
A distinct profile of serum levels of soluble intercellular adhesion molecule-1 and intercellular adhesion molecule-3 in mycosis fungoides and Sézary syndrome

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Background: Cell adhesion molecules (CAMs) play a pivotal role in cutaneous localization of T cells. Tissue-selective localization of T lymphocytes to the skin is crucial for immune surveillance and in the pathogenesis of skin disorders.

Objective: To detect the profile of soluble CAMs in patients with cutaneous T-cell lymphoma (CTCL), we investigated the levels of intercellular adhesion molecule-1 (ICAM-1, soluble ICAM-1 [sICAM-1]); intercellular adhesion molecule-3 (sICAM-3); vascular cell adhesion molecule-1 (sVCAM-1); and E-selectin (sE-selectin) in sera from patients with T-cell-mediated skin diseases.

Methods: Serum levels of the 4 CAMs were measured by enzyme-linked immunosorbent assay in 42 participants including 11 patients with early stages of CTCL; 7 with advanced stages of CTCL including Sézary syndrome; 12 with inflammatory skin diseases (psoriasis and atopic dermatitis); 8 with skin diseases that may evolve into CTCL; and healthy individuals. Levels were correlated with biological parameters known as prognostic factors in non-Hodgkin lymphomas.

Results: In patients with CTCL, significantly increased levels of sICAM-1 and sICAM-3 were found when compared with healthy individuals and patients with inflammatory dermatosis. Soluble E-selectin and sVCAM-1 levels were not increased. There were significant positive correlations between sICAM-1 and sICAM-3 levels and each of them with β 2-microglobulin levels.

Limitations: Limited number of patients was a limitation.

Conclusion: There is a distinct profile of soluble CAMs in patients with CTCL. However, future studies with a larger group of patients are needed to confirm these findings. We propose that high sICAM-1 and sICAM-3 levels have important implications in the context of immune response and immune surveillance in these patients. (J Am Acad Dermatol 2009;61:263-70.)

Key words: cutaneous T-cell lymphoma; soluble E-selectin; soluble intercellular adhesion molecule-1; soluble intercellular adhesion molecule-3; soluble vascular cell adhesion molecule-1.

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Supported by grants from Agustí Pedro i Pons Foundation and IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer).

Conflicts of interest: None declared.

Accepted for publication March 3, 2009.

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0190-9622/\$36.00

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doi:10.1016/j.jaad.2009.03.041

During the last 15 years there have been great advances in the understanding of cellular and molecular mechanisms of cell adhesion and migration. Cell adhesion molecules (CAMs) can be classified, based on structural and sequential homologies, into several families that include members of the immunoglobulin superfamily, selectins, integrins, and cadherins.^{1,2} These cell surface proteins play a critical role in a wide array of biologic processes such as cell growth, differentiation, embryogenesis, immune cell transmigration and response, and cancer metastasis. The loss of adhesive

interactions and their stimulation may result in disease states.²

The mechanisms of leukocyte trafficking suggest general principles regarding the interactions of malignant cells in lymphomas because the adhesion receptors regulating the trafficking of normal lymphocytes are also expressed in their malignant counterparts.

Tissue-selective localization of T lymphocytes to the skin is not only crucial for immune surveillance and the pathogenesis of skin disorders including inflammatory diseases but also for cutaneous T-cell lymphoma (CTCL).^{3,4} These diseases comprise a heterogeneous group of entities, including mycosis fungoides (MF) and its leukemic counterpart, Sézary syndrome. The World Health Organization/European Organization for Research and Treatment of Cancer classification distinguishes them as lymphomas with indolent and aggressive clinical behavior, respectively.⁵ MF is the most common type of CTCL. The neoplastic cells in MF typically have a mature CD3⁺, CD4⁺, CD45RO⁺ T-cell phenotype. However, establishing a definitive diagnosis of MF in its patch or early plaque phase is often difficult because of overlapping features with benign inflammatory dermatoses and insufficient pathological criteria.⁶

Tissue distribution, structure, counter-ligands, expression regulation, and function of the cell surface forms of CAMs have been described in detail.^{1,7-9} Here we briefly mention some key features. Intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule-1 (sVCAM-1) are members of the immunoglobulin superfamily. Although ICAM-1 and ICAM-3 share 5 similar extracellular immunoglobulin-like domains, they have a differential expression pattern and cellular distribution. The interaction of ICAM-1 (CD54) and ICAM-3 (CD50) with lymphocyte function associated antigen 1 (LFA-1) is integral to the normal functioning of the immune system. ICAM-3 also binds to dendritic cell-specific ICAM-3-grabbing nonintegrin, a C-type lectin expressed on dermal dendritic cells, which support T-cell proliferation.¹⁰ In addition, ICAM-3 contributes to macrophage recognition of apoptotic leukocytes that normally express this glycoprotein.¹¹

In endothelium, ICAM-1 and VCAM-1 (CD106) are involved in leukocyte rolling/capture and firm

adhesion whereas E-selectin (endothelial leukocyte adhesion molecule-1, CD62E) plays a major role in cell rolling. It is responsible for adherence of neutrophils, monocytes, eosinophils, memory T cells, and some tumor cells. Furthermore, E-selectin, ICAM-1, and VCAM-1 are transcriptionally up-regulated in response to inflammatory stimuli.^{12,13} In

human serum and other body fluids from healthy individuals and patients with a variety of diseases, soluble circulating forms of CAMs (soluble CAM [sCAM]) have been detected, suggesting a pathological role.¹⁴

In this study, to determine the profile of sCAMs in patients with CTCL, we analyzed soluble forms of ICAM-1 intercellular adhesion molecule-1 (sICAM-1), intercellular adhesion molecule-3 (sICAM-3), vascular

cell adhesion molecule-1 (sVCAM-1), and E-selectin (sE-selectin) in sera from patients with CTCL, benign T-cell-mediated dermatoses, and chronic dermatoses with potential to evolve into true CTCL.¹⁵ A secondary aim was to compare serum levels of these molecules in patients with CTCL and biological parameters known as prognostic factors in non-Hodgkin lymphomas.

METHODS

Patients

A total of 38 patients from the Department of Dermatology of the Hospital Clínic of Barcelona, Spain, were included in the study (June 1, 2002, through December 31, 2003). The patients were divided into 4 groups: (1) early CTCL: MF, patch and plaque lesions (11 patients IA, IB; t1 = 6, t2 = 5); (2) advanced CTCL (aCTCL) (n = 7): tumoral MF (one patient, IIB), erythrodermic MF (two patients, IIB) and Sézary syndrome (4 patients); (3) inflammatory skin diseases (n = 12): psoriasis (9 patients) and atopic dermatitis (3 patients); (4) skin diseases that could develop CTCL (pre-CTCL) (n = 8): parapsoriasis (4 patients) and chronic nonspecific dermatitis (4 patients). The pre-CTCL group included patients with chronic skin conditions: persistent erythematous and often scaling plaques clinically suggestive of MF without meeting the histologic criteria for MF. Furthermore, there was no known triggering event (no evidence of allergic reaction or connective-tissue disorder). Histopathological findings were consistent with parapsoriasis or chronic nonspecific dermatitis.

CAPSULE SUMMARY

- We detected a distinct profile of sCAMs in patients with CTCL.
- Increased levels of sICAM-1 and sICAM-3 may have important implications in the context of immune response and immune surveillance in patients with this disease.
- These findings may contribute to our understanding of the pathological mechanisms involved and provide new targets for treatment of CTCL.

Abbreviations used:

aCTCL:	advanced cutaneous T-cell lymphoma
CAM:	cell adhesion molecule
CTCL:	cutaneous T-cell lymphoma
ICAM:	intercellular adhesion molecule
LDH:	lactate dehydrogenase
LFA:	lymphocyte function-associated antigen
MF:	mycosis fungoides
sCAM:	soluble cell adhesion molecule
sE-selectin:	soluble E-selectin
sICAM:	soluble intercellular adhesion molecule
sVCAM-1:	soluble vascular cell adhesion molecule
VCAM-1:	vascular cell adhesion molecule

The diagnosis was made on both clinical and histopathological findings. Clinical evaluation, skin biopsies, laboratory tests, and staging procedures according to diagnosis were performed. Clinical parameters recorded included sex, age, histologic diagnosis, extent of cutaneous involvement, and blood test results: lactate dehydrogenase (LDH) and β 2-microglobulin levels, leucocytes, lymphocytes, and Sézary cell count. None of the patients were undergoing treatment when samples were collected and none had received systemic therapy for their skin conditions.

Four apparently healthy donors were used as a control group. Informed consent to participate in this study was obtained from all participants. This study was approved by the hospital's ethics review board.

Soluble adhesion molecule analysis

Venous blood samples were collected by venipuncture for blood tests and the measurement of serum concentrations of sCAMs. Sera samples from 42 participants were numbered and stored frozen at -20°C until use. All serum samples were assayed in duplicate for detecting sE-selectin, sICAM-1, sICAM-3, and sVCAM-1. Specific commercial enzyme-linked immunosorbent assay kits (Bender MedSystems, Vienna, Austria) were used following the manufacturer's recommendations. Briefly, one antibody directed to one epitope on the particular sCAM was coated onto the micrometer wells and an antibody directed to another epitope that is conjugated to the enzyme horseradish peroxidase was incubated with the sample or standard. Any sCAM forms a bridge between the two antibodies. After removal of unbound material, tetramethyl benzidine substrate was added; this reaction yielded a colored product proportional to the amount of conjugate. Reaction products were measured spectrophotometrically at 450 nm with a BioWhittaker plate reader 2001 (BioWhittaker, Walkersville, MD). Quantitative

results were obtained in relation to standard curves. The assays had a lower limit of detection of 3.3 ng/mL for sICAM-1, 0.5 ng/mL for sE-selectin, 0.9 ng/mL for sVCAM-1, and 0.58 ng/mL for sICAM-3.

Statistical analysis

Statistical analysis was performed with software (Statistical Package for the Social Sciences SPSS 9.0, SPSS Inc, Chicago, IL). Data are presented as mean $\pm$ SD. Statistical analysis of results was performed with the nonparametric Kruskal-Wallis and Mann-Whitney U tests. Spearman rank correlation coefficient was used to test relationships. Statistical significance was defined as *P* less than .05.

RESULTS

The male:female ratio was 1.2:1. The affected body surface area in patients with inflammatory dermatoses was $30.83\% \pm 19.65\%$ (range 3%-60%). A summary of the clinical characteristics of the analyzed participants is shown in Table I.

The concentrations of the 4 soluble adhesion molecules in patients and control subjects are shown in Figs 1 through 4. Mean serum value of sICAM-1 was 271.28 ± 147.16 ng/mL (range 55.8-563.3 ng/mL). Serum levels of sICAM-1 showed significant statistical differences among groups (*P* < .001). Mean serum value of sICAM-3 was 91.82 ± 30.54 ng/mL (range 45.73-179.85 ng/mL). A significant statistical difference of circulating levels of sICAM-3 was found (*P* = .001). Mean serum value of sVCAM-1 was 1983.08 ± 1444.8 ng/mL (range 683.28-9863.93 ng/mL) and of sE-selectin was 57.33 ± 43.10 ng/mL (range 19.32-222.07 ng/mL). No differences among groups were detected for sVCAM-1 (*P* = .226) and sE-selectin levels (*P* = .522).

sICAM-1 and sICAM-3 levels were significantly elevated in lymphoma and pre-CTCL groups compared with control and inflammatory disease groups (Table II). sICAM-1 also showed statistical differences between aCTCL and pre-CTCL groups. All patients with CTCL showed both serum levels of sICAM-1 and sICAM-3 above 200 ng/mL and 72 ng/mL, respectively. However, no statistically significant differences for sICAM-1 and sICAM-3 levels between early CTCL and aCTCL could be detected. The patients with aCTCL had higher serum sE-selectin levels but no significant difference was demonstrated.

The mean levels of LDH and β 2-microglobulin were 347.36 ± 114.9 UI/L (range 224-916 UI/L) and 1.48 ± 0.55 mg/L (range 0.8-3.1 mg/L), respectively. As expected, higher levels for LDH and β 2-microglobulin were found in the aCTCL group. Patients with psoriasis/atopic dermatitis showed higher statistically significant values for LDH compared with

Table I. Clinical and biologic data

	eCTCL N = 11	aCTCL N = 7	Psoriasis/AD N = 12	Pre-CTCL N = 8	Control N = 4	Reference range
Age, y	58.91 ± 20.16	65.86 ± 12.50	46.50 ± 20.54	63.50 ± 12.19	44.00 ± 17.38	
Evolution prior sampling, mo	111.18 ± 91.11	49.43 ± 54.84	139.00 ± 126.21	112.75 ± 109.74		
Leukocytes, 10 ⁶ /L	7463.64 ± 1984.58	8571.43 ± 3490.80	7454.55 ± 1679.50	7550.00 ± 2567.38	5880.00 ± 2106.42	4000-11,000
Lymphocytes, %	29.31 ± 7.54	24.79 ± 7.02	27.38 ± 7.77	32.61 ± 7.86	32.88 ± 6.03	
Lymphocytes, 10 ⁶ /L	2121.82 ± 554.76	2175.71 ± 1234.04	1980.91 ± 533.09	2438.75 ± 877.62	1884.00 ± 637.79	
LDH, U/L	295.00 ± 36.24	522.29 ± 187.22	333.55 ± 33.31	325.88 ± 68.17	282.40 ± 29.26	250-450
β2-Microglobulin, mg/L	1.49 ± 0.48	2.07 ± 0.79	1.27 ± 0.37	1.54 ± 0.30	1.00 ± 0.23	<2.3

aCTCL, Advanced cutaneous T-cell lymphoma; AD, atopic dermatitis; eCTCL, early cutaneous T-cell lymphoma; LDH, lactate dehydrogenase; pre-CTCL, skin diseases that could develop cutaneous T-cell lymphoma.

± Values are mean ± SD.

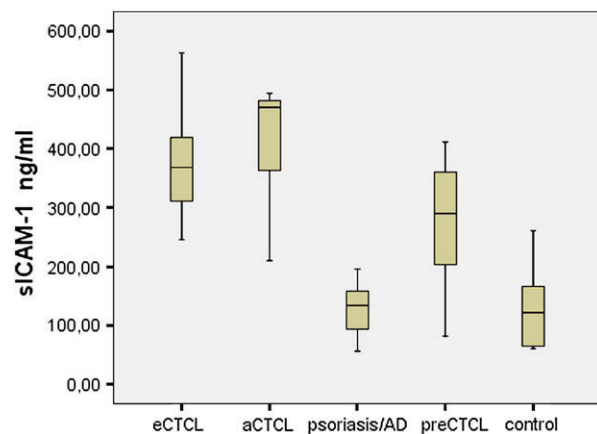


Fig 1. Soluble intercellular adhesion molecule-1 (sICAM-1) concentrations (ng/mL) in patients with early cutaneous T-cell lymphoma (eCTCL); advanced CTCL (aCTCL); inflammatory skin diseases (psoriasis and atopic dermatitis [AD]); skin diseases that could develop into CTCL (preCTCL); and healthy individuals (control). Box plots represent median (line), 25th and 75th percentiles (box), and 10th and 90th percentiles (whiskers) in each group.

healthy individuals, however, they were into the normal range (data not shown).

We next compared the serum levels of the 4 measured CAMs and several clinical parameters in patients with CTCL. The relationship between the levels of all sCAMs and peripheral blood leukocytes was examined. A significant negative correlation was obtained only for sE-selectin levels when compared with leukocyte cell count ($r = -0.39$, $P = .01$). However, sE-selectin levels showed no significant correlation with lymphocyte cell count. Serum sICAM-1, sICAM-3, and sVCAM-1 levels had no significant correlation with leukocyte or lymphocyte cell count in peripheral blood, respectively. Total leukocyte counts were used as there is differential expression of the adhesion molecules on the various leukocyte subsets.

The study of prognostic significance of serum markers is made difficult by the long natural history of classic MF Alibert-Bazin type and its indolent course with slow progression over the years. Two common markers, namely LDH and β2-microglobulin, which are used as prognostic factors in non-Hodgkin lymphomas, were chosen for this study. With regard to the correlation analyses of sCAM concentrations and LDH and β2-microglobulin in patients with CTCL, a significant positive correlation was obtained for sE-selectin levels when compared with LDH levels ($r = 0.337$, $P = .03$) and both sICAM-1 and ICAM-3 levels strongly correlated with β2-microglobulin levels ($r = 0.52$, $P = .001$ and $r = 0.48$, $P = .002$, respectively).

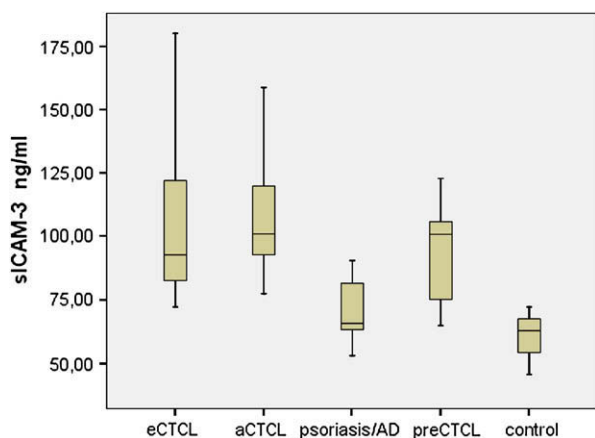


Fig 2. Soluble intercellular adhesion molecule-3 (sICAM-3) concentrations (ng/mL) in patients with early cutaneous T-cell lymphoma (eCTCL); advanced CTCL (aCTCL); inflammatory skin diseases (psoriasis and atopic dermatitis [AD]); skin diseases that could develop into CTCL (preCTCL); and healthy individuals (control). Box plots represent median (line), 25th and 75th percentiles (box), and 10th and 90th percentiles (whiskers) in each group.

When the serum levels of each sCAM were directly compared with the levels of another sCAM, only a significant positive correlation between the levels of sICAM-1 and sICAM-3 was found ($r = 0.596$, $P < .01$).

DISCUSSION

To our knowledge, this study provides the first measurement of a panel of 4 sCAMs in CTCL. Our study shows that there is a differential profile of sICAM-1, sICAM-3, sVCAM-1, and sE-selectin in the serum of patients with CTCL relative to healthy individuals and to patients with benign T-cell-mediated dermatoses. A distinct pattern of elevation and correlation between levels of sICAM-1 and ICAM-3 was also demonstrated. However, no significant statistical differences among the groups of patients in the serum levels of sVCAM-1 or sE-selectin were found.

A variety of CAMs have been shown to be cell-associated and soluble proteins.^{14,16,17} The mechanism by which sCAMs are released from the cell surface is generally thought to be by proteolytic cleavage close to the membrane of surface-expressed forms,^{18,19} although the presence of messenger RNA transcripts specific for sICAM-1 in cells has been previously reported.²⁰ Increased levels of these molecules are frequently found in blood samples from patients with infection,²¹ cancer,²² and inflammatory and autoimmune diseases,^{19,23,24} and in patients at risk for cardiovascular disease.²⁵ In

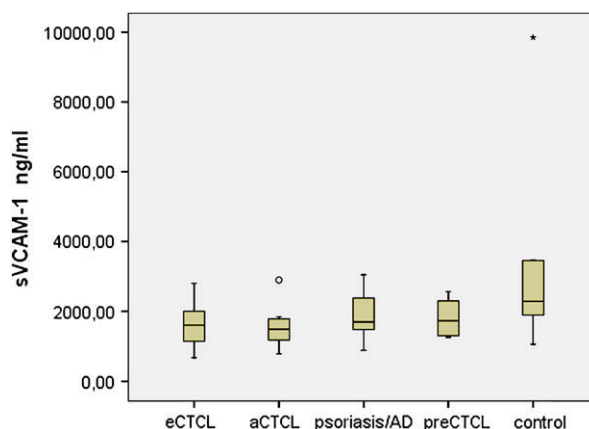


Fig 3. Soluble vascular cell adhesion molecule-1 (sVCAM-1) concentrations (ng/mL) in patients with early cutaneous T-cell lymphoma (eCTCL); advanced CTCL (aCTCL); inflammatory skin diseases (psoriasis and atopic dermatitis [AD]); skin diseases that could develop into CTCL (preCTCL); and healthy individuals (control). Box plots represent median (line), 25th and 75th percentiles (box), and 10th and 90th percentiles (whiskers) in each group. Asterisk and open circle indicate serum values > 90th percentile value.

some studies increased concentrations correlate with disease activity or are associated with a fatal outcome. Serum levels of sICAM-1, sVCAM-1, and sE-selectin seem to be higher in a variety of patients with cancer than in healthy individuals. The levels of some, but not all, of these molecules correlate with tumor progression and patient survival in specific malignancies.^{22,26} Moreover, elevated serum levels of sICAMs have been shown to be associated with a poor prognosis in Hodgkin disease and non-Hodgkin lymphomas, including extranodal lymphomas.²⁷⁻²⁹

There have been several reports of elevated expression of single or various sCAMs in patients with inflammatory skin diseases, including psoriasis and atopic dermatitis, compared with healthy control subjects.³⁰⁻³² Levels of sICAM-3 and sICAM-1 were found to be significantly increased in sera of patients with psoriasis when compared with control subjects.³³ Furthermore, other endothelial sCAMs, sE-selectin and sVCAM-1, are increased in patients with severe psoriasis³⁰ and in those with atopic dermatitis,³⁴ and elevated levels of sICAM-1 and sE-selectin seems to correlate with clinical scores and disease activity in these diseases.

In our study there was no significant difference in serum levels between patients with inflammatory skin diseases and healthy control subjects. We included patients with mild to moderate atopic dermatitis and plaque-type psoriasis that clinically could resemble MF.

We demonstrated that serum sICAM-3 and sICAM-1 levels significantly correlated with each other. A

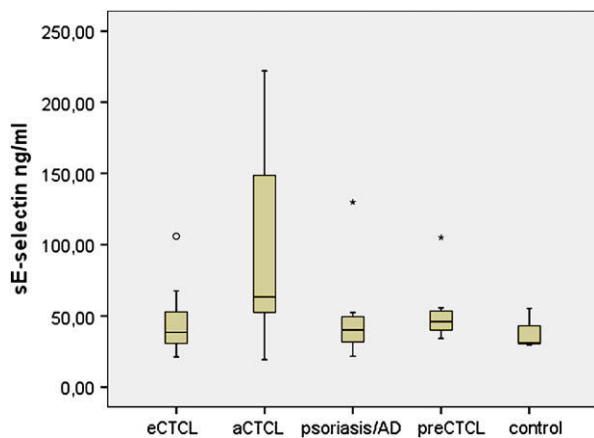


Fig 4. Soluble E-selectin (*sE-selectin*) concentrations (ng/mL) in patients with early cutaneous T-cell lymphoma (*eCTCL*); advanced CTCL (*aCTCL*); inflammatory skin diseases (psoriasis and atopic dermatitis [*AD*]); skin diseases that could develop into CTCL (*preCTCL*); and healthy individuals (*control*). Box plots represent median (*line*), 25th and 75th percentiles (*box*), and 10th and 90th percentiles (*whiskers*) in each group. Asterisks and open circle indicate serum values > 90th percentile value.

positive correlation has also been found in other cutaneous diseases,³³ but serum levels of sICAM-3 did not correlate with sICAM-1 concentrations in patients with other diseases, who had either elevated sICAM-3 or sICAM-1 levels but not both.²³

No association of sICAM levels with leukocyte or lymphocyte counts in patients was observed, indicating that elevated sICAMs do not merely reflect an increase in the leukocyte population.

The stronger expression of ICAM-3 on resting leukocytes when compared with ICAM-1 was not reflected by higher ICAM-3 levels in healthy persons.²³ In our study, this expression profile was also observed in serum levels of these molecules in patients with CTCL. In patients with cancer, these sICAMs may be produced by the tumor cells and/or by cells in the tumor microenvironment.

Based on these data, malignant cells may not be the sole source of increased sICAM levels in patients with CTCL. As ICAM-3 is only rarely expressed in endothelial cells, the high levels of sICAM-3 may also be derived from leukocytes or antigen-presenting cell lineage.³⁵ sICAM-1 is also shed from dermal endothelium and from keratinocytes, activated mononuclear cells, and dermal dendritic cells.³⁶ These need to be tested individually and specifically.

The function of sICAMs remains to be established. Ectodomain shedding can have multiple functional roles. Theoretically, activation of ectodomain shedding can lead to release of soluble antagonists, which can prevent further receptor-ligand interactions or can induce cellular repulsion of two interacting cells

Table II. *P* values

	sICAM-1	sICAM-3
eCTCL/psoriasis-AD	<.001	.002
eCTCL/control	.004	.013
aCTCL/psoriasis-AD	.001	.002
aCTCL/pre-CTCL	.048	ns
aCTCL/control	.007	.017
Psoriasis-AD/pre-CTCL	.011	.019
Pre-CTCL/control	.042	.03

aCTCL, Advanced cutaneous T-cell lymphoma; *AD*, atopic dermatitis; *eCTCL*, early cutaneous T-cell lymphoma; *ns*, non-significant; *pre-CTCL*, skin diseases that could develop cutaneous T-cell lymphoma; *sICAM*, soluble intercellular adhesion molecule.

by cleavage of a receptor-ligand complex on the opposing cell.

In vitro, sICAM-1, sVCAM-1, and sE-selectin have previously been found to be capable of supporting leucocyte or cell line adhesion³⁷ and sE-selectin and sVCAM-1 can act as potent angiogenic factors.³⁸ Indeed, sICAM-1 retains its ability to bind to leukocyte integrins and reduces leukocyte recruitment in diverse in vivo models of inflammation.¹⁴

Regarding the interactions of ICAM-1 and ICAM-3 with LFA-1, molecular and cellular competition experiments demonstrate that sICAM-1 and sICAM-3 compete with each other for binding to LFA-1. The affinity of the sICAM-3/LFA-1 interaction is approximately 9 to 10 times weaker than the sICAM-1/LFA-1 interaction.³⁹ Many authors have suggested that because of its high constitutive expression on leukocytes, ICAM-3 may be responsible for the initial phases of the immune response.^{8,40} It is possible that LFA-1/ICAM-3 interactions are involved in the initial T-lymphocyte/antigen-presenting cell contact during the primary interactions in an immune response, and that ICAM-1/LFA-1 interactions mediate the subsequent leukocyte/leukocyte and leukocyte/target cell interactions. In fact, ICAM-1 and ICAM-3 appear to function synergistically and/or additively with each other as demonstrated by the ability of monoclonal antibodies to ICAM-1 and ICAM-3 to have synergistic or additive effects in vitro in inhibiting the mixed lymphocyte reaction, antigen/mitogen-induced proliferation.⁴¹ Circulating ICAM might act in several ways by preventing adhesion, by competing with the membrane ICAMs on endothelial cells, and by regulating cell interactions because of its ability to bind their ligands.

We propose that increased levels of sICAM-1 and sICAM-3 have important implications in the context of the immune response and immune surveillance in patients with CTCL. High levels of sICAM-1 might block the attachment of natural killer cells and cytotoxic inflammatory cells preventing the

recruitment of these cells, leading to escape from immunosurveillance.^{42,43}

Moreover, the interaction of LFA-1 with ICAM molecules facilitates the initial contact between antigen-presenting cells and T cells. This is important for initiating immune responses and provides essential accessory adhesion signals in many immune interactions including those between T and B lymphocytes and cytotoxic T cells and their targets. Thus, impaired LFA-1/ICAM and ICAM-3/dendritic cell-specific ICAM-3-grabbing nonintegrin interactions are a possible explanation for "immunodeficiency," opportunistic infections, and increased risk of second malignancies in patients with CTCL.

Serum levels of sICAM-1 and sICAM-3 were significantly higher in patients with CTCL and pre-CTCL compared with healthy individuals. The detection of a distinct profile of sICAMs in early stages of MF and in diseases that could develop CTCL is in concert with the theory of "inflammation" leading to lymphoma.⁴⁴

These findings may contribute to our understanding of the pathological mechanisms involved in these diseases, and they may provide targets for the treatment of patients with lymphoma. One must keep in mind that levels of these soluble adhesion molecules are increased in vivo in a variety of diseases, so that they have limited diagnostic significance, although they may be helpful for monitoring disease progression or response to therapy.

In conclusion, we report that levels of sICAM-1 and sICAM-3, but not those of sVCAM-1 or sE-selectin, are significantly elevated in CTCL, which exhibits a distinct profile of soluble adhesion molecules. High levels of circulating sICAM-1 and sICAM-3 in patients with CTCL and pre-CTCL suggest a pathological role in these diseases. Further investigation will be required to define the function of sICAM-1 and sICAM-3 in CTCL and to establish whether these CAMs can function as markers of disease activity in these patients. Circulating levels of sICAM-1 and sICAM-3 seem to correlate with β 2-microglobulin levels. However, future studies are needed to confirm these findings in a larger group of patients. Moreover, inhibition of their expression and/or inhibition of their interactions with other cells may be useful in developing future treatment strategies.

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