β_2 -Microglobulin as an Indicator of Interstitial Cell Infiltration in IgA Nephropathy

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Dear Sir,

β_2 -Microglobulin (β_2 -MG) is a low-molecular-weight protein of 11,800 daltons composed of 99 amino acids with a single disulfide bridge. Normally, about 95% of free β_2 -MG can pass through the glomerular filter barrier, and about 99.9% of the filtered β_2 -MG can be reabsorbed and catabolized by the proximal tubular cells. Increased urinary excretion of β_2 -MG is observed as a result of diminished tubular reabsorption, when the proximal tubules are damaged [1]. On the other hand, it has been recognized that the grade of renal tubulointerstitial lesions correlates with renal function [2-5] and constitutes an important factor in renal diseases. In IgA nephropathy, localization of β_2 -MG in the renal tissues and its significance have not been elucidated. In the present study, we have investigated whether the localization of β_2 -MG in the renal tissues is an indicator of interstitial cell infiltration in patients with IgA nephropathy.

This study included 36 renal biopsies from IgA nephropathy diagnosed by histological studies with light, immunofluorescent and electron microscopy and 12 renal biopsies from patients who had mild microscopic hematuria without proteinuria, renal dysfunction or histological renal involvement as controls. The sequential frozen sections (2- μ m) were stained using indirect immunofluorescence, followed by periodic acid-Schiff (PAS) staining. The entire surface of the biopsy specimens stained with PAS was evaluated to determine the surface

area occupied by interstitial cell infiltration and then assessed semiquantitatively in three categories: grade I, segmental cell infiltration in less than 10% of the interstitium; grade II, cell infiltration in less than 50% of the interstitium over grade I; grade III, cell infiltration in more than 50% of the interstitium. Immunofluorescent study was performed by indirect immunofluorescent staining using anti-human β_2 -MG monoclonal antibody (Dakopatts, Denmark) as primary antibody.

In control kidneys, β_2 -MG was found to be localized in the glomerular capillary walls and peritubular capillaries as previously described [6]. In patients with IgA nephropathy, β_2 -MG in glomeruli was localized in the same areas of control kidneys and is independent on the degree of proteinuria. However, the localization of β_2 -MG in the proximal tubules of nephrotic patients was increased compared with those with proteinuria of < 1.0 g/day. According to the presence of β_2 -MG, we divided all patients into two groups. Group 1 consisted of 24 patients with β_2 -MG deposition in the renal tissue and group 2 of 12 patients without renal β_2 -MG deposition.

The average age of group 1 was statistically higher than that of group 2 (43 ± 7 vs. 28 ± 6 , $p < 0.05$). No significant difference in the degree of proteinuria and hematuria was observed between the groups. The average values of creatinine clearance in both groups were 78.2 ± 12.5 and $82.5 \pm$

25.1 ml/min, respectively, which showed no statistically significant difference. Urinary β_2 -MG concentration was significantly higher in group 1 than in group 2 (682 ± 49 vs. 248 ± 35 ng/ml, $p < 0.01$).

In order to elucidate the relationship between interstitial cell infiltration and renal β_2 -MG deposition, we compared renal biopsy specimens from the patients of group 1 using light microscopy and immunofluorescent microscopic analysis. As shown in figure 1, β_2 -MG deposition was observed in the same areas of cell infiltration in the renal interstitium in the patients of group 1. In addition, we examined the relationship between the grade of interstitial cell infiltration and urinary β_2 -MG concentration. In patients with grade III, urinary β_2 -MG concentration was significantly increased compared with the patients with grade I and II (fig. 2). In 2 of 22 patients with normal ranges of urinary β_2 -MG concentration, both renal β_2 -MG deposition and interstitial cell infiltration were observed.

Although an increase in urinary β_2 -MG levels is reported to be very useful for the diagnosis of tubulointerstitial involvement, urinary β_2 -MG measurement does not always provide evidence of the absence of tubulointerstitial changes in the normal range. Suzuki et al. [7] reported that the immunohistochemical study of renal β_2 -MG deposition is more reliable than the determination of urinary β_2 -MG concentration to identify renal dysfunction and renal injuries,

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1,200

1,000

800

600-

400

200

Interstitial cell infiltration

Fig. 1. Indirect immunofluorescent micrograph showing localization of β_2 -MG in the same area of cell infiltration in a patient with IgA nephropathy. $\times 200$.

Fig. 2. Relationship between grade of interstitial cell infiltration and urinary β_2 -MG concentration in patients with IgA nephropathy. Grade of interstitial cell infiltration was

determined from I to III as described in Methods. * $p < 0.05$ vs. stage I; ** $p < 0.01$ vs. stage I.

especially the presence of tubulointerstitial changes, in various renal diseases.

The present study first demonstrated that immunohistochemical study of renal β_2 -MG deposition and measurement of urinary β_2 -MG concentration are associated with interstitial cell infiltration, suggesting that β_2 -MG secreted by cells infiltrating into the renal interstitium may induce tubulointerstitial changes in patients with IgA nephropathy.

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