, inflammatory processes, reaction to transplanted tissue and neoplastic dissemination [5, 16, 20]. The family of immunoglobulin-like molecules includes,

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among others, intercellular adhesion molecules (ICAM-1) and vascular cellular adhesion molecules (VCAM-1). Constitutional occurrence of ICAM-1 was demonstrated on thyrocytes in papillary thyroid cancer [13]. VCAM-1 participates in the processes of differentiation of tissues, activation of T cells and neoplastic dissemination [7]. The precise role of ICAM-1 and VCAM-1 in the process of cancerogenesis in the thyroid has not been explained so far.

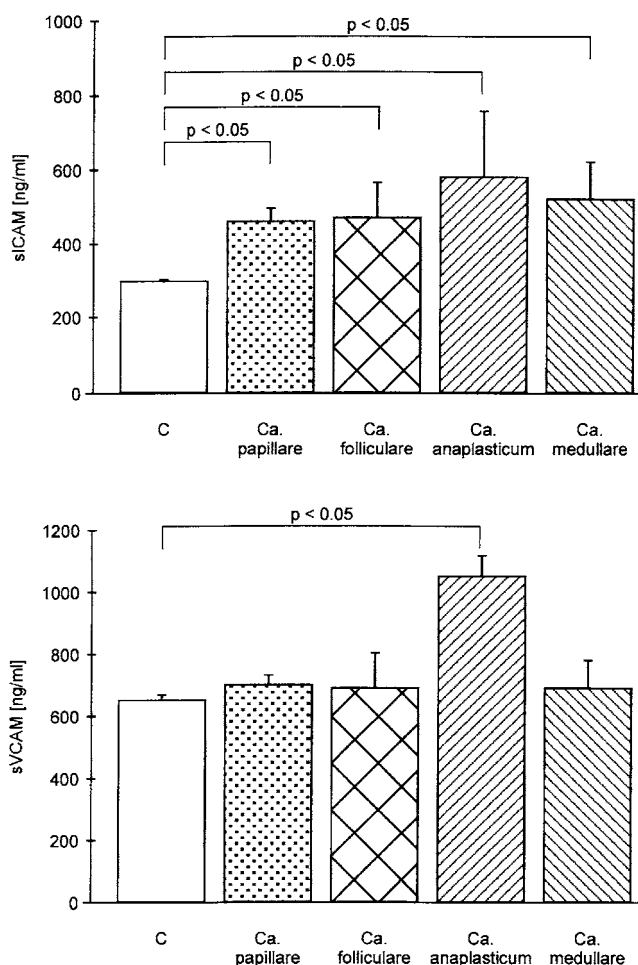
The aim of this study was to evaluate whether the concentration of the soluble form of intercellular adhesion molecules (sICAM-1) and vascular cellular adhesion molecules (sVCAM-1) in the serum of peripheral blood was related to the presence of different histological types of thyroid cancer in patients before surgery.

### Material and methods

The study comprised 48 euthyroid patients (38 women and 10 men; aged from 18 to 87 years; mean  $53.69 \pm 16.23$  years) in whom fine needle aspiration biopsy revealed cancer of the thyroid. Postoperative histopathological examination showed papillary cancer in 35 patients, follicular cancer in 5 patients, anaplastic cancer in 4 and medullary cancer in 4 patients. The control group comprised 26 healthy persons (18 women and 8 men; aged from 21 to 44 years; mean  $26.59 \pm 1.47$  years). Blood for examination was sampled from a peripheral vein, on the day preceding the operation. Material obtained during surgery was used for routine histopathologic investigation and final verification of diagnosis. The concentration of sICAM-1 (sensitivity  $<0.35$  ng/ml; intra-assay precision and inter-assay precision: 4.3% and 7.4%) and sVCAM-1 (sensitivity  $<2.0$  ng/ml; CV: 5.0% and 9.0%) in serum was determined by ELISA (R&D Systems, USA). The differences between different forms of cancer were calculated using the analysis of variance and LSD test. Linear correlation between the concentrations of sICAM and sVCAM in the serum of patients with thyroid cancer and in the control group was also determined. The study was approved by the Ethical Committee for Scientific Studies of the Medical University of Łódź.

### Results

We have found statistically significant increase of sICAM-1 concentration in serum in all forms of cancer, in comparison with the control group ( $p < 0.05$ ). Mean concentrations of sVCAM-1 were as follows: in papillary cancer patients  $455.23 \pm 28.66$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; in follicular cancer  $455.60 \pm 95.21$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; in anaplastic cancer  $570.00 \pm 170.89$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ ; and in medullary cancer  $512.00 \pm 11.46$  vs.  $299.62 \pm 11.54$  ng/ml,  $p < 0.05$ . The highest



**Figure 1.** Concentration of sICAM-1 and sVCAM (mean  $\pm$  SEM) in the serum patients with thyroid cancer and in control group (C).

mean sICAM-1 concentration was seen in anaplastic cancer (Fig. 1). The mean concentration of sVCAM-1 in serum was higher than in the control group only in case of anaplastic cancer  $1033.75 \pm 86.30$  vs.  $644.58 \pm 27.30$  ng/ml;  $p < 0.05$  (Fig. 1).

There was a positive linear correlation between sICAM and sVCAM in patients with thyroid cancer ( $r = 0.447$ ,  $p < 0.01$ ) and in the control group ( $r = 0.395$ ,  $p < 0.01$ ).

### Discussion

The process of cancerogenesis is complex and multistep. The development of a tumor depends on neoangiogenesis and on the efficacy of defense mechanisms in the organism. One of these defense mechanisms is immunological response. The interaction between a neoplastic cell and T lymphocyte is possible due to the presence of adhesive molecules on lymphocyte surface and expression of a corre-

sponding ligand on the cellular membrane of the neoplastic cell. The adhesive molecules connected with the function of leukocytes are integrins LFA-1 and VLA-4 and their ligands are intracellular adhesion molecules ICAM-1 and VCAM-1. The expression of molecules HLA-DR and ICAM-1 was demonstrated on thyrocytes in papillary cancer [15], and the expression of ICAM-1 in distant metastases of papillary cancer [6]. The interaction between molecules of cellular adhesion LFA-1/ICAM-1 and VLA-4/VCAM-1 enables immunological cellular response against a neoplastic cell. Soluble circulating forms of sICAM-1 and sVCAM-1 can bind to the superficial integrins of lymphocytes, limiting their ability to react with the membrane form of ICAM-1 and VCAM-1 on target cells, thus limiting the defense mechanisms. High expression of ICAM-1 and VCAM-1 was demonstrated on endothelial cells of capillaries in papillary thyroid cancer, accompanied by accumulation of lymphocytes VLA-4 and LFA-1 positive [24]. More and more broadly presented argument shows, that measurement of these parameters can become an important element in the diagnostics and monitoring of conservative and surgical treatment of some tumors. Therefore, in our patients with thyroid cancer, we have estimated the level of sICAM-1 and sVCAM-1 in peripheral blood serum. Increased concentration of sICAM-1 and sVCAM-1 in peripheral blood was demonstrated in many forms of cancer: uterine cervix cancer, breast, ovarian cancer, liver, stomach, colon, rectum, lung, larynx and malignant lymphoma [2, 3, 4, 8, 9, 10, 11, 12, 14, 15, 17, 19, 22, 23, 25]. In our neoplastic patients significant increase of the level of sICAM-1 was seen in all investigated forms of thyroid cancer: papillary, follicular, medullary and anaplastic. Elevated level of sVCAM-1 was present in anaplastic cancer. Even though significantly high levels of sICAM-1 were observed in all forms of thyroid cancer, the highest levels were seen in patients with undifferentiated cancer. The discussed adhesive factors play a double role in tumor growth, on the one hand intensifying the processes of neoangiogenesis, on the other enabling the neoplastic cell to avoid immunological response [1, 16, 18]. This allows more rapid development of the tumor and its transformation from a differentiated form into a more advanced form of cancer – anaplastic. Therefore, high levels of these factors in patients with cancer of the thyroid may be connected with greater advancement of neoplastic process and worse prognosis of the effectiveness of treatment.

In conclusion, the obtained results confirm essential role of the investigated adhesive factors in the process of thyroid cancer growth. The increased levels of sICAM-1 and sVCAM-1 in the peripheral blood of patients with anaplastic type of thyroid cancer are related to the high aggressiveness of neoplastic process.

Evaluation of the level of these parameters may become an additional diagnostic and prognostic parameter in patients with cancer of the thyroid.

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