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Circulating levels of soluble adhesion molecules in patients with ANCA-associated vasculitis

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ABSTRACT: *Background*: During inflammation, activated vascular endothelial cells and other cell types express various adhesion molecules, which facilitate the binding of circulating leukocytes and their extravasation in surrounding tissue (i.e. renal tissue). The serum concentration of circulating soluble adhesion molecules is supposed to reflect the degree of this activation.
Objective: In the first part of the study, we determined if the serum levels of the soluble intercellular adhesion molecule (sICAM)-1 and the soluble endothelial cell-leukocyte adhesion molecule (sELAM)-1, in patients affected by microscopic polyangiitis (MPA), associated with myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibodies (ANCA), were related to the active and the inactive vasculitis phase. In the second part of the study, we examined the changes in circulating sICAM-1 and sELAM-1 levels and the clinical outcome of renal function in these patients.
Methods: We examined 20 MPO-ANCA-positive MPA patients in an acute phase and in a remission phase, after 6 months of treatment, and 50 subjects as controls, 30 with autosomal dominant polycystic kidney disease (ADPKD) in stable chronic renal failure (CRF) and 20 healthy volunteers (HS) with normal renal function.
Results: Regarding serum creatinine (Cr) concentration, no significant differences were found comparing active and inactive phases in the MPA group and the CRF group. Mean serum adhesion molecule levels in the MPA group were higher in the active phase compared to the inactive phase and to the CRF and HS groups. In addition, considering the outcome of serum Cr concentrations in the MPA group, the serum adhesion molecule levels were higher and decreased more slowly in patients with final high serum Cr concentrations than in patients with final normal serum Cr concentrations.
Conclusion: Our data suggest that in MPO-ANCA-positive MPA patients, higher sICAM-1 and sELAM-1 levels during the active phase and their slower decline during the treatment period, could be a prognostic risk factor for CRF development.

Key Words. Vasculitis, Microscopic polyangiitis, Adhesion molecules, Chronic renal failure

Introduction

Inflammatory responses are mediated through a multi-step process initiated by the release of the early response cytokines (i.e. interleukin (IL)-1α and IL-6, tumor necrosis factor (TNF)-α) and other acute-phase reaction components, which lead to the up-regulation of selectins (P-, L- and E-selectin) and other cellular adhesion molecules (i.e. vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, endothelial cell-leukocyte adhesion molecule (ELAM)-1, etc) on vascular endothelial cell surfaces within and around the inflammation site (1, 2). Selectin molecules, interacting with cell surface carbo-hydrate counter-receptors (sialyl Lewis X family), mediate leukocyte rolling along the vascular endothelial surface in such a way that the leukocytes slow down in the circulatory flow (2, 3). This permits the development of leukocyte adhesion to endothelial cell-expressed adhesion molecules (VCAM-1, ICAM-1 and ELAM-1) at the inflammation site (2, 4). Soluble forms of these adhesion molecules (termed sVCAM-1, sICAM-1 and sELAM-1) are shed into the plasma by the proteolytic cleavage of their membrane-bound counterparts from activated leukocytes and vascular endothelial cells. Elevated serum levels of the soluble forms of these molecules have been reported in several immune, inflammatory and ischemic diseases (5, 6).
Vasculitis refers to the inflammation of the vessel walls, and the kidney is involved in many types of systemic vasculitis. Microscopic polyangiitis (MPA) is a form of small vessel vasculitis with renal involvement, associated with anti-neutrophil cytoplasmic antibodies (ANCA), anti-endothelial antibodies and anti-laminin antibodies (7-9).
Serum concentrations of soluble adhesion molecules have been reported in patients with ANCA-positive small vessel vasculitis (10, 11), but also in other nephropathies such as IgA nephropathy (12) and, finally, in pre-dialysis patients with stable chronic renal failure (CRF) (13). Data available in the literature are contradictory concerning the meaning of serum adhesion molecule levels in renal diseases (14).
This study aimed to analyze whether circulating ICAM-1 and ELAM-1 could be helpful in evaluating the inflammatory activity of MPO-ANCA-positive MPA and determining whether serum adhesion molecule levels are related to renal failure development.

Materials and methods

Patients

Our patient population consisted of 20 MPO-ANCA-positive patients with biopsy-proven MPA. The patients were classified according to the definitions adopted by the "Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides" (8).

CHARACTERISTICS OF POPULATION STUDY

TABLE I

	Healthy subjects N=20	Patients with CFR N=30	Patients with MPA N=20
Age	39.8 ± 11.9	58.9 ± 10.2	62.3 ± 6.8
Sex (M/F)	14/6	20/10	12/8
Clinical manifestation:			
- systemic[a]	0/20	0/30	20/20
- renal involvement[b,c]	0/20	30/30b	20/20b,c
- pulmonary involvement	0/20	0/30	3/20
- other[d]	0/20	0/30	14/20
Serum Cr (mg/dL)			
- baseline*	0.9 (0.8-0.9)	2.7 (1.9-3.5)	2.6 (1.9-3.3)
- after 6 months**	ND	ND	3.9 (2.4-5.3)
CRP (mg/dL)			
- baseline*	0.32 (0.26-0.37)	0.37 (0.31-0.43)	6.40 (5.78-7.01)
- after 6 months**	ND	ND	0.41 (0.35-0.46)
p-ANCA, c-ANCA (IFI)			
- baseline*	0/20	0/20	20/20
- after 6 months**	ND	ND	0/20
MPO (Titre IU)			
- baseline*	<10	<10	97.40 (91.56-103.23)
- after 6 months**	ND	ND	<10

*[a] included anorexia, malaise, myalgia, arthralgia and/or fever; [b] serum Cr >1.5 mg/dL; [c] microhematuria or hematic cell cast and proteinuria; [d] skin vasculitis; *at the time of diagnosis prior to beginning the therapy (only MPA patients); ** at remission time (only MPA patients).*
CRF, chronic renal failure; MPA, MPO-ANCA-positive microscopic polyangiitis.

Table I summarizes the clinical and biochemical features at the time of diagnosis and at the time of acute phase vasculitis remission. Patients were treated with immunosuppressive drugs that included steroids (1 mg/kg/die), with swift subsequent tapering, and cyclophosphamide (2 mg/Kg/die), to induce remission.

Controls

As controls, we examined 50 subjects, 30 with stable CRF and 20 healthy volunteers. Patients were affected by autosomal dominant polycystic kidney disease (ADPKD). None of these CRF patients had neoplasias, liver diseases or concomitant infections. The healthy volunteers were enrolled from the laboratory staff.
Written informed consent was obtained from each participant and the Institutional Review Board of the Department of Internal Medicine, University of Palermo, Italy, approved the study, which was conducted according to the 1975 Helsinki declaration.

Design of study

MPA sera were obtained at the time of diagnosis, after 1 month, after 3 months and during the remission period (6 months). Clinical vasculitis activity was assessed using the Birmingham Vasculitis Activity Score (BVAS) (15). According to the BVAS, patients with a score >5 were considered to have active vasculitis. Biological activity was assessed by serum C-reactive protein (CRP) concentrations (normal values <0.8 mg/dL). Clinical vasculitis remission was defined as the absence of clinical activity using the BVAS list (score <5), supported by normal serum CRP levels. Renal remission was defined as the absence of microhematuria or hematic cell cast, together with improved or stable renal function.
Sera of patients and controls were stored frozen in aliquots at -70°C until used.

Measurement of soluble adhesion molecules

sICAM-1 and sELAM-1 levels were analyzed using a sandwich ELISA, following the manufacturer's instructions, using commercial kits (R&D System, Abingdon, UK). Measurements were performed in duplicate. Briefly, the principle of the assays was a sandwich enzyme

immunoassay that used a monoclonal antibody (MoAb) immobilized on a solid phase to capture antigen from the test specimen, and a peroxidase-conjugated MoAb added to bind the antigens captured by the first antibody. After incubation with patient and control samples and standards at appropriate dilutions, the color reaction was developed with tetramethybenzidine, and the plates were read on an automated multiscanner at 450 nm (reference wavelength 600 nm).
The calculated intra-assay coefficient of variation was 1.9% for sICAM-1 and 2.71% for sELAM-1.

Measurement of CRP

Serum CRP levels were measured by standard nephelo-metry. Values <0.8 mg/dL were considered normal.

Detection of ANCA by indirect immunofluorescence

p-ANCA and cytoplasmic (c)-ANCA were detected by indirect immunofluorescence (IFI) according to the standard procedure delineated at the first ANCA workshop with minor modifications (16, 17).
ELISA for MPO-ANCA

Sera were tested for the presence of MPO-ANCA by ELISA as previously described (7, 18).

Statistical analysis

Data are expressed as mean and 95% confidence
interval (95%CI). Comparisons of serum adhesion molecule levels between the MPA group (active and remission phase), the CRF group and healthy subjects (HS) were analyzed by covariance analysis (ANOVA). Differences between means were performed by Bonferroni's multiple range test (set at 95%CI). A paired Student's t-test was used to compare differences between serum adhesion levels during active and remission phases in MPA patients. An unpaired Student's t-test was used to compare differences between serum adhesion levels during active and remission phases in MPA patients based on serum creatinine (Cr) at 6 months. Statistical analyzes were performed using Systat software version 10.0 (SPSS Inc, Chicago, USA). Differences were considered as significant at $p<0.05$.

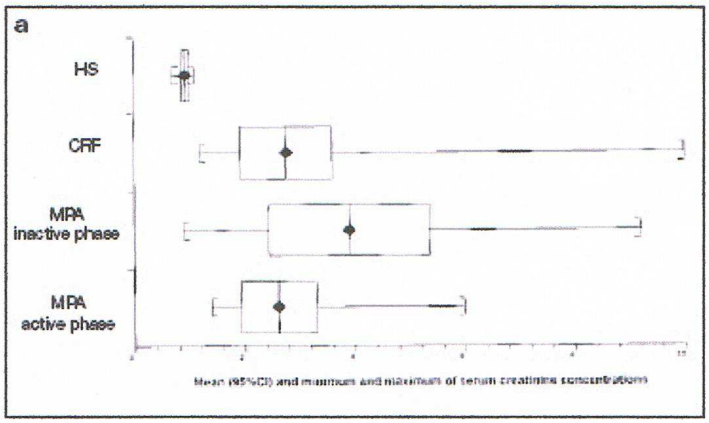
Results

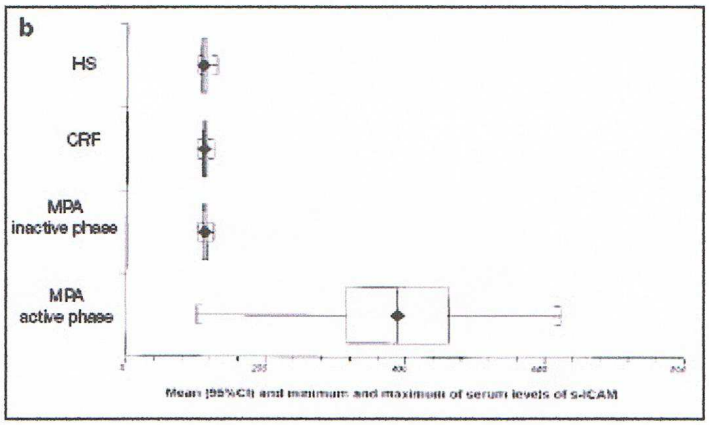
Concentrations of serum creatinine

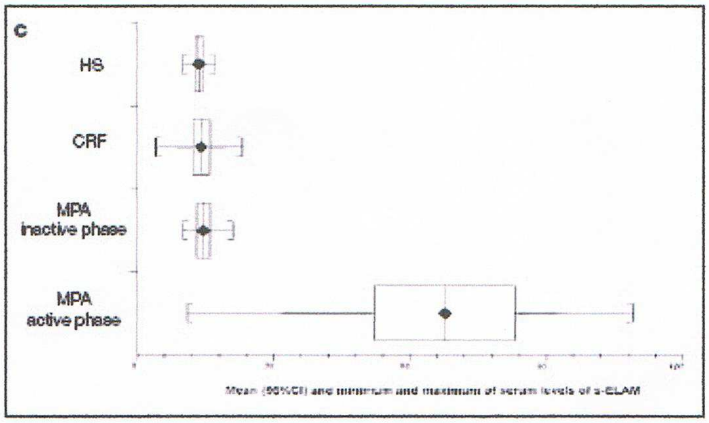
Means serum Cr concentrations were higher both in the MPA group, at the time of diagnosis (2.8 (95%CI 1.9-3.3) mg/dL) and in the remission phase (3.9 (95%CI 2.4-5.3) mg/dL), and in the CRF group (2.7 (95%CI 1.9-3.5) mg/dL) compared to the HS group (0.9 (95%CI 0.8-0.9) mg/dL) ($p=0.0002$). We found no difference between the MPA group at the time of diagnosis and in the remission phase and in the CRF group ($p=0.09$) (Fig. 1a, Tab. II).

(a) Serum Cr concentrations, (b) serum s-ICAM levels, and (c) s-ELAM levels.

Fig.1







SERUM CREATININE CONCENTRATION AND SERUM sICAM-1 AND sELAM-1 LEVELS *

TABLE II

	Healthy subjects N=20	Patients with CFR N=30	Patients with MPA N=20	
			At the time of diagnosis	In remission phase
Serum Cr (mg/dL)°	0.9 (0.8-0-9)	2.7 (1.9-3.5)	2.8 (1.9-3.3)	3.9 (2.4-5.3)
Serum sICAM-1 levels (ng/mL)°°	109.2 (105.8-112.6)	111.3 (108.8-113.7)	388.7 (315.6-461.8)	112.0 (108.9-115.0)
Serum sELAM-1 levels (ng/mL)°°°	13.4 (12.5-14.3)	14.0 (12.2-15.8)	67.7 (52.2-88.1)	14.5 (13.0-15.9)

** Data are reported as mean (95 % CI). ° HS group vs. MPA group at the time of diagnosis, HS group vs. MPA group in remission phase and HS vs. CRF group (p=0.002). °° HS group vs. MPA group at the time of diagnosis (p<0.001), CRF group vs. MPA group at the time of diagnosis (p<0.001) and MPA group at the time of diagnosis vs. MPA group in remission phase (p<0.001). °°° HS group vs. MPA group at the time of diagnosis (p<0.001), CRF group vs. MPA group at the time of diagnosis (p<0.001) and MPA group at the time of diagnosis vs. MPA group in remission phase (p<0.001).*

Circulating serum soluble levels of adhesion molecules

Mean serum adhesion molecule levels in the MPA group were higher at the time of diagnosis (active phase) than during remission (remission phase), and we found significant differences in comparing the
active phase with the remission phase in the MPA group and the active phase in the MPA group with the CRF and HS groups. No differences were recorded comparing the remission phase in the MPA group with the CRF group and the HS group. Finally, we did not find any difference between the CFR group and the HS group.
In particular, mean serum sICAM-1 levels in the MPA group were 388.7 (95%CI 315.6-461.8) ng/mL in the active phase and 112.0 (95%CI 108.9-115.0) ng/mL in the remission phase. The mean difference between the two periods was -276.7 (95%CI -347.5 to -205.9) ng/mL ($p<0.001$).
Mean serum sICAM-1 levels in the CRF group and the HS group were 111.3 (95%CI 108.8-113.7) ng/mL and 109.2 (95%CI 105.8-112.6) ng/mL, respectively.
The mean difference between the MPA group, in the active phase, and the CRF group was 277.4 (95%CI 229.3-325.5) ng/mL ($p<0.001$). In addition, no significant differences were recorded between the MPA group, in the remission phase, and the CFR group (mean difference: 0.7 (95%CI -3.1-4.5) ng/mL, $p=0.7$). Similarly, the mean differences between the MPA group, in the active and remission phases, and the HS group were 279.5 (95%CI 226.8-332.1) ng/mL ($p<0.001$) and 2.5 (95%CI -1.5-7.0) ng/mL ($p=0.2$), respectively. Finally, no difference was recorded between the CRF group and the HS group. The mean difference between the two groups was 2.0 (95%CI -46.0-50.1) ng/mL ($p=0.9$) (Fig. 1b, Tab. II).
Similar results were observed when sELAM-1 was considered. In particular, mean serum sELAM-1 levels in the MPA group were 67.7 (95% CI 52.2-88.1) ng/mL in the active phase and 14.5 (95%CI 13.0-15.9) ng/mL in the remission phase. The mean difference between the two periods was -45.2 (95%CI -60.8 to -29.5) ng/mL ($p<0.001$).
Means serum sELAM-1 levels in the CRF group and the HS group were 14.0 (95%CI 12.2-15.8) ng/mL and 13.4 (95%CI 12.5-14.3) ng/mL, respectively.
The mean difference between the MPA group, in the active phase, and the CRF group was 45.6 (95%CI 34.9-56.4) ng/mL ($p<0.001$). In addition, no differences were recorded between the MPA group, in the remission phase and the CRF group (mean difference: 0.7 (95%CI -3.1-4.5) ng/mL, $p=0.7$). Similarly, the mean differences between the MPA group, in the active and remission phases, and the HS group were 46.2 (95%CI 34.4-58.0) ng/mL ($p<0.001$) and 1.0 (95%CI -1.3-3.4) ng/mL ($p=0.2$), respectively. Finally, no difference was recorded between the CRF group and the HS group. The mean difference between the two groups was 0.6 (95%CI -1.5-2.7) ng/mL ($p=0.5$) (Fig. 1c, Tab. II).

Correlation between serum soluble levels of adhesion molecules and serum creatinine

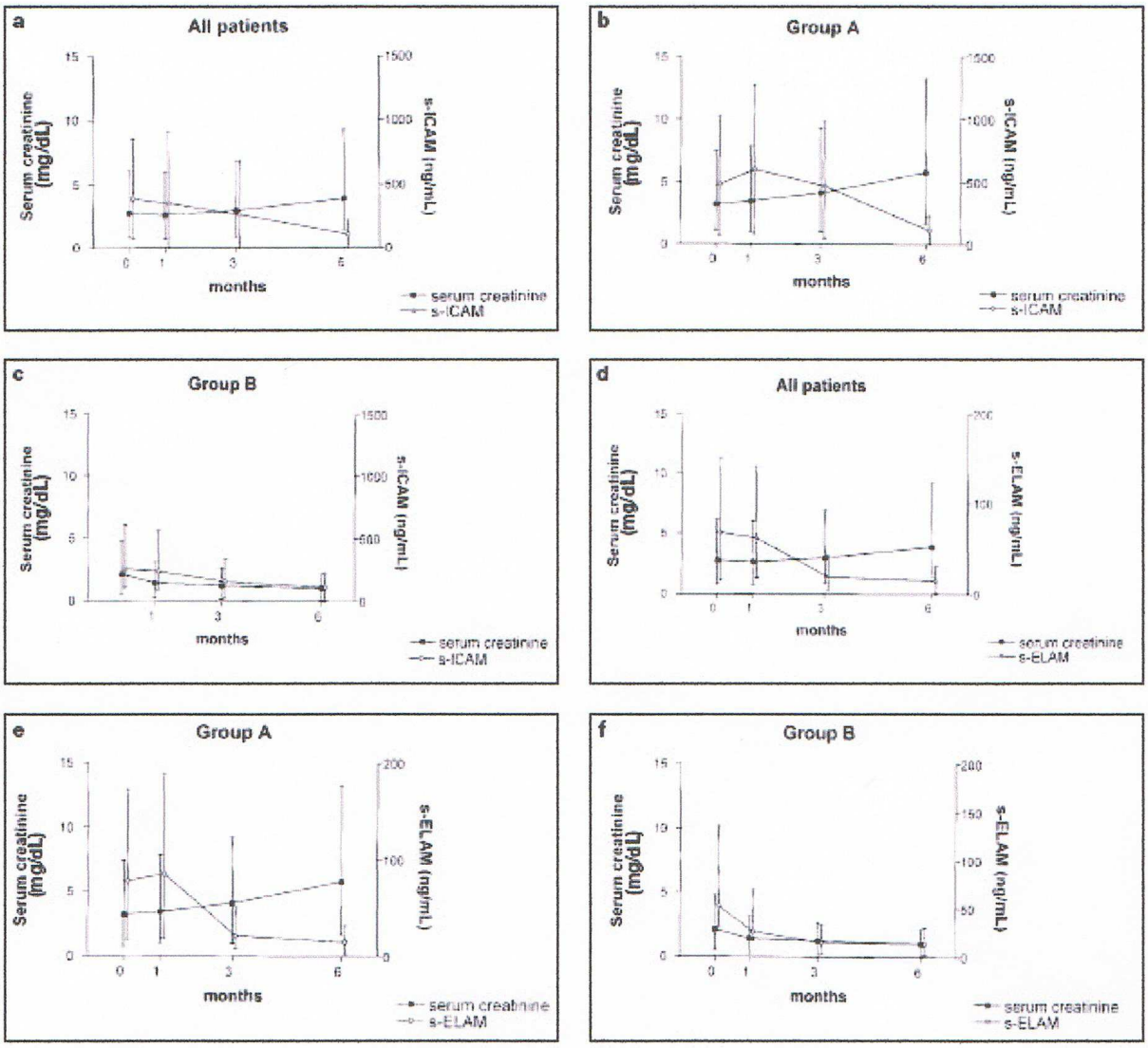
No correlation was recorded between sICAM-1 levels and serum Cr concentration both in the active phase ($r=0.38$ (95%CI -0.06-0.70), $p=0.09$) and in the remission phase ($r=-0.04$ (95%CI -0.41-0.47), $p=0.8$) of MPA.
Results failed to suggest any link between the reduction in sICAM-1 and sELAM-1 from the active to the remission phase and the variations in serum Cr concentrations.

Clinical outcome of patients with MPA

After 6 months from the time of diagnosis, MPA
patients presented a BVAS score of 0, CRP levels <0.8 mg/dL and negative MPO-ANCA. Regarding the serum Cr concentrations, 8/20 patients were <1.5 mg/dL (mean 1.1 (95%CI 0.9-1.2) mg/dL) and 12/20 patients were >1.5 mg/dL (mean 5.8 (95%CI 4.1-7.4) mg/dL).
When we considered serum adhesion molecule levels, at the time of MPA diagnosis, both sICAM-1 (mean 480.6 (95%CI 419.4-541.9) ng/mL) and sELAM-1 (mean 77.7 (95%CI 60.5-94.9) ng/mL) were higher in patients who developed CRF (serum Cr concentrations >1.5 mg/dL) as a final outcome of vasculitis, compared to patients with normal renal function in the remission phase (sICAM-1: mean 250.8 (95% CI 146.8-354.9) ng/mL; sELAM-1: mean 52.6 (95%CI 21.4-83.7) ng/mL), $p<0.001$ and $p<0.001$, respectively.
Therefore, we examined sICAM-1 and sELAM-1 in these two subgroups: subgroup A, with CRF in the remission phase (serum Cr >1.5 mg/dL) and subgroup B, without CRF in the remission phase (serum Cr <1.5 mg/dL). We found that the serum adhesion molecule levels were higher and decreased more slowly in subgroup A patients than in subgroup B patients.
In particular, after 1 month from MPA diagnosis, sICAM-1 levels were, in subgroup A, 600.0 (95%CI 525.0-674.0) ng/mL and, in subgroup B, 235.0 (95%CI 145.8-324.8) ng/mL ($p<0.001$). After 3 months from diagnosis, sICAM-1 levels were, in subgroup A, 469.1 (95%CI 422.6-515.0) ng/mL and, in subgroup B, 156.2 (95%CI 132.6-179.8) ng/mL ($p<0.001$). Finally, after 6 months from diagnosis, no differences were found between the two groups: 112.0 (95%CI 108.3-115.8) ng/mL in subgroup A and 111.8 (95%CI 105.5-118.0) ng/mL in the subgroup B ($p=0.9$) (Fig. 2a-c, Tab. III).

(a-c) Serum Cr concentrations and serum s-ICAM levels, and (d-f) serum s-ELAM levels, respectively, in patients affected by MPA at the time of diagnosis after 1 month, 3 months and 6 months.

Fig.2



SERUM sICAM-1 AND sELAM-1 LEVELS RELATED TO CLINICAL OUTCOME OF MPA*

TABLE III

	Group A Serum Cr concentration (>1.5 mg/dL) (n=12 patients)		Group B Serum Cr concentration (<1.5 mg/dL) (n=8 patients)	
	sICAM-1 (ng/mL)	sELAM-1 (ng/mL)	sICAM-1 (ng/mL)	sELAM-1 (ng/mL)
At the time of diagnosis	480.6 (419.4-541.9)	77.7 (60.5-94.9)	250.8 (146.8-354.9)	52.6 (21.4-83.7)
After 1 month	600.0 (525.0-674.0)	85.0 (66.8-103.2)	235.0 (145.8-324.8)	52.6 (21.4-83.7)
After 3 months	469.1 (422.6-515.0)	21.2 (13.2-29.2)	156.2 (132.6-179.8)	15.2 (12.7-17.7)
After 6 months	112.0 (108.3-115.8)	14.9 (12.7-17.0)	111.8 (105.5-118.0)	13.8 (11.4-16.2)

** Data are reported as mean (95% CI). Differences between group A vs. group B, both sICAM-1 and sELAM-1, at the time of diagnosis, after 1 month, after 3 months ($p<0.001$).*

Regarding sELAM-1, after 1 month from diagnosis, the soluble adhesion molecule levels were, in subgroup A, higher than those of subgroup B: 85.0 (95%CI 66.8-103.2) ng/mL and 52.6 (95%CI 21.4-83.7) ng/mL ($p<0.01$), respectively. After 3 months from diagnosis, sELAM-1 levels were no different between subgroup A in comparison with subgroup B: 21.2 (95%CI 13.2-29.2) ng/mL and 15.2 (95%CI 12.7-17.7) ng/mL ($p=0.5$), respectively. In addition, after 6 months from diagnosis, no differences were found between subgroup A (14.9 (95%CI 12.7-17.0) ng/mL) and subgroup B (13.8 (95%CI 11.4-16.2) ng/mL) ($p=0.9$) (Fig. 2d-f, Tab. III).

Discussion

Serum sICAM-1 and sELAM-1 levels in patients with active phase, ANCA-positive, small vessel vasculitis (MPA) were higher than those recorded in controls, CRF patients and healthy subjects. Molecule levels fell sharply on clinical vasculitis remission, independently of serum Cr concentrations. Finally, in the inactive vasculitis phase, no differences were found between the serum sICAM-1 and sELAM-1 levels in the MPA
patients and CRF patients and healthy subjects.
Considerable experimental and clinical evidence has been reported to support the suggestion that adhesion molecules are important tissue injury mediators in inflammatory diseases (19-21). On the other hand, elevated serum concentrations of soluble adhesion molecules are found in patients without any apparent inflammatory disease, affected by chronic congestive heart failure (22) and in hemodialyzed patients (23). The latter finding raises the possibility that the
increase in circulating soluble cell adhesion molecule levels could simply represent the accumulation of substances due to impaired renal elimination (19). The kidney normally clears many circulating proteins; therefore, when renal function is impaired, the half-life and the circulating levels of these proteins become markedly elevated (24).
The clearance mechanisms of soluble adhesion molecules are unknown, but our data indicate that sICAM-1 and sELAM-1 levels could provide a valuable tool for differentiating between active and inactive phase
patients with MPA. Serum sICAM-1 and sELAM-1
concentrations, in MPO-ANCA-positive MPA patients, increased only during the active phase compared to the remission phase, suggesting that renal and
endothelium inflammation could be the cause of elevated serum levels of these proteins, and that serum adhesion molecule levels are related to an increase in the production of these molecules rather than to a
reduction in renal clearance.
The results of our study suggest that an enhanced synthesis/release of adhesion molecules could contribute to elevated serum levels of these molecules independently of renal function. As did other authors previously, we observed no correlation between Cr concentrations and serum sICAM-1 and sELAM-1 levels (11, 25, 26).
The reduction in soluble adhesion molecule levels could be linked to the treatment. It has been shown that corticosteroids reduce cytokine synthesis; therefore, possibly reducing adhesion molecule expression and their function (27).
Renal damage can also probably be dependent on high sICAM-1 levels in the serum of patients with MPO-ANCA-positive MPA. ICAM-1 is expressed basally in significant amounts in a limited number of cell types, including endothelial cells and monocytes, and it is widely inducible or up-regulated on many cells
including endothelial cells, epithelial cells, dendritic cells, lymphocytes and monocytes under appropriate stimuli. ELAM-1 is exclusively expressed by endo-thelial cells (28). Previous studies on MPA showed that sICAM-1 levels mimic the clinical course of the disease (11) an the successful prevention of MPA has been experimentally demonstrated with anti-ICAM-1 antibody treatment (29). Moreover, our data suggest that in patients with MPO-ANCA-positive MPA, higher sICAM-1 and sELAM-1 levels during the active phase can be a prognostic risk factor for future CRF. The infiltration of glomeruli and renal interstitium by polymorphonuclear cells plays an important role in the pathogenesis of all types of glomerulonephritides. On activation, the polymorphonuclear cells release protease and reactive oxygen species, resulting in damage to the renal parenchyma and, consequently, functional renal failure.
However, in this study, the number of patients was small and this association should be interpreted with caution. Further prospective studies, with a larger number of patients, are needed to confirm this finding.

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