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Prognostic Significance of Soluble Adhesion Molecules in Hodgkin's Disease

K.N. SYRIGOS, E. SALGAMI, A.J. KARAYIANNAKIS, N. KATIRTZOGLOU, E SEKARA and P. ROUSSOU

Oncology/Haematology Unit, 3rd Department of Medicine, Athens Medical School, Sotiria General Hospital, Athens, Greece

Abstract. *Background: Cell adhesion may play a pivotal role in the development, progression and metastasis of solid malignancies. We evaluated the serum concentration of four adhesion molecules and their prognostic significance in patients with Hodgkin's Disease (HD). Patients and Methods: Serum samples from 20 HD patients were collected at diagnosis, after 3 cycles of chemotherapy and at completion of treatment and compared with a control group of 29 apparently healthy subjects. Soluble forms of E-Selectin (sE-Selectin), ICAM-1 (sICAM-1), VCAM-1 (sVCAM-1) and E-Cadherin (sE-Cad) were measured by standard ELISA assays. Results: Significantly increased serum levels of sICAM-1 and sE-Selectin were determined in HD patients at diagnosis compared to controls ($p<0.0001$), while sVCAM-1 at diagnosis correlated significantly with both sICAM-1 and sE-Selectin levels ($r=0.5$, $p=0.03$). Chemotherapy resulted in a significant decrease of sICAM-1 and sE-Selectin levels ($p=0.02$ and $p=0.002$, respectively). Conclusion: Serum levels of ICAM-1 and E-Selectin in newly diagnosed HD patients were found significantly increased, suggesting a possible involvement of these two molecules in the pathogenesis of the disease. Their rapid decrease following chemotherapy was found to be an independent predictor of response to treatment.*

There is now a growing body of evidence suggesting that cell adhesion is fundamental for the establishment and maintenance of multicellular organisms: the normal development and function of tissues is governed by the interactions of cells with each other and with their acellular environment, as they are mediated by adhesion. Furthermore, interactions between the cytoskeleton and the adherens junctions allow maintenance of cell polarity and regulate or significantly contribute to a variety of functions, including signal transduction, cell growth, differentiation, site-specific gene expression, morphogenesis, immunologic function, cell motility, wound healing and inflammation (1). Adhesion molecules also play a distinct role in the immune system by promoting cell-cell and cell-stroma interactions and by regulating leucocyte trafficking (2).

In addition to significantly contributing to a variety of normal cell functions, adhesion molecules may play a pivotal role in the development and progression of the malignant phenotype in a range of tumour types. Adhesion molecules are intimately involved in the control of such processes as morphological differentiation, cellular proliferation, invasion and colonisation of distant organs (3). Reduced cell-matrix adhesion allows neoplastic cells to circumvent the control of differentiation induced by the normal extracellular environment (4), while loss of the intercellular adhesion allows malignant cells to escape from their site of origin, degrade the extracellular matrix, acquire a more motile and invasive phenotype and finally invade and metastasise (5).

The four major families of adhesion molecules are the selectins, the integrins, the cadherins and the immunoglobulin superfamily. E-Selectin is expressed by activated endothelial cells and binds to specific ligands containing sialyl-Lewis residues. Several *in vitro* and *in vivo* studies suggest that E-Selectin-mediated binding of malignant cells to human endothelium correlates with tumour dissemination and facilitates the formation of haematogenous metastasis (6,7). Increased serum levels of E-Selectin have been associated with tumour progression and metastatic potential in several solid malignancies, including colorectal, gastric and pancreatic adenocarcinomas (8,9).

Intercellular adhesion molecule-1 (ICAM-1, CD54) and vascular cell adhesion molecule (VCAM, CD106) are both members of the immunoglobulin superfamily of adhesion molecules. ICAM-1 is constitutively expressed by endothelial cells and by some leukocytes and serves as a ligand for the leucocyte β_2 integrin receptors, lymphocyte function-

Correspondence to: Konstantinos N. Syrigos, MD, PhD, Ass. Professor of Oncology in Medicine, Athens University School of Medicine, 3rd Department of Medicine, Building Z, Sotiria General Hospital, 152, Mesogion Ave , 115 27 Athens, Greece. Tel: (+30 210) 778103, Fax: (+30 210) 7719981, e-mail: knsyrigos@usa.net

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associated antigen-1 (LFA-1) and Mac-1. VCAM-1 is expressed mainly by activated endothelial cells and serves as ligand for the $\alpha_4\beta_1$ integrin receptor. The endothelial cells of small blood vessels express both ICAM-1 and VCAM-1 and their expression is up-regulated by cytokines (10,11). Increased serum levels of sICAM-1 and sVCAM-1 have been associated with tumour progression and metastatic potential in several solid malignancies, including colorectal, gastric and pancreatic adenocarcinomas (8,9).

E-Cadherin (E-Cad) is a cell-adhesive molecule found in epithelial cells in a variety of embryonic and adult tissues. It is a member of cadherins, a family of transmembrane glycoproteins with an adhesive role: they mediate homophilic Ca^{2+}-dependent cell-cell adhesion. It has been shown to play a crucial role in cell migration and tissue morphogenesis, while E-Cad also participates in wound healing and cell migration. Several recent studies have suggested a link between unstable or reduced expression of E-Cad and tumour progression in solid neoplasms (12-16). Soluble forms of E-Cad are found as 80-84 kDa peptides released from the human carcinoma cell line (MCF-7) into the culture medium. These fragments are degradation products of the 120 kDa form of the intact E-Cad. They disrupt intercellular connections in cultural epithelial cells and they have been shown to be a good indicator of the regeneration of E-Cad *in vivo* (17-20). Although the expression of E-Cad in solid malignancies has been thoroughly examined, little is known about its expression in haematological malignancies.

Soluble counterparts of adhesion molecules are probably shed from the cell surface of activated endothelium and haematopoietic cells and retain their functional capability to recognise their ligands. Soluble forms of all four adhesion molecules have been detected in the supernatants of cytokine-activated endothelial cells and in the culture media of several malignant cell lines. Recently, elevated serum levels of E-Selectin, ICAM-1, VCAM-1 and E-Cad have been described in patients with various solid tumours, including colorectal, gastric, pancreatic and breast cancer (8,9,11).

In this study we evaluated the serum concentration of E-Selectin (sE-Selectin), ICAM-1 (sICAM-1), VCAM-1 (sVCAM-1) and E-Cadherin (sE-Cad) in patients with Hodgkin's Disease (HD) and we correlated them with clinicopathological features and patients' survival.

Patients and Methods

Subjects. Our study included two groups (Table I). The twenty consecutive, newly diagnosed patients with HD, treated at the Haematology Unit, 3rd Department of Medicine, Athens Medical School, Sotiria General Hospital, Athens Greece included 10 (50%) males and 10 (50%) females with a median age of 33 years (range 19-68 years). The patients were diagnosed and staged according to the Ann Arbor classification system (21). All patients were evaluated by medical history, physical examination, blood and biochemical count, computed tomography of the chest, abdomen and pelvis and unilateral bone marrow biopsy. The pathological diagnosis of HD was based on the histology criteria described by Lukes and Butler (22). Haemoglobin concentration (Hb), white blood cells count (WBC), erythrocyte sedimentation rate (ESR), serum albumin, serum alkaline phosphate (ALP) and serum lactate dehydrogenase (LDH) levels were measured by standard assays. For the statistical evaluation of our results, low albumin was defined as <3.5 g/dl and high ALP and LDH as >150% upper normal limit at our institution. Serum β_2-microglobulin was measured by a radioimmunoassay (normal values 1.0-2.4 mg/l). Anaemia was defined as the presence of haemoglobin levels <13 g/dl for males and <11.5 g/dl for females. Leukocytosis was defined as WBC>15,000/mm^3 and lymphocytopenia as absolute lymphocyte count <8% of WBC. Bulky disease was defined as a mediastinal mass with a diameter over one third of maximal mediastinal width or any tumour mass with a diameter more than 10 cm.

Table I. *Demographic and four adhesion molecules' median values of the two groups of the study, HD patients (n=20) and controls (n=29).*

Characteristics	Number (%)
Patients (n=20)	
Age (years)	33.00 (19-68)***
sICAM-1 (ng/ml)	33.14 (24.72-39.70)**
sVCAM-1 (ng/ml)	15.87 (14.44-18.65)**
sE-Selectin (ng/ml)	4.78 (3.34-6.80)**
sE-Cad (ng/mL)	793.75 (743.40-984.57)**
Controls (n=29)	
Age (years)	32.50 (19-62)***
sICAM (ng/ml)	20.78 (18.15-26.45)**
sVCAM (ng/ml)	13.90 (13.28-18.64)**
sE-Selectin (ng/ml)	1.44 (1.07-2.25)**
sE-Cad (ng/ml)	970.50 (647.33-1323.81)**

* mean (SD)
** median (interquartile range)
*** median (min, max)
Abbreviations: sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; sE-Cad: soluble E-Cadherin.

All patients received standard chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), while selected patients with bulky disease received additional low-dose, involved field radiotherapy. Response to chemotherapy was defined as complete remission (CR), partial response (PR) and progressive disease (PD), according to criteria previously described (23).

Twenty-nine apparently healthy volunteers, age and sex-matched (17 males and 12 females) were used as a control group (median 32.5 years; range 19-62 years) (Table I). The absence of disease was assessed by clinical history, physical examination and routine laboratory tests, including blood count and liver and renal functional tests.

Methods. Peripheral venous blood samples were drawn into sterile glass tubes (Vacutainer, Becton Dickinson, Plymouth, UK). All samples were allowed to coagulate at room temperature for 30 min, centrifuged at 2000g for 10 min and serum was separated, aliquoted and stored at -80˚C until assay. Serum samples from

HD patients were collected at diagnosis, after the completion of the third cycle of chemotherapy and at the end of chemotherapy.

All samples were blindly tested with the application of an immunoenzymatic method. Serum E-Selectin and VCAM-1 concentrations were determined using a solid phase, enzyme-linked immunosorbent assay (ELISA) designed to measure soluble levels of E-Selectin and VCAM-1 in cell culture supernatant, serum and plasma (Parameter, R&D Systems, Minneapolis, MN, USA). The assays employ the quantitative sandwich enzyme immunoassay technique using recombinant human E-Selectin and VCAM-1 with antibodies raised against the recombinant proteins, respectively. Their sensitivity was 1ng/ml for sE-Selectin and 2 ng/ml for sVCAM-1.

Serum levels of sICAM-1 and sE-Cad were also measured by an ELISA using commercially available kits designed for the quantitative measurement of human sICAM-1 (Cellfree, Endogen, Woburn, MA, USA) and sE-Cad (Takara Shuzo Co, Ltd, Kioto, Japan), with a sensitivity of 0.3 ng/ml and 0.8 ng/ml, respectively.

Statistical analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (24). Data were tested for normality and were found to be non-normally distributed. Accordingly, all data are presented as medians (interquartile range). The Kruskal-Wallis analysis of variance (ANOVA), the Mann-Whitney *U*-test and the Wilcoxon rank test were used to evaluate differences between multiple groups, unpaired and paired observations, respectively. Correlations were evaluated using the Spearman rank test. Survival curves were obtained by the Kaplan-Meier method and comparisons were made with the log-rank test. The Cox proportional hazards regression model was used for the multivariate analysis, after univariate analysis had defined the relevant prognostic variables. Significance was presumed at $p<0.05$.

Results

Serum levels of cell adhesion molecules in healthy controls and HD patients. All four soluble adhesion molecules were detectable in all control subjects and HD patients. There were no significant differences within either the control or the HD population between males and females or according to age. Serum levels of sICAM-1 and sE-Selectin in HD patients at diagnosis were significantly higher than those of healthy controls ($p<0.0001$). With regard to sVCAM-1 and sE-Cad levels, there was no statistically significant difference between HD patients levels at diagnosis and healthy controls. Finally, there was no statistically significant difference for all adhesion molecules, between healthy controls and the samples drawn in the middle and at the completion of chemotherapy (Table II).

With regard to the correlation of serum levels of all adhesion molecules measured and clinicopathological variables of HD patients, according to our data, increased levels of sVCAM-1 and sICAM-1 correlated positively with β-symptoms ($p=0.02$ and $p=0.007$, respectively) and negatively with lymphocytosis ($p=0.04$ and $p=0.005$, respectively). Furthermore, sICAM-1 correlated with reduced PLT ($p=0.005$) and increased ALP ($p=0.009$). No statistically significant difference was established with either of the molecules measured and the stage or the bulk of the disease or laboratory findings at diagnosis such as Hb, WBC, ESR, LDH, total albumin, globulins and β_2-microglobulin.

Table II. *Median values of the molecules studied between control subjects and HD patients at diagnosis and at the completion of chemotherapy.*

	Controls (n=29)	Patients (n=20) At diagnosis	Completion of chemotherapy	Significance*
sE-Selectin ng/ml	1.44 (1.07-2.25)	4.78 (3.34-6.80)	2.28 (1.47-4.33)	0.0001
sICAM-1 ng/ml	20.78 (18.15-26.45)	33.146 (24.72-39.78)	27.923 (21.74-31.95)	0.001
sVCAM-1 ng/ml	13.90 (13.28-18.64)	15.87 (14.44-18.65)	15.98 (14.47-17.16)	0.305
sE-Cad ng/ml	970.50 (647.33-1323.81)	793 (743.40-984.57)	782.52 (511.54-1025.8)	0.229

sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; sE-Cad: soluble E-Cadherin. *Statistical significance of differences, patients at diagnosis *versus* controls (Mann-Whitney *U*-test). Values are medians (interquartile range).

Serum levels at diagnosis of sVCAM-1 correlated significantly with both sICAM-1 and sE-Selectin levels ($r=0.5$, $p=0.03$).

The effect of chemotherapy on the serum levels of sICAM and sE-Selectin. Initiation of chemotherapy was followed by a rapid decline of the levels sICAM-1: 33.14 (24.72-39.70) *versus* 24.21 (19.50-33.72) after the completion of the 3rd cycle *versus* 27.92 (21.72-31.95) ng/ml at the end of chemotherapy {median (interquartile range)}. The difference was statistically significant ($p=0.02$). The decrease was more intense for sE-Selectin levels: 4.78 (3.34-6.80) *versus* 2.60 (1.73-3.54) after the completion of the 3rd cycle *versus* 2.28 (1.47-4.33) ng/ml at the end of chemotherapy {median (interquartile range)}. The difference was statistically significant ($p=0.002$). For all the molecules studied, there were no significant differences after the completion of the 3rd cycle and the end of chemotherapy.

Discussion

In Hodgkin's Disease (HD) the origin of the malignant cells (Hodgkin and Reed-Sternberg cells) remains uncertain, although there are accumulating data suggesting a B-cell origin (25). It is also recognized that in HD the malignant cells constitute only a small fraction of all cells present in the nodes, the majority of which represent inflammatory cells, including

lymphocytes, plasma cells, eosinophils and histiocytes. It has been demonstrated that interactions between neoplastic and surrounding reactive cells, mediated by adhesive molecules, play an important role in the pathogenesis of HD, contributing to HD vascular dissemination (26).

The ICAM-1 molecule in normal B cells mediates homotypic adhesion. It is expressed by lymphocytes and endothelial cells and its production is mainly regulated by cytokines. Furthermore, it participates in the immune response, facilitating antigen recognition by the T-cell receptor complex and thus activating the T-cells. It is also involved in lymphoid trafficking and extravasation controlling lymphocyte/endothelial cells interactions. There are several studies indicating that ICAM-1 is involved in neoplastic neovascularization and colonisation of distant sites in solid tumours. It has been shown that ICAM-1 is overexpressed in solid malignancies, such as lung, bladder, colorectal, gastric and pancreatic cancer. Increased tissue expression and circulating levels of ICAM-1 in patients with those malignancies has been associated with poor differentiation of the tumours, advanced stage and worse outcome of the disease. With regard to haematologic malignancies, ICAM-1 expression is more heterogeneous: in chronic lymphocytic leukemia (CLL) and in mantle-cell lymphomas it is weakly expressed, if at all, while in follicular or diffuse lymphomas its expression is enhanced. Loss of ICAM-1 expression has been associated with decreased infiltrating-infiltrating T lymphocytes in diffuse large B-cell lymphomas. Also a positive correlation has been described between low expression of ICAM-1 and advanced stage, bone marrow and extranodal involvement, poor response to treatment and worse survival in patients with non-Hodgkin's lymphoma. High serum levels of the soluble form of this molecule correlated with adverse clinical outcome of patients with non-Hodgkin's lymphoma and CLL (27).

VCAM-1 is normally expressed by bone marrow stromal cells, vascular endothelial cells and follicular dendritic cells and its production is up-regulated by cytokines. In immunohistochemistry studies, VCAM-1 overexpression was found in biopsy material from patients with non-Hodgkin's lymphoma and acute leukemias (28). In NHL patients in particular, VCAM-1 overexpression has been associated with advanced stage of the disease (28). Selectins comprise a family of adhesion receptors expressed by leukocytes, platelets and endothelial cells. These molecules are particularly implicated in intravascular cell-cell adhesion. Several studies have demonstrated that the serum levels of L-selectin and P-selectin (two other members of the selectins family) were found to be significantly elevated in both HD and NHL patients (29).

In our study we evaluated the circulating levels of four adhesive molecules: sE-selectin, sVCAM-1, sICAM-1 and sE-Cad. Although the cellular source, mechanism of release and the structure of these soluble isoforms are currently unknown, it is likely that these soluble products are the result of enzymatic cleavage from endothelial, leucocyte or neoplastic cell surfaces, perhaps induced by cytokines. As far as we know, our study is the first to investigate sE-Selectin levels in HD patients and to correlate them with the serum levels of the other molecules. In fact, HD patients demonstrated significantly higher serum levels of the cell adhesion molecules E-Selectin and ICAM-1, when compared with healthy individuals. We also documented a strong positive association of both molecules with β-symptoms indicating that these two molecules may contribute to the development of these symptoms, possibly through interaction with the cytokines IL-1 and CD25.

Serum levels of both molecules fell significantly after initiation of treatment and, by the completion of the 3rd cycle of chemotherapy, serum levels of HD patients were not statistically different from the control group. Serum levels of E-Selectin and ICAM-1 were further decreased by completion of chemotherapy. The above finding is in accordance with previous studies suggesting that both molecules comprise a sensitive marker of response to curative treatment (*i.e.* their levels rapidly fell after radical resection in colorectal cancer) (9). Our study, as far as we can tell, is the first in the reported literature that suggests the use of these two molecules as an early marker of response to chemotherapy.

Previous studies have introduced VCAM-1 as the principal adhesion molecule involved in the pathogenesis of both HD and NHL. According to our data, although sVCAM-1 was found increased in HD patients, a strong correlation was demonstrated between VCAM-1 and the molecules E-Selectin and ICAM-1, suggesting that the serum levels elevation of these adhesion molecules may be a co-ordinated event in HD pathogenesis and development. In fact, it has been shown *in vitro* that soluble E-Selectin up-regulates ICAM-1 and VCAM-1 expression in a range of human tumour cell lines. The above observation is consistent with our study, since we also demonstrated that E-Selectin was the molecule most increased in HD patients. It is therefore suggested that E-Selectin could be the main adhesion molecule involved in the pathogenesis of HD and that serum elevation of sICAM-1 and sVCAM-1 could be a corresponding event. Furthermore, since increased serum E-Selectin levels were independent of the stage and positively correlated with the symptoms of the disease, it is suggested that this rise is an early event in the development of HD and that E-Selectin may participate in the pathogenesis of the disease.

In conclusion, we demonstrated, for the first time, significantly increased serum levels of the molecules E-Selectin and ICAM-1 in patients with HD. It seems that serum levels of both molecules increase early in the progress of HD and their rapid fall after initiation of chemotherapy is an independent, predictor of response to treatment. Our results, if confirmed by larger studies, could form the basis for establishment of serum

E-Selectin and ICAM-1 levels at diagnosis, as predictors of response to chemotherapy in HD patients. A study correlating E-Selectin and ICAM-1 levels with immunohistochemistry of lymph node and/or bone marrow biopsy specimens is currently being undertaken to clarify the role of these two molecules in the pathogenesis of this disease.

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