Soluble ELAM-1 Is Elevated with the Progression of IgA Nephropathy but Not with That of Polycystic Kidney Disease

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Dear Sir,

The endothelial leukocyte adhesion molecule (ELAM)-1, a member of the selectin family with a lectin-like N-terminal domain [1], binds granulocytes, monocytes and a subset of memory T cells [2-4]. ELAM-1 is expressed only on vascular endothelium, predominantly on postcapillary venules [5-7]. Expression of ELAM-1 on vascular endothelium can be observed in the proximity of cells producing inflammatory cytokines such as interleukin-1 and the tumor necrosis factor, stimuli which, in vitro, are known to induce an upregulation of adhesion [5].

Recently, a quantitative sandwich ELISA for ELAM-1 in the fluid phase (soluble ELAM-1, s-ELAM-1) has been developed [6]. The expression of ELAM-1 has been described only on activated endothelial cells, not on other cell types; therefore, levels of ELAM-1 in serum may provide a basis for the assessment of endothelial damage or activation [6, 7]. We examined the level of s-ELAM-1 in patients with IgA nephropathy (IgAN), and those with polycystic kidney disease (PCK), paying special attention to its correlation with the decline of renal function.

A total of 38 patients were enrolled in the present study: 24 with IgAN, and 14 with PCK with varying degrees of renal function. Twenty-seven healthy adult volunteers served as normal controls for s-ELAM-1 assay. They were determined healthy by biochemical tests and urinalysis. All blood samples were obtained in the morning (07.00-09.00) at Sendai Shakaihoken Hospital. In 5 patients with IgAN, blood samples were obtained twice: before steroid therapy and 1

Fig. 1. Correlation between creatinine clearance and levels of s-ELAM-1 in patients with IgAN. The shaded area represents the normal range.

signed rank test was used for statistical analysis.

The s-ELAM-1 level in 27 normal subjects was 34.6 ± 11.7 ng/ml. The normal range was determined to be less than 58.0 ng/ml or within 2 SD of the mean value. In patients with IgAN, a linear regression was observed between the elevation of the s-ELAM-1 level and the decrease in creatinine clearance (fig. 1). This correlation was not observed in patients with PCK (fig. 2). month after starting steroid administration. Serum was collected immediately after centrifugation and frozen at -70°C until use.

A quantitative sandwich ELISA kit (British Bio-technology Products, UK) for ELAM-1 in the fluid phase was employed. The assay was used according to the manufacturer's instructions. Duplicate aliquots of 100 μ l of serum diluted 5 times were tested. Correlation coefficients were calculated by linear regression analysis. The Wilcoxon

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p < 0.01

Fig. 2. Correlation between creatinine clearance (Ccr) and levels of s-ELAM-1 in patients with PCK.

Fig. 3. Changes in s-ELAM-1 level as a result of steroid therapy.

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Initial

After steroid

J 3

To determine the effects of steroid therapy on the s-ELAM-1 level, s-ELAM-1 values were compared before and 1 month after steroid therapy (30 mg prednisolone daily). The mean value of creatinine clearance did not change significantly (67.7 ± 11.2 - 70.2 ± 9.8 ml/min). In contrast, the s-ELAM-1 level decreased significantly, from 62.6 ± 5.7 to 44.5 ± 9.9 ng/ml (fig. 3).

The biological significance of elevated s-ELAM-1 in serum as well as the mechanism by which ELAM-1 is released from the endo-thelium into the circulation have not been elucidated [7].

However, ELAM-1 has been reported to be expressed only on endothelial cells to date.

Therefore, it has been postulated that the level of s-ELAM-1 in serum should reflect the state of the endothelium in disease [7]. In the present study, s-ELAM-1 increased with the decline of renal function in patients with IgAN, but not in those with PCK. These observations suggest that the deterioration of renal function is not a sine qua non of increased s-ELAM-1 in patients with renal diseases. Although they have not yet been clarified, they might be ascribed to the different mechanisms linked to the progression of renal disease. It has been postulated that the compression of normal parenchyma resulting from the enlargement of cysts is a central factor in the pathogenesis of chronic renal failure in patients with PCK

[8, 9]. On the other hand, in patients with IgAN, interstitial leukocyte infiltration and fibrosis are well correlated with the decline of renal function [10, 11]. Moreover, Lai et al. [12] recently reported that there was a significant correlation between the levels of s-ELAM-1 and the severity of glomerular and interstitial lesions. Thus, it can be assumed that enhanced synthesis of ELAM-1 in the vasculature of the kidney, which promotes the migration of leukocytes to the interstitium, may be associated with the elevated s-ELAM-1 level in advanced IgAN.

Although several investigations, including ours, have pointed out the usefulness of steroid therapy to ameliorate the course of the disease in patients with IgAN [13, 14], the mechanisms involved have yet to be elucidated. In vitro, steroids are effective in inhibiting the expression of ELAM-1 on endotoxin-treated endothelial cells [15]. Our present study demonstrated that

steroid therapy induced a decrease in s-ELAM-1 levels, which was probably closely associated with the downregulation of ELAM-1 synthesis in the vasculature. In conclusion, the suppression of ELAM-1 synthesis may be involved in the amelioration of renal injuries in IgAN when steroids are used.

References

- Bvilacqua MD, Stengelin S, Gimbrone MA, Seed B: Endothelial leukocyte adhesion molecule 1: An incident receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 1990;243:1160-1165.
- Phillips ML, Nudelman E, Gaeta FCA, Perez M, Singhal AK, Hakomori SI, Paulson JC: ELAM-1 mediates cell adhesion by recognition of a carbohydrate ligand, sialyl-Lex. *Science* 1990;250:1130-1132.
- Pickler LJ, Kishimoto TK, Smith CW, War-nock RA, Butcher EC: ELAM-1 is an adhesion molecule for skin-homing T cells. *Nature* 1991;349:796-799.
- Shimizu Y, Shaw S, Graber N, Gopal TV, Horgan KJ, van Seventer GA, Newman W: Activation-independent binding of human memory T cells to adhesion molecule ELAM-1. *Nature* 1991;349:799-802.
- Roco LP, Pomponi D, Pigott R, Stoppacciaro A, Monardo F, Uccini S, Borashi D, Tagliabue A, Santoni A, Dejana E, Baron CD: Cytokine production (IL-1 α , IL-1 β and TNF α) and endothelial cell activation (ELAM-1 and HLA-DR) in lymphadenitis, Hodgkin's disease, and non-Hodgkin's lymphoma: An immunochemical study. *Am J Pathol* 1990;137:1163-1171.
- Newman W, Beall LD, Carson CW, Hunder GG, Graben N, Randhawa ZI, Gopal TV, Weiner-Kronish J, Matthay MA: Soluble E-selectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. *J Immunol* 1993; 150:644-654.

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Gearing AJT, Hemingway I, Pigott R, Hughes J, Rees AJ, Cashman SJ: Soluble forms of vascular adhesion molecules, E-selectin, ICAM-1, and VCAM-1: Pathological significance. *Ann NY Acad Sci* 1992;667:324-331.

Franz KA, Reubi FC: Rate of functional deterioration in polycystic kidney disease. *Kidney Int* 1983;23:526-529.

Gabow PA, Ikle DW, Holmes JH: Polycystic kidney disease: Prospective analysis of non-azotemic patients and family members. *Ann Intern Med* 1984;101:238-247.

Hotta O, Yoshizawa N, Oshima S, Takeuchi A, Kawamura O, Kondo S, Kubota T, Niwa H: Significance of renal hyaline arteriosclerosis and tubulointerstitial change in IgA glomerulonephritis and focal glomerulosclerosis. *Nephron* 1987;47:262-265.

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D'Amico G, Barbiano di Belgioioso G, Imbas-ciati E, Fogazzi G, Radaelli L, Ferrario F, Filin G, Ponticelli C, Minetti L: Idiopathic IgA mes-angial nephropathy: Natural history. *Contrib Nephrol* 1984;40:208-213.

Lai KN, Wong KC, Li PKT, Li CKW, Chan CHS, Lui SF, Chui YL, Haskard DO: Circulating leukocyte-endothelial adhesion molecules in IgA nephropathy. *Nephron* 1994;68:294-300.

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Hotta O, Taguma Y, Kurosawa K, Sudo K, Suzuki K, Horigome I: Early intensive therapy for clinical remission of active IgA nephropathy: A three-year follow-up study. *Jpn J Nephrol* 1993;35:967-973. Kobayashi Y, Fujii K, Hiki Y, Tatenos S, Kurokawa A, Komiyama A: Steroid therapy in IgA nephropathy: A retrospective study in heavy proteinuric cases. *Nephron* 1988;48:12-17. Cronstein BN, Kimmel SC, Levin RL, Martiniuk F, Weissmann G: A mechanism for the anti-inflammatory effects of corticosteroids: The glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci USA* 1992;89:9991-9995.

Obituary

NEPHRON regrets the untimely death of Prof. Raines at an early age which has robbed nephrology of a fine brain.

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