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Circulating adhesion molecules ICAM-1, VCAM-1 and E-selectin in systemic vasculitis: marked differences between Wegener's granulomatosis and systemic lupus erythematosus

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Abstract. Inflammatory systemic disorders with renal tissue damage require the adherence of polymorphonuclear leukocytes to the endothelium, which is mediated by cell surface adhesion molecules. This study measured the serum concentrations of circulating adhesion molecules [intercellular adhesion molecule 1 (cICAM-1), vascular cell adhesion molecule 1 (cVCAM-1), cE-selectin] by sandwich enzyme-linked immunosorbent assay in Wegener's granulomatosis ($n=25$) and systemic lupus erythematosus ($n=50$). Active Wegener's granulomatosis with cellular crescent formation was associated with significantly raised cICAM-1 levels, an elevated histological activity index, and a high rate of hemodialysis in comparison to Wegener's granulomatosis with fibrocellular crescents or lupus nephritis. The activity index and cICAM-1 levels can be used as parameters to predict renal outcome in Wegener's granulomatosis. cVCAM-1 levels in Wegener's granulomatosis were significantly higher in patients with hemodialysis compared to those without hemodialysis. In lupus nephritis only cVCAM-1, not cICAM-1 or cE-selectin, were significantly higher ($P<0.01$) than controls. cVCAM-1 levels in both diseases were significantly higher than in controls. Only in Wegener's granulomatosis did cICAM-1 and cVCAM-1 levels decrease with clinical remission; in systemic lupus erythematosus the levels remained unchanged. cE-selectin levels were not significantly elevated in systemic vasculitis or collagen disease although individual patients revealed high serum concentrations. These data suggest that levels of circulating adhesion molecules reflect different pathophysiological processes in systemic vasculitis and collagen disease and may be used as markers of disease activity and renal outcome.

Key words: cE-selectin – cICAM-1 – cVCAM-1 – Rapidly progressive glomerulonephritis – Systemic lupus erythematosus – Wegener's granulomatosis

The etiology and pathophysiology of systemic necrotizing vasculitides without immune deposits such as Wegener's granulomatosis (WG) is rarely understood which is in contrast to immune-complex associated collagen diseases such as systemic lupus erythematosus (SLE). WG and SLE are associated with autoantibodies [anti-neutrophil cytoplasmic autoantibody (c-ANCA) in WG; double-stranded DNA antibody, anti-nuclear antibody (ANA) in SLE] and elevated cytokine levels in active generalized disease [16,25]. Neutrophils are involved in the initial vascular lesions in WG. This accumulation of polymorphonuclear leukocytes depends upon a cascade of complex events. Cell surface adhesion molecules are thought to play a critical role in establishing the intercellular contacts that are essential for these inflammatory and immunological reactions. The expression of cytokine-inducible adhesion molecules on leukocytes and on endothelial cells leads to the adherence of inflammatory cells to the vessel wall, their activation, and subsequent extravasation.

Intercellular adhesion molecule 1 (ICAM-1, CD54, immunoglobulin supergene family) is found on various cell types [27] and plays an important role in inflammatory and immunological processes. The circulating form of ICAM-1 (cICAM-1) is

Abbreviations: AI = activity index; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic autoantibody; cICAM-1 = circulating intercellular adhesion molecule-1; cVCAM-1 = circulating vascular cell adhesion molecule-1; CI = chronicity index; IFT = immunofluorescence test; LFA-1 = lymphocyte function-associated antigen 1; LN = lupus nephritis; RPGN = rapidly progressive glomerulonephritis; SLE = systemic lupus erythematosus; WG = Wegener's granulomatosis

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thought to be a fragment of surface-expressed ICAM-1 that retains the ability to bind specifically to the ICAM-1 ligand lymphocyte function associated antigen 1 (LFA-1) [24].

Vascular cell adhesion molecule 1 (VCAM-1) belongs to the immunoglobulin supergene family and acts as a ligand for the α_4 integrins $\alpha_4\beta_1$ (very late activation antigen, VLA-4) and $\alpha_4\beta_7$. VCAM-1 is less widely distributed and found on monocytes, lymphocytes, macrophages, renal parietal epithelium, basophils, and eosinophils [22]. VCAM-1 mediates the adhesion of leukocytes to human umbilical vein endothelial cells [22]. A circulating variant has been described [11,17].

Endothelial leukocyte adhesion molecule 1 (E-selectin) belongs to the selectin family and influences the initial adhesion of unstimulated leukocytes (neutrophils/monocytes/T-memory lymphocytes) to its ligand sialylated Lewis X and related oligosaccharides on activated endothelial cells [7,12]. A circulating form obtains biological reactivity [11, 17].

This study compared the levels of the three circulating adhesion molecules in patients with WG and SLE to evaluate their role as a parameter of disease activity and their possible pathogenetic implication in the development of renal tissue damage.

Patients and methods

Sera and patients

Serum samples were obtained from 25 patients with WG and 50 with SLE and from 10 healthy donors. All patients with WG (16 males, 9 females; average age 56.8 years, range 16–82) met the American College of Rheumatology criteria for the classification of WG [15]. Organ involvement was documented according to the clinical presentation and results of technical examinations such as X-ray or biopsies (Table 1). Active generalized WG was diagnosed in presence of positive c-ANCA results [cytoplasmic staining in indirect immunofluorescence test (IFT), anti-proteinase-3 antibody levels above 20 IU/ml in enzyme-linked immunosorbent assay, Progen, Heidelberg) and disease manifestations in at least two of three organ systems: upper airways, lung, and kidney (Table 1). Serum samples were obtained within 3 weeks after diagnosis was established in active patients (range 3 days – 5 weeks). These received corticosteroids, cyclophosphamide or, azathioprin as immunosuppressive therapy or additional hemodialysis or plasmapheresis at the time the blood sample was taken.

Table 1. Clinical and serological characteristics of patients with *WG* and *SLE*

	WG		SLE	
	Active ($n=19$)	Inactive ($n=6$)	Active ($n=30$)	Inactive ($n=20$)
Anti-proteinase-3 antibodies (U/ml)	72	12	–	–
Anti-dsDNA-antibodies (%)	–	–	75	15
Organ involvement (%)				
Flu like symptoms	82	0	72	0
Kidney	100	67	35	16
Joint	50	17	87	18
Eye, ear, nose	38	33	5	0
CNS/PNS	29	0	15	0
Skin	25	17	68	12
Lung	25	0	32	0
Myalgia	13	17	56	0
Raynaud's syndrome	0	0	15	5
Anemia, leukopenia (%)	32	0	68	8
Hypocomplementemia				
ANA (%)	–	–	100	35
Creatinine (µmol/l)	552	240	310	180
Immunosuppression (n)	19	6	30	12

Therapy had to be stopped due to leukopenia in four patients, two other patients died of sepsis within 2 months of the diagnosis. Clinical and serological improvement was achieved in 90% of patients after 3 months, but seven patients had to be hemodialyzed chronically. "WG in remission" was diagnosed in six other well-known WG patients in the absence of pulmonary infiltrates or fever, but in presence of a stable renal function with minor abnormalities of the urine sediment with erythrocyte casts, anti-proteinase-3 antibodies below 20 IU/ml, and negative IFT results. Serum samples of patients in remission were obtained within 6 months (range 3–9 months) after diagnosis had been made.

Patients with SLE (12 males, 38 females; average age 64.5 years, range 15–76) met the American College of Rheumatology criteria [29]. Of the 50 SLE patients 30 had an active disease, which was diagnosed in presence of at least four or more clinical and serological abnormalities (double-stranded DNA antibody level higher than 20% in the Farr assay, hypocomplementemia, positive ANA, leukopenia, organ manifestations; Table 1). Two patients presented with a venous thrombosis. One patient died because of an intracerebral hemorrhage. No patient was hemodialyzed. All 30 patients were treated with immunosuppressive therapy. Twenty patients with well-known SLE were in remission (ds-DNA level below 20%). Serum samples were obtained within 13 months in inactive

patients (range 6-18 months). Only 12 of the 20 inactive SLE patients were treated with immunosuppression; 8 were in remission without further therapy. No patient with SLE had c-ANCA (confirmed by anti-PR3 antibody enzyme-linked immunosorbent assay and IFT).

Healthy donors (2 males, 8 females, average age 25.3 years) served as controls.

Serum was separated from clotted blood samples by centrifugation and stored at −70°C until assayed. Serum samples were taken because the levels of circulating adhesion molecules are reported to be elevated in heparin blood and suppressed in EDTA/citrate samples [20].

Histological evaluation

A renal biopsy was performed in 21 of 25 WG patients and examined by immuno-histochemistry/light microscopy. Kidney biopsies were scored according to an activity index (AI) and chronicity index (CI, Table 2), which was adapted from the scoring system used in SLE [3,10]: semiquantitative scale (0–3; absent, mild, moderate, severe); necrosis, cellular, and fibrous crescents are multiplied by a factor of 2; the maximal AI is 24 and the maximal CI 18. Glomerular lesions were classified into four categories (Table 3).

Renal biopsy was performed in 10 of 50 SLE patients. Lupus nephritis (LN) was scored according to a semiquantitative AI and CI (0–3, absent, mild, moderate, severe). AI is the sum of glomerular proliferation, leukocyte exudation, fibrinoid necrosis ($\times 2$), cellular crescents ($\times 2$), hyaline deposits and interstitial inflammation; CI is the sum of glomerular fibrosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. Maximal AI 24 and maximal CI 18 [3]. The histological examination was made according to the WHO classification (Table 3).

Circulating adhesion molecule assay

Serum levels of circulating adhesion molecules cICAM-1, cVCAM-1, and cE-selectin were measured with commercially available sandwich enzyme-linked immunosorbent assays (British Biotechnology Products, Oxford, UK). Briefly, standards (lyophilized recombinant circulating ICAM-1, VCAM-1, or E-selectin) and serum samples were transferred to coated microtiter wells (coated with murine antibody to either human ICAM-1, E-selectin, or VCAM-1) and incubated with streptavidin horseradish peroxidase conjugate and monoclonal mouse anti-human antibody at room temperature. Afterwards the wells were incubated with the substrate O-phenylendiamine/H_2O_2. The reaction was stopped with sulfuric acid 2 N, and the optical density was taken with a plate reader at 492 nm (cICAM-1) or 450 nm with a correction wavelength of 620 nm (cVCAM-1, cE-selectin). Results were calculated corresponding to a standard curve.

Statistical analysis

Data were analyzed using SPSS/PC+. Results were not normally distributed when examined and were therefore analyzed using the nonparametric Mann-Whitney U test ($P<0.05$). All data are expressed as the mean or range.

Results

The results of renal biopsies in WG and SLE are shown in the Tables 2 and 3. Crescents/glomerular proliferation, necrosis, and interstitial mononuclear cell infiltration were found in the majority of biopsies. Necrotizing vasculitis was a rare histological finding and granuloma formation was not observed in WG biopsies. In WG rapidly progressive glomerulonephritis (RPGN) with cellular crescent formation had significantly greater cICAM-1 concentrations ($P=0.005$) than biopsies with fibrocellular crescents, LN in general, and healthy controls. The highest levels were found in patients with diffuse crescent formation in all glomeruli. Nine of ten WG patients (90%) with cellular crescents had to be hemodialyzed (mean serum creatinine 610 μmol/l) compared to only two of nine WG patients (22%) with fibrocellular crescents (mean serum creatinine 1145 μmol/l). Even LN with crescent formation had lower cICAM-1 levels than cellular crescentic RPGN in WG (NS). cVCAM-1 levels in WG and SLE were similar, and both were significantly elevated compared to controls. Cellular crescent formation in WG and diffuse proliferative/crescentic LN, however, tend to have higher cVCAM-1 levels than the other histological groups (NS). cE-selectin concentrations in WG did not differ significantly from healthy controls. However, cE-selectin levels in diffuse proliferative LN (WHO class IV) and in LN with crescent formation tended to be higher than in WG and control patients (too few cases for statistical analysis).

Hemodialysis became necessary in 11 of 25 WG patients (mean serum creatinine 822 μmol/l, range 407–1521). One patient had additional plasmapheresis. Hemodialyzed WG patients revealed a significantly higher ($P=0.002$) AI and a slightly lower CI (NS) than patients without hemodialysis

Table 2. *AI* and *CI* in renal biopsies from WG and SLE

	AI	CI
WG, RPGN		
Glomerular abnormalities	Cellular crescents (86%) Necrosis (86%) Leukocyte infiltration (62%)	Fibrous crescents (43%) Sclerosis (48%)
Tubulointerstitial abnormalities	Mononuclear cell infiltration (91%) Periglomerulitis (19%) Interstitial hemorrhage (5%)	Interstitial fibrosis (43%) Tubular atrophy (62%)
Blood vessel abnormalities	Necrotizing vasculitis (14%)	Fibrosing vasculitis (5%)
SLE, Lupus Nephritis		
Glomerular abnormalities	Glomerular proliferation (67%) Leukocyte exudation (50%) Fibrinoid necrosis (0%) Cellular crescents (33%) Hyaline deposits (0%)	Glomerular fibrosis (50%) Fibrous crescents (50%)
Tubulo-interstitial abnormalities	Interstitial inflammation (67%)	Tubular atrophy (67%) Interstitial fibrosis (83%)

Table 3. Histological classification of renal biopsies and serum levels (ng/ml) of circulating adhesion molecules in *WG* and *SLE*

	sICAM-1	sVCAM-1	sE-selectin
WG, RPGN ($n=21$)	440 ± 78	1223 ± 148	64 ± 14
RPGN with cellular crescents			
Focal ($n=6$)	524	1319	55
Diffuse ($n=4$)	619	1206	58
RPGN with fibrocellular crescents			
Focal ($n=5$)	333	1086	64
Diffuse ($n=4$)	287	1142	73
Mesangioproliferative glomerulonephritis with crescents ($n=1$)	528	1541	95
Unclassified ($n=1$)	365	1276	59
SLE, LN ($n=10$)	312 ± 62	1247 ± 302	90 ± 16
Class II, mesangial LN ($n=5$)	285	1340	67
Class III, focal prolif. ($n=1$)	309	1286	70
Class IV, diffuse prolif. ($n=3$)	362	1495	112
Class V, membranous ($n=1$)	215	1234	76
Glomerular crescents ($n=3/10$)	389	1495	91
Healthy controls ($n=10$)	245	582	48

(WG/SLE). cICAM-1 levels in HD patients were significantly raised ($P=0.0001$, Table 4) compared both to WG/SLE without hemodialysis (WG: $n=13/25$, mean serum creatinine 282 µmol/l, range 106–729) and healthy controls. LN in ten patients was associated with a mild elevation of ds-DNA antibody concentrations at the time of biopsy (mean 26%, range 1–67%), which could explain the low AI and CI. WG patients with hemodialysis had significantly higher cVCAM-1 levels than those without ($P=0.019$) or controls, but comparable levels as in LN. cE-selectin levels did not differ significantly between WG with and without hemodialysis and controls (Table 4) but tended to be lower than in LN (NS).

cICAM-1 levels were significantly raised in 19 patients with active WG compared to 6 patients with inactive WG ($P=0.004$), 30 active SLE patients ($P=0.0001$), 20 inactive SLE patients ($P=0.006$), and healthy donors ($P=0.0006$, Table 5).

cVCAM-1 levels were significantly higher in active WG ($P=0.0005$) and active or inactive SLE ($P=0.027$) than in healthy donors ($P=0.0005$). Ac-

Table 4. *AI, CI* and levels of circulating adhesion molecules (ng/ml) in *WG* ($n=21$) and *SLE* ($n=10$)

	AI	CI	cICAM-1	cVCAM-1	cE-selectin
WG with RPGN					
With hemodialysis ($n=11$)	15	3	526±80	1376±136	60±11
Without hemodialysis ($n=10$)	8	6	354±75	1069±161	68±16
SLE with LN					
Without hemodialysis ($n=10$)	4	4	310±62	1247±302	90±16

Table 5. Circulating adhesion molecules cICAM-1, cVCAM-1 and cE-selectin in patients with WG or SLE and in healthy donors

	WG		SLE		Control
	Active	Inactive	Active	Inactive	
cICAM-1					
Mean	499±106	347±145	267±56	319±64	245±42
Range	143–912	156–528	79–501	118–515	151–321
cVCAM-1					
Mean	1130±235	1047±345	893±310	1049±220	582±123
Range	672–1879	425–1882	308–2270	451–1713	262–809
cE-selectin					
Mean	68±14	83±13	55±12	55±15	48±11
Range	26–142	46–121	23–112	24–137	27–73

tive WG, however, was associated with even significantly higher cVCAM-1 levels than active SLE ($P=0.016$). cVCAM-1 levels in inactive WG were comparable to controls whereas inactive SLE ($P=0.005$) had significantly elevated levels when compared to controls (Table 5).

The serum levels of cE-selectin were not significantly raised in WG and SLE compared to healthy donors. All patients had comparable cE-selectin levels as healthy controls (NS). However, the maximum cE-selectin concentrations were measured in individual patients with WG (max 142 ng/ml) and SLE (max 137 ng/ml; Table 5).

Discussion

This study presents marked differences between the serum concentrations of the circulating adhesion molecules ICAM-1, VCAM-1, and E-selectin in c-ANCA positive WG and SLE.

Both diseases are known to be associated with elevated levels of proinflammatory cytokines and various immunological markers of inflammation. The clinical disease course can be effectively monitored by measuring the autoantibody concentration (ANCA in WG, ds-DNA antibody in SLE). In contrast to SLE, there is no in situ immune deposition in WG (so-called "pauci-immune").

Active c-ANCA positive WG is associated with significantly raised cICAM-1 levels compared to inactive WG in remission and healthy controls. Increased cICAM-1 concentrations may be used as an additional marker of disease activity in WG. This is in contrast to SLE in this study and to patients with rheumatoid arthritis [8] in whom cICAM-1 concentrations did not change with disease activity. The cellular source of the circulating adhesion molecules cannot be determined from their presence in the serum. The lower concentration of cICAM-1 in SLE, which has also been found by others [18], may suggest a differential activation of cells capable of expressing adhesion molecules or differences in the expression or cleavage. ICAM-1 is released from mononuclear cells as a consequence of cytokine induction (interleukin-1, tumor necrosis factor-α, interferon-γ) during inflammation and tissue damage. As active WG is associated with elevated cytokine levels [25] increased cICAM-1 concentrations may therefore reflect a systemic exposure to elevated cytokine levels.

The majority of WG patients (90%) with RPGN and cellular crescent formation were hemodialyzed. The renal biopsy of hemodialyzed WG patients revealed a significantly raised AI and was associated with high cICAM-1 serum concentra-

tions. The combination of a high AI and a tremendous systemic exposure to high cICAM-1 levels seems to predict a high renal fatality outcome in spite of immunosuppressive therapy. However, a longitudinal study must still confirm this hypothesis. High cICAM-1 levels probably promote the adhesion of inflammatory cells such as monocytes/macrophages to the glomerular endothelial cells with consecutive vascular damage, fibrin exudation, and crescent formation. In contrast, fibrocellular crescent formation, which is the result of a longer disease course, was rarely associated with the necessity of hemodialysis. Renal biopsies with fibrocellular crescents revealed significantly lower AI, and serum concentrations of cICAM-1 were comparable to the low levels in LN without hemodialysis.

The functional consequences of these results are not clear. ICAM-1 can inhibit the non-MHC-restricted natural killer cell mediated cytotoxicity [5]. Thus immunocompetent cells may escape immunosurveillance by altering their surface ICAM-1 molecule and promoting the deadhesion of leukocytes and a rapid transendothelial migration. In the antiglomerular basement membrane disease of rats the upregulation of glomerular endothelial ICAM-1 plays a critical role in the early adhesion of inflammatory cells via the Mac-1 ligand and the migration of macrophages via the ß2 integrin LFA-1 [13]. The development of autoimmune antiglomerular basement membrane disease and of crescent formation can be suppressed by anti-ICAM-1 antibodies [21]. An increase in ICAM-1 expression on glomeruli was seen only in the early stage of RPGN [19]. Increased concentrations of circulating ICAM-1 have been reported in different diseases such as renal allograft rejection [28], chronic liver disease [1], and human malignancies [4].

VCAM-1 expression on cytokine-induced endothelial cells suggests a role in mediating cell migration to perivascular sites of inflammation. This study demonstrates that WG and SLE are both associated with significantly higher cVCAM-1 levels than healthy controls. However, cVCAM-1 levels are significantly higher in active WG than in active SLE. The mechanisms for the lack of correlation between cICAM-1 and cVCAM-1 are unclear. The comparable elevation of cVCAM-1 concentrations in crescentic glomerulonephritis in WG and in LN, however, suggests a general participation of VCAM-1 in the process of renal vascular damage. This serological result reflects the immunohistological finding of extensive glomerular cVCAM-1 expression in crescentic RPGN in systemic vasculitis [26]. In WG, cVCAM-1 may serve as an additional parameter in assessing the clinical activity (decrease in remission) and renal outcome, as can be concluded from the significantly lower levels in WG without hemodialysis. VCAM-1 expression has been found in graft rejection [2] and in rheumatoid arthritis [9].

E-selectin expression is restricted to activated endothelial cells [6], promotes the initial rolling of inactive leukocytes at activated endothelial cells, and may also be capable of generating intracellular signals. cE-selectin has been found in cytokine-activated endothelial cells [23], septic shock [20], and rheumatoid arthritis [14]. cE-selectin is not statistically elevated in systemic vasculitis or collagen-vascular disease. Individual patients with WG and SLE and especially patients with diffuse proliferative/crescentic LN, however, have raised E-selectin serum concentrations. Though the number of LN with elevated cE-selectin levels is too small for a statistical analysis the tendency of this result suggests that cE-selectin is shed at sites of constant antigenic stimulus which leads to immune complex formation in LN.

The results of this study suggest different pathophysiological mechanisms in autoimmune systemic vasculitis and collagen-vascular disease. Circulating adhesion molecules may be useful parameters to assess the clinical activity and renal outcome in these disorders.

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