ORIGINALES

Glomerular and tubulointerstitial expression of the intercellular adhesion molecule-1 (ICAM-1) and leucocyte function associated antigen-1 (LFA-1) in membranous glomerulopathy (MGN) and mesangial proliferative glomerulonephritis (MesProGN). A comparative study

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SUMMARY

Glomerular and tubulointerstitial distribution of intercellular adhesion molecule-1 (ICAM-1) and leucocyte function associated antigen-1 (LFA-1) was evaluated in renal tissue from 20 patients with membranous glomerulopathy (MGN) and from 20 with mesangial proliferative glomerulonephritis (MesProGN). We calculated the correlation between the number of LFA-1 positive cells and the expression of ICAM-1; the degree of interstitial renal fibrosis and the expression of ICAM-1; and the degree of renal fibrosis and the number of interstitial LFA-1 positive cells.

Results: *In the renal specimens from patients with MGN there was no evidence of increased glomerular expression fo ICAM-1 or LFA-1 compared with normal controls. We found increased glomerular and tubulointerstitial expression ICAM-1 and an increased number of glomerular and interstitial immune cells bearing LFA-1 in renal biopsies from patients with MesProGN. In MesProGN strong mesangial staining of ICAM-1 was observed while in MGN the glomerular expression of ICAM-1 was mainly endothelial. There were no significant differences between MGN and MesProGN in the number of interstitial LFA-1 positive cells or the tubulointerstitial expression of ICAM-1. ICAM-1 was expressed on endothelial cells of peritubular capillaries, interstitial cells, infiltrating immune cells and tubular epithelial cells, particularly of atrophic tubules. In both types of glomerulopathy the number of glomerular and interstitial LFA-1 positive cells correlated positively with the expression of ICAM-1. The tubulointerstitial staining of ICAM-1 and LFA-1 correlated positively with the degree of renal fibrosis.*

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In conclusion, *our results support the hypothesis that ICAM-1 and LFA-1 are important participants in both types of nephropathy studied and indicate the role of upregulated expression of these molecules in the pathogenesis and progression off the diseases.*

Key words: ***Adhesion molecules. Human glomerulonephritis.***

RESUMEN

Se evaluó la distribución glomerular y tubulointersticial de la molécula de adhesión intracelular, ICAM-1 y del antígeno de función leucocitaria asociado, LFA-1 en tejido renal de 20 pacientes diagnosticados de glomerulonefritis membranosa (MGN) y en otros 20 con glomerulonefritis mesangioproliferativa (MesProGN). Se calculó la correlación entre el número de células LFA-1 positivas y la expresión de ICAM-1, el grado de fibrosis intersticial y la expresión de ICAM-1; y el grado de fibrosis renal y el número de células LFA-1 positivas en el intersticio.

Resultados: *En las muestras renales de pacientes con MGN no hubo incremento en la expresión glomerular de ICAM-1 o LFA-1 comparado con los controles. Se encontró un incremento de la expansión glomerular y tubulointersticial de ICAM-1 y un incremento del número de glomérulos y de las células inmunes intersticiales expresando LFA-1 en las biopsias de los pacientes con MesProGN. Se observó una fuerte tinción mesangial de ICAM-1 en la MesProGN,siendo endotelial en el caso de la MGN. No hubo diferencias significativas entre la MGN y la MesProGN en cuanto al número de células intersticiales LFA-1 positivas o en cuanto al número de células instersticiales LFA-1 positivas o en cuanto a la expresión tubulointersticial de ICAM-1. ICAM-1 se expresó en células endoteliales de los capilares peritubulares, células intersticiales, células inmunes infiltrativas y células epiteliales, especialmente en los túbulos atróficos. En ambos tipos de glomerulopatías el número de glomérulos y de células intersticiales LFA-1 positivas se correlacionó positivamente con la expresión de ICAM-1. La tinción tubulointersticial de ICAM-1 y de LFA-1 se correlacionó positivamente con el grado de fibrosis renal.*

En conclusión. Nuestros resultados apoyan la hipótesis de que ICAM-1 y LFA-1 son participes importantes en ambos tipos de nefropatía estudiadas e indican el papel de la sobrerregulación en la expresión de ambas moléculas en la patogénesis y progresión de la enfermedad.

Palabras clave: ***Moléculas de adhesión. Glomerulonefritis humana.***

INTRODUCTION

It is now well-recognized that a critital function of inflammation is the delivery of leucocytes to the sites of injury. Leucocyte adhesion and transmigration are determined by the binding of complementary adhesion molecules on the leucocyte and endothelial surfaces. The intercellular adhesion molecule-1 (ICAM-1) which belongs to the immunoglobulin family molecules interacts with integrins found of leucocytes. The principal integrin receptors for ICAM-1 are the β_2-integrins LFA-1 (CD11 a/CD18) and MAC-1 (CD11b/CD18). The LFA-1/ICAM-1 interaction causes adhesion to the endothelium and are necessary for the transmigration across the endothelium[1,2].

ICAM-1 was isolated in the vascular component of the nephron, and to a much lesser extent in parietal cells of Bowman's capsule and some interstitial cells in kidneys from healthy humans[3,4]. LFA-1 is expressed on most leucocytes, particularly activated T cells[1,5]. Experimental investigations indicate that these molecules play distinct roles in the pathogenesis of immune-mediated renal diseases[6-8]. Recently, aberrant expresion of adhesion molecules has been demonstrated in human glomerulonephritis and renal allograft rejection[9-12].

In view of the above, we decided to investigate ICAM-1/LFA-1 expression in proliferative and non-proliferative form of glomerulonephritis and to define any morphological correlations.

MATERIAL AND METHODS

Patients

The kidney tissue specimens were obtained for diagnostic purposes by percutaneous biopsy from 40 patients with primary glomerular diseases: 20 pa-

tients with idiopathic diffuse membranous glomerulopathy-stage II (MGN, mean age = 34.7, range 19-48, male/female ratio = 12:8) and 20 with mesangial proliferative (IgA-negative) glomerulonephritis (MesProGN, mean age = 25.2, range 17-49, male/female ratio = 13:7). None of the patients had the evidence of secondary disease. The mean duration of the disease prior to the biopsy was 5.8 months in MGN and 6.1 months in MesProGN. None of these patients had been treated with immunosuppressive drugs prior to the renal biopsy. In all cases the diagnosis of glomerulonephritis was based on the characteristic findings by light and electronmicroscopy as well as immunofluorescence. The classification of the histopathological lesions refers to that of the World Health Organization[13].

Histologically normal portions of the kidney tissue, obtained from 15 adult patients (aged from 43-49, mean age = 49.8) with renal trauma (n = 5) or renal tumours (n = 10) were used as controls.

Laboratory data including urinanalysis, 24-hour protein excretion and serum creatinine level were collected from each patient. The clinical and laboratory data are summarized in table I.

For the study biopsies containing less than 5 glomeruli were neglected. For light microscopy, the tissue samples were fixed in buffered formalin, embedded in paraffin, and sections (4 µm) were cut and stained with hematoxylin and eosin, periodic acid-Schiff (PAS) + alcian blue. Silver impregnation (Jones) and Masson-Trichrome were performed as well. For immunofluorescence, a portion of a biopsy sample was snap-frozen, and cryostat sections (5 µm) were cut and stained with fluorescein-isothiocyanated (FITC) conjugated anti-IgG, anti-IgA, anti-IgM and anti-C_3 antibodies (DAKO A/S, Glostrup, Denmark).

Other biopsy tissue portions were processed for electron microscopy: these samples were fixed in glutaraldehyde, post-fixed in 1% osmium tetroxide, embedded in epon, sectioned with a LKB ultratome, stained by lead acetate and uranyl acetate, and viewed in a JEM 100B electron microscope.

Immunohistochemistry

An indirec StreptABComplex/HRP technique was carried out as follows: 5 µm thick cryostat sections were fixed in acetone for 10 min, air- dried, and after blocking of endogenous peroxidase activity by 0.6% hydrogen peroxide in methanol, rinsed in Tris-buffered saline (TBS). After blocking by normal rabbit serum (DAKO A/S, Glostrup, Denmark) for 20 min (dilution 1:5), the sections were incubated with the following anti-human monoclonal antibodies (DAKO, A/S, Glostrup, Denmark) (followed by TBS washing): CD54 (ICAM-1; 1:50) and CD11a (clone MHM24, LFA-1; 1:100) in a moist chamber for 30 min at room temperature. Afterwards sections were incubated with biotinylated rabbit anti-mouse immunoglobulin (DAKO A/S, Glostrup, Denmark) diluted 1:600 in TBS for 20 min and StreptABComplex/HRP (DAKO, A/S, Glostrup, Denmark) for 30 min prepared according to the instructions of the manufacturer. Visualisation was performed by incubation the sections with 0.5 mg 3,3'-diaminobenzidine (DAKO, A/S, Glostrup, Denmark) /ml Tris-HCL buffer, pH 7.6, containing 0.02% hydrogen peroxide, for 10 min. After washing, sections were counter-stained with hematoxylin and coversliped. For each monoclonal antibody and for each sample a positive control (sections of surgically removed lymph nodes and an inflamed tonsils) and a negative control were processed. Negative controls were carried out by incubation in the absence of the primary antibody and yielded negative results.

Quantification

For each section, both the number of all intraglomerular LFA-1-positive cells and the number of glomeruli were counted using a computer image analysis system equipped with a A Ver 2000 card (ADDA Technologies, Taiwan). The colored microscopic images were stored serially in the memory of a computer. The numer of LFA-1 positive cells per glomerular

Table I. Clinical and laboratory data in patients with membranous glomerulopathy (MGN) and mesangial proliferative glomerulonephritis (MesProGN).

Groups	Micro-hematuria	Gross hematuria	Proteinuria < 1g/24 h	Proteinuria 1-2g/24 h	Proteinuria 2 –3g/24 h	Nephrotic syndrome	Renal function impairment[1]	Hypertension (> 150/90)
MGN (n = 20)	8	3	1	5	7	7	3	7
MesProGN (n = 20)	12	2	4	4	7	5	6	8

[1] Serum creatinine > 1.5/dl.

cross-section in each section was obtained (semiautomatic function) and used for the analysis. The number of LFA-1 positive cells and the number of ICAM-1 positive cells in the interstitium was determined by counting all positive cells (semiautomatic function) in a sequence of ten consecutive computer images of 400 x high power fields - 0.0047 mm^2 each. Adjustments of the field were only made to avoid glomeruli and large vessels. The results were expressed as mean number of immunopositive cells per mm^2.

The grade of ICAM-1 staining in glomeruli, tubular epithelium and vessels was evaluated by the two authors. According to the method described by Dal Canton et al.[14] the degree of ICAM-1 expression was scored semiquantitatively on a three-point scale: 0 = staining equal to negative control, 1 = staining present, but less intense than positive control, 2 = staining present with the same or higher intensity than in positive control. The mean grade was calculated by averaging grades assigned by the two authors and approximating the arithmetical mean to the nearest unity. Glomerular staining was scored in all glomeruli within renal biopsy specimens. Tubular and vascular staining were scored in 10 consecutive high power fields, avoiding glomeruli.

Renal relative cortical interstitial volume was measured using point counting method, which is an adaptation of the principles of Weibel[15]. For these measurements the image analysis system was programmed to use a stereological net with regulated number of points. The point spacing being 16 µm. Total number of the points of a net was 169, and total area was 0.0369 mm^2. Under the net described above, seven fields of the renal cortex were investigated. Glomeruli and large vessels were neglected. The percentage interstitial volume was an expression of the numer of points overlying renal cortical interstitium as a percentage of the total points counted.

Table II. Glomerular expression of ICAM-1/LFA-1 in the controls, MGN and MesProGN.

Groups	LFA-1- positive cells	Mean score of ICAM-1
Controls (n = 15)	0.29 ± 0.14	0.63 ± 0.14
MGN (n = 20)	0.45 ± 0.29	0.73 ± 0.29
MesProGN (n = 20)	1.15 ± 0.64	1.15 ± 0.47
	P value:	
MGN vs.controls	NS	NS
MesProGN vs.controls	P < 0.001	P < 0.001
MGN vs. MesProGN	P < 0.001	P < 0.002

Data are expressed as mean ± standard deviation.
NS = not significant.

Statistical analysis

All values were expressed as the mean ± SD (standard deviation). The differences between groups were tested using analysis of variances (one-way ANOVA) preceded by evaluation of normality and homogenity of variances with Levene's test. Additionaly the Mann-Whitney U test was used where appropriate. Correlations between selected parameters were calculated using the Spearman Rank Order method. Results were considered statistically significant if $p < 0.05$.

RESULTS

Intraglomerular and interstitial LFA-1 positive cells and expression of ICAM-1. The results of the immunohistochemical finding are summarized in tables II and III.

Controls. The number of glomerular LFA-1-positive cells was 0.29 ± 0.14 per cross-sectioned glomerulus.

Table III. Tubulointerstitial expresion of ICAM-1/LFA-1 and relative interstitial volume in controls, MGN and MesProGN.

Groups	LFA-1-positive cells/l mm^2	Mean score of ICAM-1 (vessels)	Mean score of ICAM-1 (tubuli)	ICAM-1-positive cells/l mm^2	Interstitial volume (%)
Controls (n = 15)	38.7 ± 21.7	0.7 ± 0.29	0	31.6 ± 18.4	11.1 ± 1.2
MGN (n = 20)	176.9 ± 29.6	0.9 ± 0.32	0.97 ± 0.45	211.6 ± 48.1	21.8 ± 7.5
MesProGN (n = 20)	181.5 ± 48.1	0.86 ± 0.35	1.2 ± 0.33	201.34 ± 55.3	24.1 ± 11.4
			P value:		
MGN vs.controls	P < 0.001	NS	P < 0.001	P < 0.001	P < 0.01
MesProGN vs.controls	P < 0.001	NS	P < 0.001	P < 0.001	P < 0.01
MGN vs. MesProGN	NS	NS	NS	NS	NS

Data are expressed as mean ± standard deviation.
NS = not significant.

The numer of interstitial LFA-1-positive cells was 38.7 ± 21.7 cells/mm^2. ICAM-1 was slightly expressed by glomerular endothelial cells, but not by glomerular mesangial or epithelial cells. In the interstitium ICAM-1 was present on endothelial cells in a limited number of capillaries and venules. Neither proximal nor distal tubules expressed ICAM-1. The number of interstitial ICAM-1-positive cells was 31.6 ± 18.4 per mm^2.

MGN vs. controls. In MGN the number of glomerular LFA-1 positive cells was 0.45 ± 0.29 per glomerular cross section., and numerous leukocytes in the interstitium were positive for LFA-1 (fig. 1) and ICAM-1. The glomerular distribution of ICAM-1 was weak and mainly diffuse, located along glomerular capillary walls. No staining of ICAM-1 was observed on mesangium. In the glomeruli in MPG patients the mean values of the expression of ICAM-1 and the mean values of LFA-1 positive cells were higher when compared with control, but these differences have not reach statistical significance. The tubular expression of ICAM, the number of interstitial ICAM-1 positive cells as well as the number of interstitial LFA-1-positive cells in MGN revelaed significant differences in comparison with control ($p < 0.001$).

MesProGN vs. controls. As shown in table II and table III the significant increase in the number of LFA-1-immunoreactive cells was seen in tissue samples in patients with MesProGN. The glomerular ICAM-1 was expressed with variable intensities, aminly along capillary walls and on mesangial cells (fig. 2). In comparison with controls the glomerular expression of ICAM-1 was evident and increased in MesProGN. In the interstitium ICAM-1 was found to be expressed with variable intensities on endothelial cells of peritubular capillaries, vessels, infiltrating immune cells and on the luminal side of tubular epithelial cells, particularly of atrophic tubuli. The significant increase of ICAM-1 expression in tubular epithelium as well as the number of interstitial ICAM-1-positive cell was seen in MesProGN when compared with control.

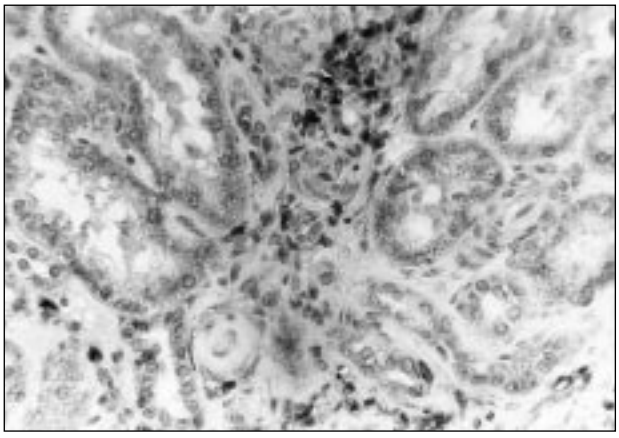

Fig. 1.—Numerous leucocytes positive for LFA-1 in the interstitium in renal tissue in case of MGN x 400.

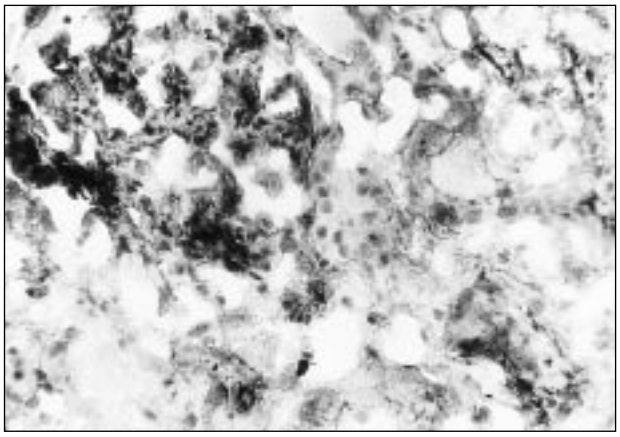

Fig. 2.—Expression of ICAM-1 on glomerular cells in MesProGN x 400.

MGN vs. MesPreGN. The comparisons between MGN and MesProGN revealed significant differences in the numer of intraglomerular LFA-1 positive cells as well as the intensity of glomerular expression of ICAM-1. In patients with MesProGN, LFA-1-immunoreactive cells per cross- sectioned glomeruli were seen in higher number than in MGN ($p < 0.001$). The grade of staining of ICAM-1 was also more intense in glomeruli in MesProGN cases ($p < 0.002$). No expression of ICAM-1 was observed in the mesangium in MGN. There were no significant differences in the number of interstitial LFA-1-positive cells, interstitial ICAM-1-positive cells and tubulointerstitial expression of ICAM-1 between MGN and MesProGN.

Morphological correlations

As shown in table IV there were possitive correlations between the number of glomerular LFA-1-positive cells and glomerular expression of ICAM-1 in both MesProGN and in MGN groups. Moreover, in these glomerulopathies the number of interstitial LFA-1-immunoreactive cells correlated positively with ICAM-1 expression noted in the tubular epithelium and with the number of interstitial ICAM-1-positive cells.

In both studied glomerulopathies there were a clear associations between the number of interstitial LFA-1-positive and the relative interstitial cortical volume, between the number of interstitial ICAM-1-positive cells and the relative interstitial cortical volume as well as between the intensity of tubular expression of ICAM-1 and the relative interstitial cortical volume (table IV).

Table IV. The morphological correlations in MGN and MesProGN.

Groups	MGN	MesProGN
Glomerular LFA-A-positive cells vs. glomerular mean score of ICAM-1	r = 0.67, p < 0.002	r = 0.57, p < 0.01
Interstitial LFA-1-positive cells vs. mean score of ICAM-1 (vessels)	r = 0.53, p < 0.02	r = 0.61, p < 0.005
Interstitial LFA-1-positive cells vs. mean score of ICAM-1 (tubuli)	r = 0.62, p < 0.005	r = 0.66, p< 0.002
Interstitial LFA-1-positive cells vs. interstitial ICAM-1-positive cells	r = 0.9, p < 0.001	r = 0.51, p < 0.05
Interstitial LFA-1-positive cells vs. interstitial cortical volume	r = 0.61, p < 0.005	r = 0.65, p < 0.005
Mean score of ICAM-1 (vessels) vs. interstial cortical volume	r = 0.39, P-NS	r = 0.44, P-NS
Mean score of ICAM-1 (tubuli) vs. interstial cortical volume	r = 0.56, p < 0.01	r = 0.52, p < 0.02
Interstitial ICAM-1-positive cells vs. interstial cortical volume	r = 0.59, p < 0.01	r = 0.46, p < 0.05

DISCUSSION

Several reports[6,16] have shown that ICAM-1/LFA-1 interaction mediates glomerular and interstitial infiltration of immune cells in various types of glomerular diseases and renal allograft rejection, and what is more interrupting the ICAM-1/LFA-1 interaction prevent disease progression[17].

In our study, we found increased glomerular and tubular expression of ICAM-1 and icreased number of interstitial ICAM-1-positive cells in renal biopsies from patients with MesProGN. The number of glomerular and interstitial immune cells bearing LFA-1 was also prominent. In contrast to these patients, in the renal specimens from cases with MGN there were no evidence of increased glomerular ICAM-1/LFA-1 expression. Although, in the glomeruli in renal biopsies in MPG the mean values of the expression of ICAM-1 and the mean values of LFA-1 positive cells were higher when compared with control, these differences have not reach statistical significance. In MGN the glomerular expression of ICAM-1 was mainly endothelial although, some parietal epithelial cells of Bowman's capsule were stained positive for ICAM-1 in these cases. Of particular interest was a strong mesangial staining of ICAM-1 in MesProGN. The increased mesangial expression of ICAM-1 in MesProGN may indicate an activation of mesangial cells in this form of nephropathy.

ICAM-1 is known to be expressed on the cell surface after stimulation by cytokines, such as interleukin-1, tumor necrosis factor-α and interferon-γ, which are secreted by T cells and macrophages[3,18]. It has been demonstrated by several authors[1,2] that LFA-1 is expressed on migrating immune cells mainly composed of macrophages; thus showed in our study strong positive correlation between the number of LFA-1-immunoreactive cells and the number of ICAM-1-immunoreactive cells as well as the intensity of tubular ICAM-1 staining, support hypothesis of interaction of ICAM-1/LFA-1 in the generation of immune response in MesProGN.

Variable expression of ICAM-1 has been reported in patients with proliferative and non-proliferative glomerulopathies[11,12,19-21]. In accordance with our results Dal Canton and co-workers[14] found no expression of ICAM-1 in the mesangium and glomerular visceral epithelial cells in patients with membranous nephropathy. Brujin and Dinklo[22] showed increased expression of ICAM-1 on parietal epithelium of glomeruli in membranous glomerulonephritis and on mesangium in Henoch-Schoenlein purpura, IgA nephropathy and membranoproliferative glomerulonephritis. The study by Muller[23] showed an increase of ICAM-1 on glomeruli only in the early stage of rapidly progressive glomerulonephritis, but an abnormal expression of this molecule was detected on proximal tubular epithelial cells in almost all types of glomerulonephritis except minor lesions and endocapillary glomerulonephritis. Showed in our investigation the increased tubular expression of ICAM-1 in all forms of studied nephropathies may be related to interstitial infiltration by immune cells in primary glomerular lesions, causing interstitial fibrosis and progression of renal disease.

Interesingly, we found no differences in the intensity of expression of ICAM-1/LFA-1 in tubuli and interstitium between MGN and MesProGN. In addition, we revealed positive correlations between the intensity of tubular staining of ICAM-1 and the degree of interstitial renal fibrosis and between the number of interstitial LFA-1 positive cells, the number of interstitial ICAM-1-positive cells and the interstitial fibrosis in both types of studied nephropathies. Furthermore, a neoexpression of ICAM-1 on tubular epithelium confined to atrophic tubuli pointed to the role of this molecule in local immune mediated injury and suggested that tubular staining of ICAM-1 may be a marker of the extent of tubular damage in glomerulonephritis. Lhotta[20] demonstrated that in various types of glomerulonephritis tubular epithelial cells show de novo ICAM-1 expression, which tends to be on luminal side. However, the role of tubular ICAM-1 expressed at luminal side of

tubular epithelium is not clear, Hill[6] suggest that in may be due to nonspecific reabsorption of ICAM-1 filtered throught a leaky glomerular barier. Wuthrich[24] suggest that ICAM-1 expression in apicolateral part of proximal tubular epithelium depends on reabsorbtion of proteins or their fragments (e.g. antigens, virus, etc.) from the primary urine. The activated tubular epithelium may than be able to present these antigens to lymphocytes located between tubular epithelial cells[25].

In summary, our study indicates that significant alterations in renal expression of ICAM-1/LFA-1 are observed in proliferative and non-proliferative glomerulopathies. In both MGN and MesProGN groups the evident positive correlations between tubulointerstitial expression of ICAM-1/LFA-1 and renal interstitial fibrosis suggest that the intensity of tubulointerstitial staining of both studied adhesion molecules may be a valuable marker of interstitial damage in these cases.

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