A Case of Early-Stage Diabetic Nephropathy Complicated by Minimal Change Nephrotic Syndrome Treated with Cyclosporin A

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Dear Sir,

In non-insulin-dependent diabetes mellitus, an increase in urinary albumin excretion is predictive of clinical proteinuria [1, 2]. However, if urinary protein excretion is increased suddenly in a patient with microalbuminuric diabetic nephropathy, a complication by an idiopathic glomerulonephritis or a secondary nephritis, such as drug-induced nephritis, must be suspected. We report here a case of microalbuminuric diabetic nephropathy complicated by minimal change nephrotic syndrome (MCNS) and effectively treated with cyclosporin A. A 62-year-old man was admitted to Fujitsuna Hospital in 1994 to undergo rehabilitation for hemiparesis due to cerebral infarction which occurred in 1985. He had been diagnosed as having diabetes mellitus in 1990, and treated with glibenclamide (1.25-5.0 mg/day, per os). His serum glucose concentration had been maintained under 200 mg/dl, and renal function had been within the normal range. Only microalbuminuria had been detected. After admission, on 24 August 1994, his medication was changed from glibenclamide to acarbose (300 mg/day, per os). Two weeks later, urinary protein excretion was increased suddenly and he developed nephrotic syndrome. Potential causative drugs, such as NSAIDs and antibiotics, had not been administered. Physical examination revealed facial and lower extremity edema, an increase in body weight, slight lung congestion, and mild cardiomegaly. His blood pressure was within the normal range and neither fever nor a heart murmur were present. Ultrasonography demonstrated normal kidney size and no pyelocaliectasis. His hemoglobin concentration was 12.6 g/dl and hematocrit was 38.5%. His remaining laboratory values were as follows: white blood cell count 4,600/mm³, platelet count 14.3×10^4 /mm³, serum blood urea nitrogen concentration 20.6 mg/dl, creatinine 0.9 mg/dl, serum uric acid 4.7 mg/dl, serum total protein 4.9 g/dl, serum albumin 2.7 g/dl, serum

total cholesterol 240 mg/dl. Liver function test and serum electrolytes were normal. Fasting blood glucose concentration was 102 mg/dl and hemoglobin A_{1c} was 5.6%. Urinary protein excretion was 11 g/day. However, hematuria, pyuria and oliguria were not observed. Antinuclear antibodies were not detected and serum complement was within normal limits.

A percutaneous renal biopsy was performed 14 days after the onset of nephrotic syndrome. On light microscopic examination, mesangial matrix increased slightly without crescent, adhesion to Bowman's capsule and increase in glomerular cells. Tubuli were partially atrophic and there was slight leukocyte infiltration in the interstitium.

Immunofluorescent study did not detect glomerular deposition of IgG, IgA, IgM, C3, C_{1q}, fibrinogen. On electron microscopic examination, the glomerular basement membrane appeared diffusely thickened and diffuse foot process effacement and increased microvillus formation were observed (fig. 1).

In this case, it was suspected that nephrotic syndrome was induced by drugs because of its sudden onset. The only drug newly administered within 1 month of the onset of nephrotic syndrome was acarbose. However, an allergic reaction against acarbose was not shown, because a lymphocyte stimulating test using acarbose was negative. In this case, it was unlikely that nephrotic syndrome was caused by diabetic nephropathy, because his blood sugar concentration had been well controlled, little proteinuria had been detected until the onset of nephrotic syndrome, and renal histologic change was mild. Thus he was diagnosed as having early stage diabetic nephropathy complicated by MCNS.

Edema was reduced by the administration of furosemide and an infusion of albumin, although massive proteinuria and decreased serum protein continued. In October 1994, he was prescribed cyclosporin A, because administration of glucocorticoids is known to increase the frequency of cerebral

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infarction and worsen the control of diabetes. His clinical course is shown in figure 2.

Proteinuria was gradually decreased, serum protein concentration was normalized and edema disappeared. His diabetes was well controlled without medication after the onset of nephrotic syndrome.

Impaired size and charge selectivities in the glomerular capillary wall are considered to be the major pathogenic mechanisms of proteinuria in diabetic nephropathy [3]. Changes in the glomerular capillary walls, usually thickening and sometimes partial thinning [4], and mesangial expansion are observed in the proteinuric stage. In the present case, the onset of nephrotic syndrome was unusual in the course of diabetic nephropathy because the patient was in the microalbuminuric diabetic nephropathy state. Although we cannot find any other reports of diabetic nephropathy complicated by MCNS, it is likely that diabetic nephropathy is occasionally complicated by idiopathic glomerular diseases. Because proteinuria gradually increases during the long time course of common diabetic nephropathy, histologic diagnosis by renal biopsy is required when the diabetic patient suddenly manifests massive proteinuria.

Cyclosporin A is a potent immunosuppressive agent that suppresses both antibody- and cell-mediated immune reactions by inhibiting cytokine production and secretion by activated T cells [5]. In 1986, cyclosporin A was reported to be effective for the treatment of MCNS [6]. Both the

high efficacy and safety of cyclosporin A in treating MCNS, including steroid-resistant MCNS, have been reported [7, 8]. In cases of MCNS with high potential for side effects of steroids, such as this case, cyclosporin A is considered to be one of the most suitable therapeutic agents.

Fig. 1. Electron micrograph of part of a glomerulus. $\times 2,000$. Fig. 2. Summary of clinical course. Cys-A = Cyclosporin A (■); • = serum total protein; ▲ = urinary protein excretion.

References

- Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G: Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes* 1992;41:736-741.
- Mykkanen L, Haffner SM, Kuusisto J, Pyörälä K, Laakso M: Microalbuminuria precedes the development of NIDDM. *Diabetes* 1994;43: 552-557.
- Gall MA, Rossing P, Kofoed-Enevoldsen A, Nielsen FS, Parving HH: Glomerular size- and charge selectivity in Type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. *Diabetologia* 1994;37:195-201.
- Matsumae T, Fukusaki M, Sakata N, Takebayashi S, Naito S: Thin glomerular basement membrane in diabetic patients with urinary abnormalities. *Clin Nephrol* 1994;42:221-226.
- Borel JF: Mechanism of action of cyclosporin A and rationale for use in nephrotic syndrome. *Clin Nephrol* 1991 ;35:S23-30.
- Hoyer PF, Krull F, Brodehl J: Cyclosporin in frequently relapsing minimal change nephrotic syndrome. *Lancet* 1986;9:335.
- Collaborative Study Group of Sandimmun® in Nephrotic Syndrome (von Greffenried B, Feutren G, Rohmann C, Brodehl J, Meyrier A, Naudet P, Ponticelli C, Nüesch E, Leininger C, Miller C): Safety and tolerability of cyclosporin A (Sandimmun®) in idiopathic nephrotic syndrome. *Clin Nephrol* 1991;35:S48-60.
- Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, Ghio L, Lusvaggi E, Gusmano R, Locatelli F, Pasquali S, Castellani A, Casa-Alberighi OD: A randomized trial of cyclosporin in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993;43:1377-1384.

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