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Case Report

Focal Segmental Glomerulosclerosis: Unremitting Proteinuria of Long Duration as a Possible Etiology ?

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TANAKA, H., WAGA, S., NAKAHATA, T., ONODERA, N. and MONMA, N. *Focal Segmental Glomerulosclerosis: Unremitting Proteinuria of Long Duration as a Possible Etiology ?* Tohoku J. Exp. Med., 2000, **192** (2), 157-163 —— A Japanese boy aged 9 years referred to our hospital because of steroid-resistant proteinuria. He had a 6-year history of unremitting proteinuria and was diagnosed as having minimal-change disease (MCD) by the repeated renal biopsies performed at the age of 3.5 years and 8.5 years, respectively. His proteinuria fluctuated ranging from 115 mg/100 ml to 645 mg/100 ml, and serum total protein ranged from 59 g/liter to 63 g/liter. The third renal biopsy at the presentation also revealed MCD. Thereafter he was treated with an anti-thrombocyte agent combined with an angiotensin converting enzyme inhibitor. Despite unremitting proteinuria of long duration, he did not have any complaints. At the age of 11.5 years, severe tubulointerstitial lesion was observed in the fourth renal biopsy. The fifth renal biopsy 6 months after the fourth finally revealed the lesion of focal segmental glomerulosclerosis (FSGS). Although the interpretation of his repeated renal biopsies were considered to be limited, these clinical observation suggested that his unremitting proteinuria of long duration might have been attributed to subsequent progression to FSGS. ———— focal segmental glomerulosclerosis; possible etiology; sequential renal biopsy; unremitting proteinuria of long duration

Primary focal segmental glomerulosclerosis (FSGS) is the histologic lesion associated with unfavorable outcome in patients with proteinuria (Rydel et al. 1995). Also, the frequency of FSGS in children with asymptomatic proteinuria has been reported to be not so rare (Yoshikawa et al. 1991). Although the

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etiology of FSGS is still unknown, persistent proteinuria itself is sometimes attributed to the development of FSGS lesion (Ichikawa and Fogo 1996), as to enhanced proteinuria of long duration is thought to be harmful to the interstitium, and that the tubulointerstitial inflammation results in subsequent glomerular alteration (Benigni et al. 1995). Hence, unremitting proteinuria of long duration may cause FSGS in the selected patient.

We encountered a Japanese boy with a 9-year history of steroid-resistant proteinuria who was finally diagnosed as having FSGS. His repeated renal biopsy findings: from the minimal-change disease (MCD) to the MCD with tubulointerstitial nephritis, and subsequently to the FSGS, suggested that his unremitting proteinuria of long duration was possibly attributed to development of FSGS. Although the interpretation of the repeated renal biopsies in this case might be limited, these clinical observation is interesting.

Case Report

A 9-year-old boy with a 6-year history of persistent isolated proteinuria was referred to our hospital because of steroid-resistant proteinuria. At the age of 5 months, he had experienced infantile spasms, and which had been successfully treated with adrenocorticotropic hormone. No mental retardation or electroencephalograph abnormalities remained. When he was 3 years old, a significant proteinuria (approximately 100 mg/100 ml) was noted by chance. Percutaneous renal biopsy performed at the age of 3.5 years revealed MCD. Because of non-nephrotic range proteinuria, he was observed closely at a regional hospital. Thereafter, he was well except for proteinuria. Hematuria was not present throughout the clinical course. Since the proteinuria gradually increased to the ranges from 200 mg/100 ml to 300 mg/100 ml, he received a repeated renal biopsy at the age of 8.5 years, and which also revealed MCD without interstitial lesion. Immunofluorescence showed no evidence of immunocomplex deposition. Although prednisolone therapy (1.5 mg/kg) was started, the treatment was not effective for his proteinuria. Then prednisolone was tapered, and he was referred to our hospital.

On admission, his body temperature was 36.8°C and blood pressure was 120/70 mmHg. No skin or mucosal lesions were observed. Physical examination was unremarkable. Urine analysis showed a specific gravity of 1.020, 24-hour-protein excretion of 2.4 g and 3 red blood cell sediments per high-powered field. Urinary β_2-microglobulin (β_2-MG) at the presentation was 146 μg/liter (normal $<$ 300 μg/liter). Laboratory studies revealed the following abnormal results: erythrocytes sedimentation rate, 30 mm per hour; serum total protein, 5.9 g/100 ml; albumin, 3.4 g/100 ml and total cholesterol, 340 mg/100 ml. Normal laboratory results included leukocyte count, hemoglobin concentration, hematocrit, thrombocyte count, sodium, pottasium, chloride, calcium, urea nitrogen (11 mg/100 ml), creatinine (0.6 mg/100 ml) and uric acid. Immunological tests revealed the

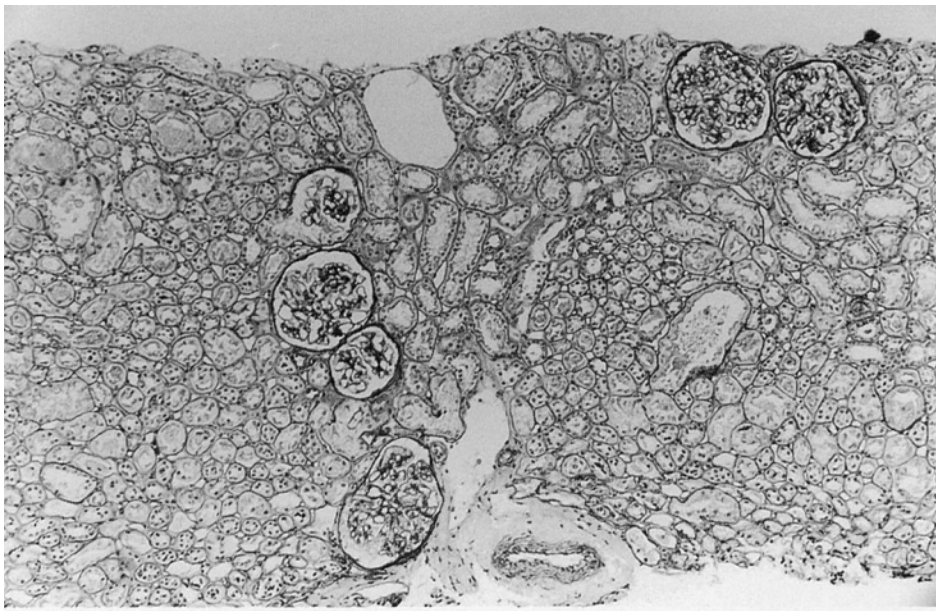

Fig. 1. The third renal biopsy (left side) at the age of 9 years. Minor glomerular abnormalities without tubulointerstitial lesion are seen. No glomerulus with sclerosis or tuft adhesion was observed in the specimen (periodic acid-Schiff, $\times 100$).

following values: immunoglobulin G (IgG), 634 mg/100 ml; IgA, 210 mg/100 ml; IgM, 256 mg/100 ml; IgE, 11 U/ml (normal range, 100-400 U/ml); C_3, 128 mg/100 ml (52-77 mg/100 ml); C_4, 42 mg/100 ml (17-44 mg/100 ml) and hemolytic complement activity (CH_{50}), 45.0 U/ml (30-40 U/ml). Anti-nuclear antibody was not present. Creatinine clearance (Ccr) was 119 ml/minutes. The selectivity index of proteinuria was 0.18.

A percutaneous renal biopsy was performed because of steroid-resistant proteinuria. Portion of 33 glomeruli were seen by light microscopy of periodic acid-Schiff (PAS) stained sections. The glomeruli showed minor glomerular abnormalities. No sclerotic glomerulus was observed in the specimen including the corticomedullary region. The interstitium was free from infiltrates or tubular atrophy (Fig. 1). There were no vascular changes to suggest underlying systemic vasculitis. Immunofluorescence revealed only a trace of IgM in the mesangium. Electron microscopic studies showed only effacement of epithelial foot processes.

Then, he was followed at outpatient clinic with an anti-thrombocyte agent combined with an angiotensin converting enzyme inhibitor administration. Despite the treatment, his proteinuria (approximately 300 mg/100 ml) fluctuated and persisted, but he did not have any complaints.

Because of persistent proteinuria, the fourth and the fifth renal biopsies were performed 18 and 24 months after the third renal biopsy, respectively. The specimen obtained by the fourth renal biopsy revealed MCD with severe tubulointerstitial nephritis. Portion of 24 glomeruli were seen by light microscopy of PAS-stained sections. A large region of the interstitium showed

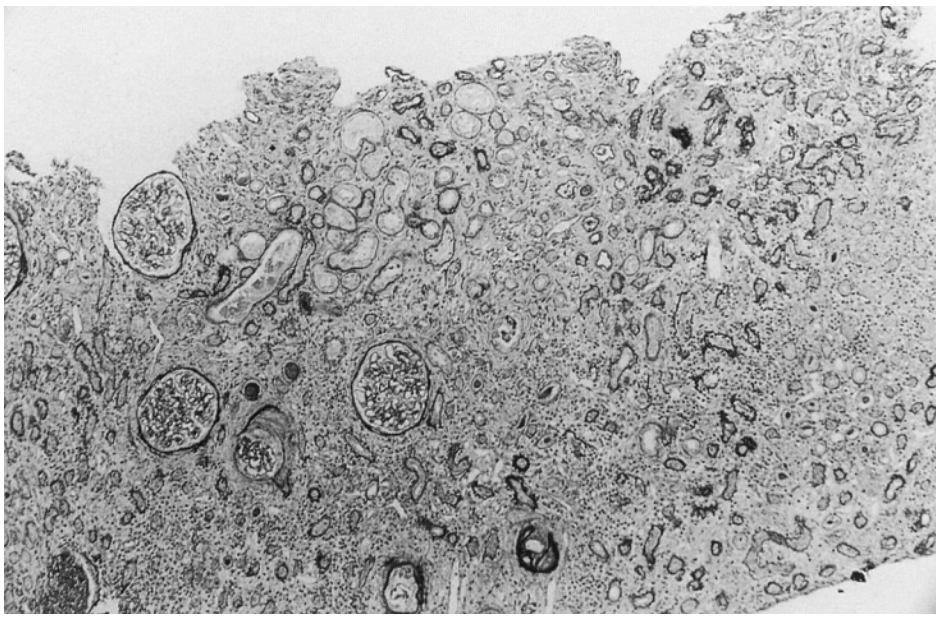

Fig. 2. The fourth renal biopsy (left side) at the age of 10.5 years. The interstitium demonstrating prominent mononuclear cells infiltrates is seen. Some glomeruli in the lesion showed global sclerosis/hyalinosis and periglomerular thickening (periodic acid-Schiff, ×100).

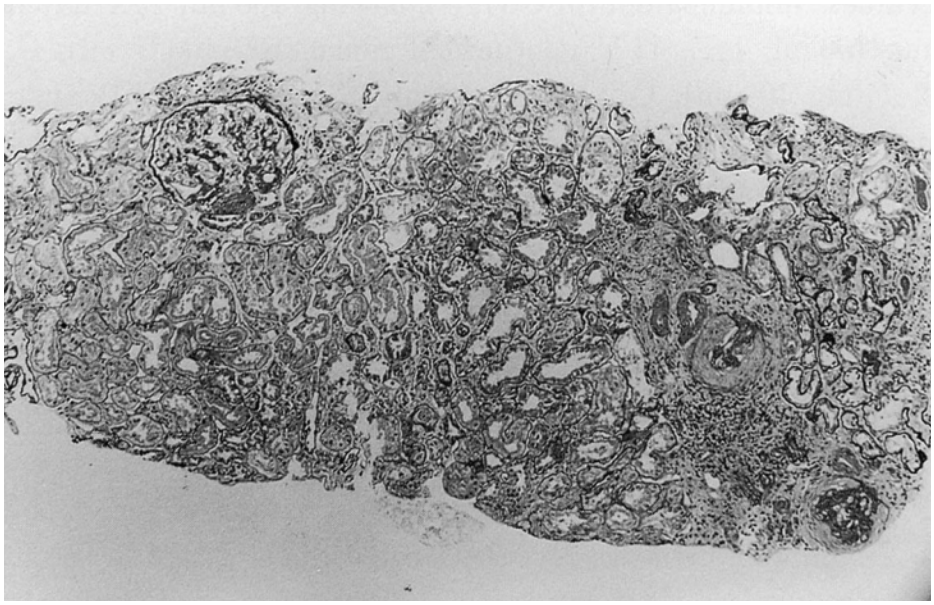

Fig. 3. The fifth renal biopsy (right side) at the age of 11 years. Glomeruli involved with segmental or global sclerosis are seen. Tubulointerstitial changes consisting with mononuclear cells infiltrates and tubular atrophy are also seen (periodic acid-Schiff, ×100).

infiltrates of mononuclear inflammatory cells associated with tubular atrophy (Fig. 2). Eosinophilic infiltration was not present. Global sclerosis and periglomerular thickening were observed in 5 (21%) and 9 (38%) glomeruli in the specimen, respectively. The remaining 10 glomeruli showed minor glomerular

abnormalities.

The light microscopic specimen obtained by the fifth renal biopsy revealed FSGS: 6 out of 22 glomeruli (27%) observed showed the lesion (Fig. 3). There were severe tubular atrophy and interstitial fibrosis. Immunofluorescence showed mesangial deposits of IgM (1+).

At the latest observation, laboratory studies revealed the following: serum total protein 6.2 g/100 ml, albumin 3.6 g/100 ml, total cholesterol 210 mg/100 ml, urea nitrogen 13 mg/100 ml and creatinine 0.4 mg/100 ml. Urine analysis showed a specific gravity of 1.030, 24-hour-protein excretion of 2.2 g and 5 red blood cell sediments per high-powered field. Urinary β_2-MG remained within the normal values of 115 μg/liter. The value of Ccr increased to 156 ml/minutes at that time. Although another course of corticosteroid or immunosuppressant therapy was often proposed, the family refused it. Since an increase level of the Ccr may reflect glomerular hyperfiltration of the patient, he is observed closely at the outpatient clinic thereafter.

Discussion

The diagnosis of FSGS is often difficult to establish because of the focal nature of FSGS (Ichikawa and Fogo 1996). Hence, the importance of sample size in the interpretation of the renal biopsy specimen has been reported (Corwin et al. 1988). In approaching the diagnosis of a focal disease such as FSGS, a biopsy sample of 20 glomeruli is the minimum which is necessary to confidently exclude focal disease (Corwin et al. 1988). In the present case, he was observed closely under the diagnosis of MCD for the first 6 years from the initial presentation. It is considered that the probability of having FSGS as an initial lesion in our patient cannot be excluded. However, the lesion suggesting FSGS in our patient was not defined from the repeated renal biopsies performed throughout a 6-year clinical course of isolated proteinuria. Also, the third renal biopsy specimen obtained in our hospital revealed 33 glomeruli of MCD including the corticomedullary region, and the number of glomeruli was thought to be enough for the interpretation (Corwin et al. 1988). While, the latest 2 biopsies containing more than 20 glomeruli easily revealed an interstitial lesion and a FSGS, respectively. Thus, it is thought that the probability of having FSGS as an initial lesion in our patient is relatively low.

Roos et al. (1987) reported two cases of FSGS associated with congenital microcephaly, infantile spasms, psychomoter retardation as a new syndrome. However, infantile spasms was successfully treated with the anti-epileptic therapy. Neither microcephaly nor psychomoter retardation were seen in our patient. Hence, the diagnosis of this new syndrome in our patient is unlikely.

The glomerular hypertrophy in children with MCD has been reported to be a key to subsequent progression to FSGS (Fogo et al. 1990). Although precise evaluation of the glomerular hypertrophy was not done in our patient, no clear

glomerular hypertrophy was observed in the sequential renal biopsies.

It has been reported that enhanced proteinuria of long duration is harmful to the interstitium, and that the tubulointerstitial inflammation results in subsequent glomerular alteration (Benigni et al. 1995). According to the sequential renal biopsy findings in our patient, the interstitial lesion is apparently important, since the lesion seemed to be an initial event for the subsequent progression to FSGS. No causative etiology, except for unremitting proteinuria of long duration, for his tubulointerstitial lesion was observed. He did not receive ciclosporin therapy for his proteinuria (Habib and Niaudet 1994). Also, the clinical course as well as the lack of eosinophilic infiltrates indicated that other explanations for the tubulointerstitial lesion, such as infection or drug-induced hypersensitivity reaction (Tanaka et al. 1997, 1999) were unlikely. Therefore, although the cause of tubulointerstitial lesion in our patient remains to be elucidated, unremitting proteinuria of long duration may play a role in the histological alteration, and that the interstitial lesion may have attributed to subsequent progression to FSGS (Benigni et al. 1995).

However, it has also been reported that unremitting proteinuria of long duration may not always lead to histopathological progression in the selected patients with persistent proteinuria (Garza et al. 1999; Tanaka et al. 2000). This discrepancy remains to be elucidated in the future. Further reports to describe similar cases are needed.

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