

Case Report

Two distinct FSGS lesions caused by distinct etiology confirmed in a single patient in pre- and post-transplantation

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Abstract: At the age of three yr, a male patient had surgical treatment for bilateral vesicoureteral reflux (VUR), and at the age of 19 yr, he developed nephrotic syndrome because of focal segmental glomerulosclerosis (FSGS). His renal function deteriorated despite treatment with temocapril and aspirin, and dialysis treatment was started when he was 19. After nine yr of dialysis, he received a living kidney transplantation from his 58-yr-old father, who had a long history of hypertension. A graft biopsy before perfusion showed moderate arteriolosclerosis. As urine protein increased to 2.15 g/d at 16 months after kidney transplantation, the graft biopsy was performed again. FSGS lesion with severe arteriosclerosis was recognized under light microscope, while the effacement of podocyte foot processes was seldom observed. The alteration of calcineurin inhibitor from cyclosporine to tacrolimus, combined with the new administration of angiotensin receptor antagonist (valsartan) and aldosterone receptor blocker, successfully decreased the amount of urine protein to 0.8 g/d within two wk. We considered that the present case showed two distinct types of FSGS lesions – one because of VUR and the other because of cyclosporine arteriopathy – in each native kidney and transplanted kidney.

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Persistent proteinuria is a poor prognostic factor for determining long-term graft survival in kidney transplant recipients (1, 2). The diagnosis and treatment of primary focal segmental glomerulosclerosis (FSGS) must be carefully conducted before kidney transplantation, because a high recurrence rate is known after kidney transplantation (3). Recurrence of primary FSGS is one of the major causes of proteinuria in recipients and usually occurs within one yr after transplantation

(4). Once FSGS relapses, the frequency of graft loss is high, from 40% to 50% (5, 6). Therefore, the correct diagnosis of primary FSGS before kidney transplantation is very important. Secondary FSGS lesions often develop in the progression of recurrent immunoglobulin A (IgA) nephropathy, chronic allograft nephropathy (7), and toxicity of calcineurin inhibitor (CNI) (8) after kidney transplantation. Because treatment varies according to the etiology of secondary FSGS, the correct

histologic diagnosis is required in cases with FSGS lesions. We report here a patient who showed two distinct types of FSGS lesions in different phases.

Case report

At the age of three, the patient was treated surgically for bilateral vesicoureteral reflux (VUR). After that, dilatation of bilateral ureter and pelvis developed and, beginning at the age of 11 yr, proteinuria appeared and gradually increased. At 19 yr, his excretion of urine protein rapidly increased to the nephrotic range (3.5 g/d). His serum creatinine was 2.2 mg/dL, and his GFR was 23.7 mL/min at that time. In the abdominal ultrasonography and CT scanning, the irregularity of kidney surface and thinning of the renal cortex were seen that supposed to the existence of renal

scarring. We have received informed consent concerning graft biopsy. Renal biopsy was performed to differentiate the glomerular diseases. Light microscopy showed focal segmental glomerular sclerosis with glomerular hypertrophy and the sludge of plasma components in Bowman's space. Many tubules were dilated and filled with colloid casts. The infiltration of inflammatory cells including lymphocytes, macrophages, and plasma cells was noticed in the interstitium with fibrotic change (Fig. 1A, B). Immunohistochemistry with anti-Tamm-Horsfall protein (THP) antibody revealed the positive findings at a part of tubules (probably distal tubules), tubular cast, and Bowman's space (Fig. 1C). Electron microscopy revealed the effacement of foot processes for about 50% of the length of the glomerular basement membrane. The administration of temocapril and aspirin was also

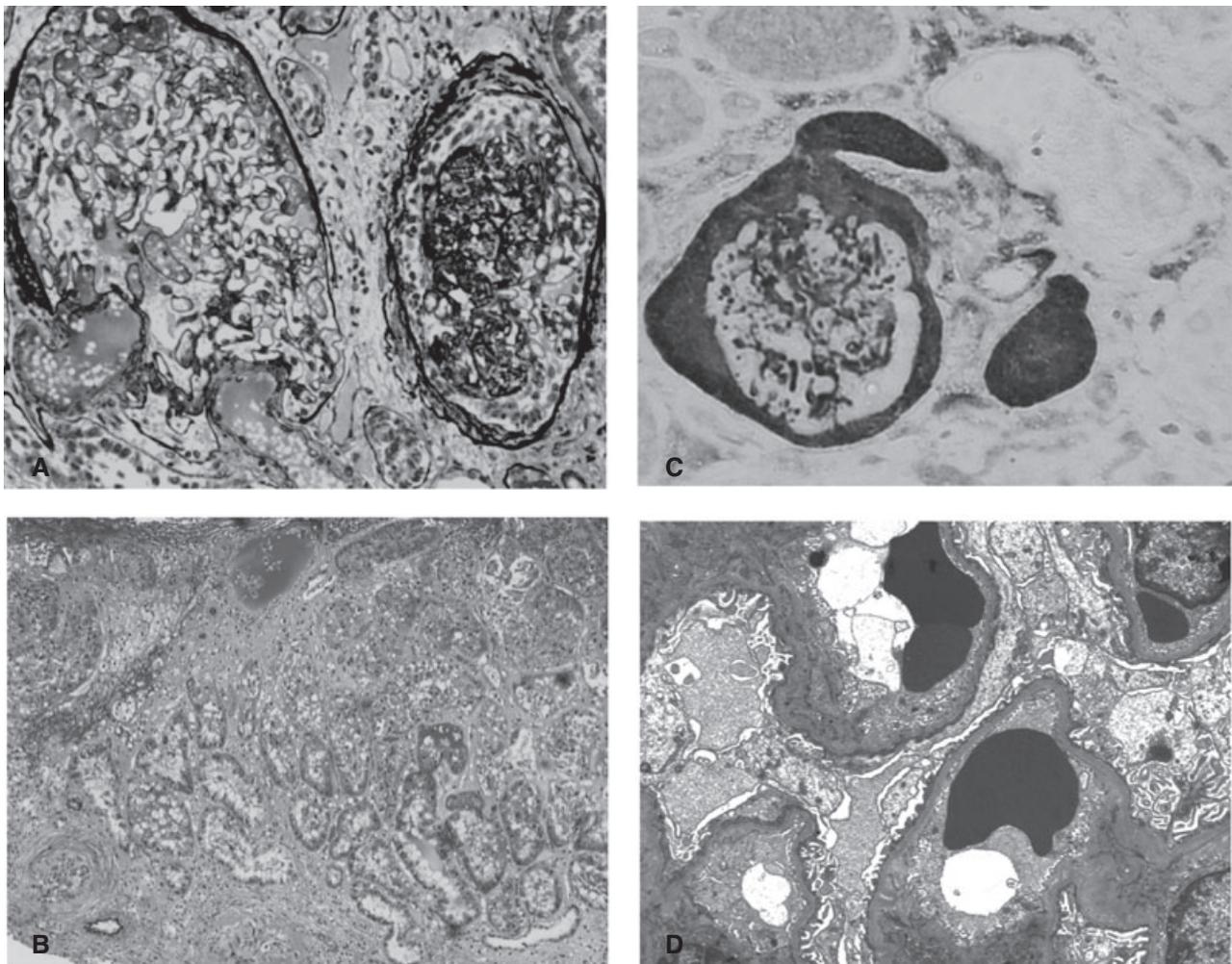


Fig. 1. Light micrograph and electron micrograph of the specimen from the first biopsy. (A) Focal segmental glomerular sclerosis with glomerular hypertrophy. (Pam masson trichrome staining $\times 200$); (B) The infiltration of inflammatory cells including lymphocytes, macrophages, and plasma cells was noticed in the interstitium with fibrotic change. (elastica masson trichrome staining $\times 125$); (C) A part of tubules, tubular cast, and Bowman's space are positive for Tamm-Horsfall protein (THP). (Immunohistochemistry with anti-THP antibody $\times 200$); (D) Foot process effacement was shown in about 50% length along glomerular basement membrane.

started. His proteinuria persisted, and his renal function deteriorated to that of the end stage of renal disease. At the age of 21 yr, regular hemodialysis began as a renal replacement treatment. At the age of 30, he received a kidney transplant from his 58-yr-old father. The donor was obese (BMI 32) but non-diabetic, and the control of his blood pressure had been poor (140~150/80~90 mmHg) for 17 yr despite anti-hypertension therapy. The donor's creatinine clearance was 144.4 mL/min, and he was negative for significant proteinuria. The blood types of the donor and recipient were compatible, and there were three mismatches in their human leukocyte antigen (HLA)-A, HLA-B, and DR typing. Graft biopsy before perfusion showed moderate arteriolo-hyalinosis (ah2) and minor glomerular abnormalities. Immunosuppressive treatment consisted of methylprednisolone, cyclosporine, mycophenolate mofetil, and basiliximab. The allograft functioned soon after the transplantation, but on the second post-operative day (POD2), his serum creatinine (s-Cr) rose from 2.1 to 4.4 mg/dL and urine output decreased. Because acute rejection was clinically suspected, methylprednisolone pulse therapy was started (500 mg/d, for two d). Hemodialysis was also necessary from POD3 to POD5. The urine output increased gradually, and s-Cr improved to around 2 mg/dL at POD 7. The diagnosis based on a protocol biopsy on POD40 was borderline changes, and there was no progression of arteriolar hyalinosis. The rates of hyalinized arterioles and arteries were 37% in one-h biopsy, and 7.5% in 40-d biopsy. The patient was discharged. His clinical course after transplantation is shown in Fig. 2. His blood pressure rose to 140/90 mmHg

on POD40, and anti-hypertensive therapy with manidipine was started on the same day. Sixteen months after transplantation, significant proteinuria reappeared and his excretion of urinary protein was 2.15 g/d. The trough levels of cyclosporine had been maintained within the ideal ranges throughout those 16 months before he was re-admitted. After readmission, he received another allograft biopsy. The biopsy specimens contained a total of six glomeruli. In one of them, the glomerular capillary walls were collapsed in a segment that exhibited foamy changes in podocytes. The severity of arteriohyalinosis (ah3) was progressed compared to that of biopsy before perfusion. Mild interstitial fibrosis and tubular atrophy, IF/TA I graded as Banff 2007 (Fig. 3A, B), was confirmed. Electron microscopy revealed no effacement of podocyte foot processes (Fig. 3 C). The deposition of IgM in the mesangial area was found in an immunofluorescent study. Cyclosporine was converted to tacrolimus, and both angiotensin receptor antagonist (valsartan) and eplerenone were also administered (Fig. 4). This led to a decrease in his urine protein level from 2.15 g/d to 0.8 g/d within two wk.

Discussion

It is most interesting that distinct types of FSGS lesions provably caused by different etiologies developed in a single patient. In native kidney biopsy, THP was detected at a part of tubular cast and Bowman's space by immunohistochemistry with anti-THP antibody, thus we considered that lasting VUR was the main cause of FSGS. The histologic findings of his native kidney were

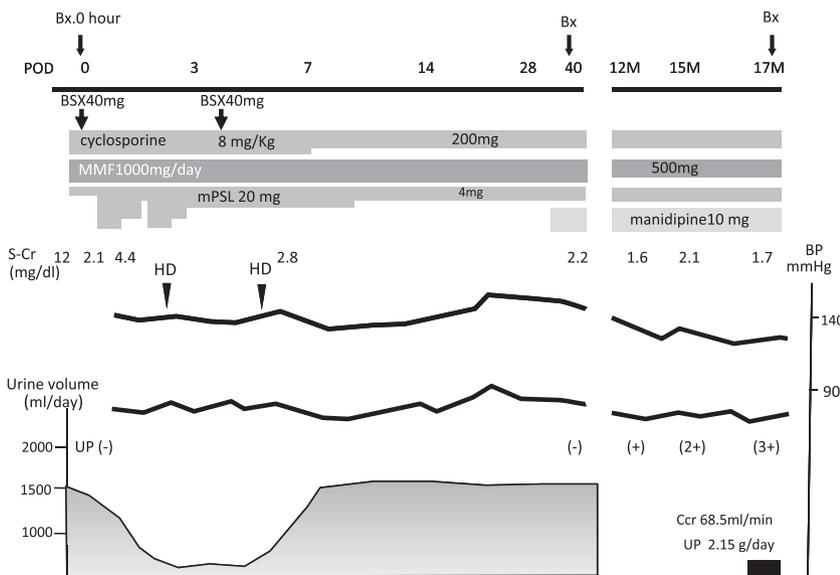


Fig. 2. Clinical course after renal transplantation. BSX, basiliximab; MMF, mycophenolate mofetil; mPLS, methylprednisolone; s-Cr, serum creatinine concentration; HD, hemodialysis; UP, urinary protein; Ccr, creatinine clearance.

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thought to be compatible with reflux nephropathy from glomerular and interstitial changes. Patients with VUR often develop with FSGS. A histologic review of 86 pediatric patients with VUR found perihilar FSGS in 20%. (9) Although the exact mechanisms leading to the development of this complication are unknown. Recent study revealed that lengthening of glomerular capillaries in young patients with VUR is a compensatory reaction to hyperfiltration. And the appearance of capillary expansion, podocyte detachment, and/or tuft adhesion to Bowman's capsule are indicators of renal prognosis in patients with VUR. These changes may lead to FSGS because of podocyte injury in patients with VUR. (10) In general, the effacement of more than 80% of podocyte foot processes is the morphological marker of primary FSGS and, in other ways, the distribution of foot process effacement is usually less than 30% in secondary FSGS (11). The electron microscopic findings showed about 50% distribution of the effacement of foot processes along the glomerular basement membrane (Fig. 1D) in the native kidney biopsy. An episode biopsy 16 months after transplantation revealed very little effacement of foot processes (Fig. 3C). In 16-month allograft biopsy, FSGS lesion was noticed with collapsed glomerular capillary and proliferation of podocytes. We thought FSGS lesion was related to CNI toxicity because we could find severe arteriolo-hyalinosis and degenerative changes in arteriolar smooth muscles suggesting cyclosporine associated arteriopathy. We considered that original donor arteriolo-hyalinosis was severe because of pre-transplant hypertension and that it was worsened by cyclosporine and post-transplant hypertension. The rapid decrease in urine protein after the additional therapy, including angiotensin receptor antagonist (valsartan) and eplerenone, seemed to support our decision.

Various etiological factors of secondary FSGS have been reported. Well-known causes of secondary FSGS include viral infections such as HIV, HCV, or parvovirus; heroin use; obesity; and other conditions, such as plasma cell proliferative disorders, urinary reflux, chronic rejection (7), and the conditions leading to nephron loss (12). Pregnancy (13) and thrombotic microangiopathy (14), the pathogenic state of which causes endothelial damage, sometimes produces FSGS lesions. FSGS lesions also are reported in graft biopsy (7). Among them, cyclosporine A associated arteriopathy (CAA) is believed to be a cause of secondary FSGS lesions. Cosio et al. (7) confirmed secondary FSGS lesions in 30% of chronic allograft nephropathy and noticed a strong correlation with CAA

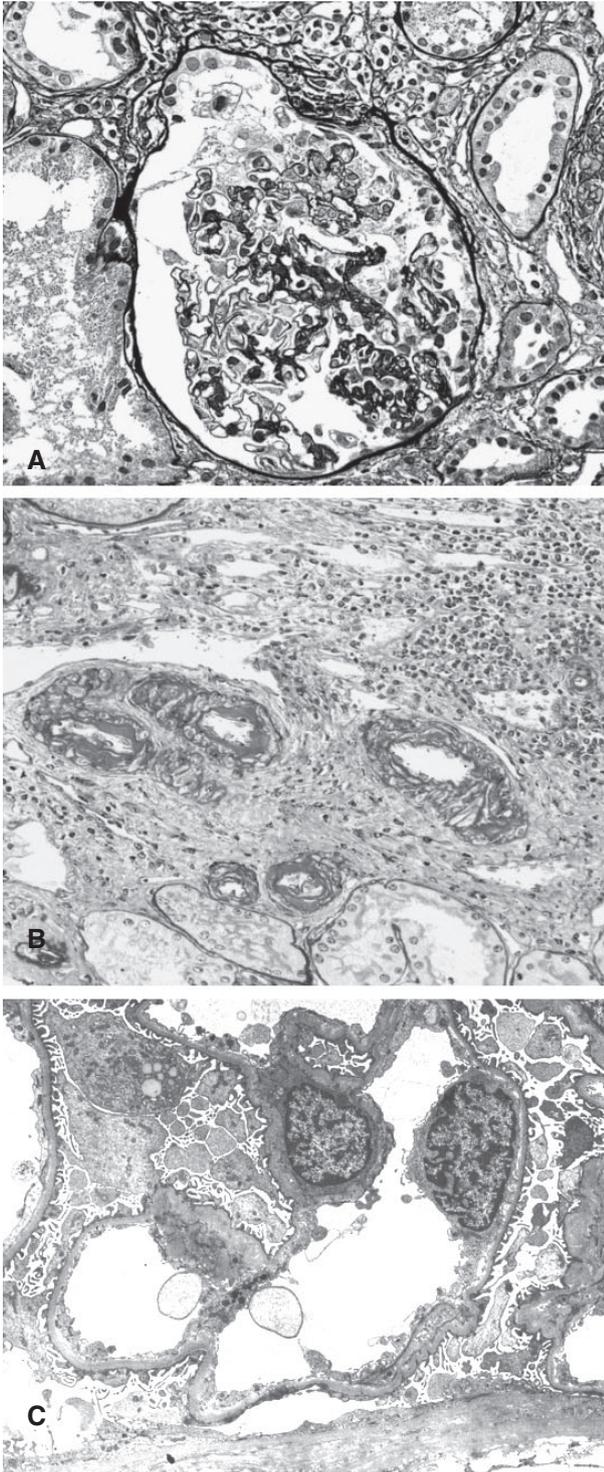


Fig. 3. Light micrograph and electron micrograph of the specimen from the biopsy 17 month after renal transplantation. (A) Glomerular capillary walls collapsed in segmental section with foamy change of podocytes. (Pam masson trichrome staining $\times 250$); (B) The severe arteriosclerosis (ah3) and mild interstitial fibrosis and tubular atrophy, IF/TA I graded as Banff 2007 was confirmed. (PAS staining $\times 200$); (C) The electron microscopy revealed no effacement of podocyte foot processes.

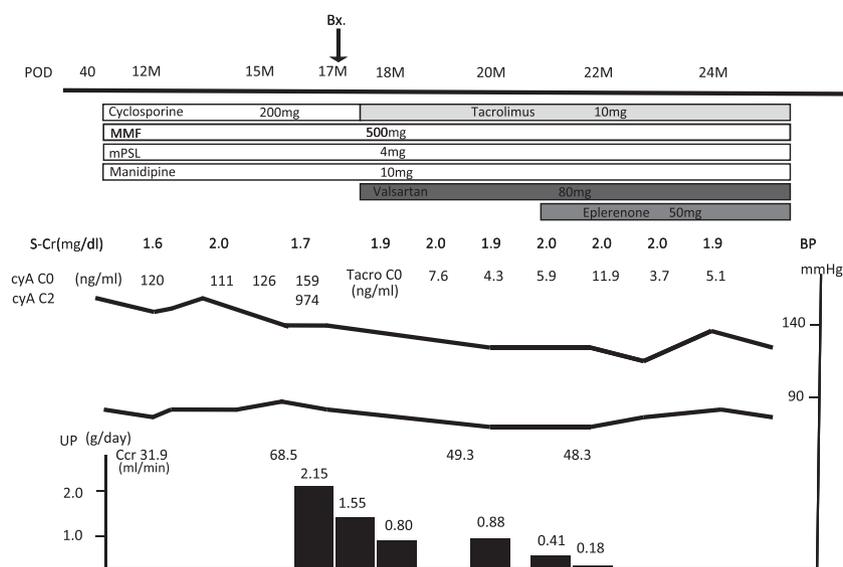


Fig. 4. Clinical course after allograft biopsy. BSX, basiliximab; MMF, mycophenolate mofetil; mPSL, methylprednisolone; s-Cr, serum creatinine concentration; UP, urinary protein; Ccr, creatinine clearance; CyA C0, cyclosporine fasting level after 12 h from last dose; CyA C2, cyclosporine concentration two h after the administration; Tacro C0 tacrolimus fasting level after 12 h from last dose.

Table 1. Graft biopsy cases with persistent proteinuria above 0.5 g/d after renal transplantation in our hospital

Histologic findings	n
Focal segmental glomerulosclerosis (FSGS) lesion (+)	9/86 (10.5%)
Acute rejection and recurrent FSGS	2
Recurrent IgAN	2
Acute rejection and thrombotic microangiopathy	1
Chronic rejection with arteriosclerosis	3
Chronic rejection and calcineurin inhibitor toxicity (arteriolopathy)	2

among their cases. In their review of 469 cases, Takeda et al. (15) reported that FSGS lesions were the most frequent glomerular lesions accompanied by CAA. In our graft biopsy cases with persistent proteinuria above 0.5 g/d, 9 (10.5%) of 86 cases presented FSGS lesions, and 5 (5.8%) of the 86 were associated with severe arteriolo-hyalinosis because of CAA or chronic rejection (Table 1). The true pathogenesis of CAA-associated FSGS lesions has not been resolved yet. In rodent models, it has been proved that chronic CsA nephrotoxicity, such as CAA and interstitial fibrosis, resulted in histologic damage from several mechanisms including hypoxia, free-radical production, and upregulation of transforming growth factor- β 1 (TGF- β 1) synthesis (16, 17). We suspect that glomerular damages, especially glomerular endothelial damages, from those mechanisms might lead to the appearance of FSGS lesions. Of course, glomerular hyperfiltration from nephron loss may

also be related to the formation of FSGS lesions. These lesions may be produced by the complex factors mentioned earlier.

Angiotensin receptor blocker (ARB) has a potential ability to inhibit the factors that cause such as hypoxia, free-radical formation, and glomerular hyperfiltration (18). In experimental models of chronic CsA toxicity, aldosterone is also thought to play an important role as a mediator of arteriopathy and interstitial fibrosis (19, 20). Feria et al. (20) reported that the reduction of TGF- β 1 production by spironolactone treatment could prevent kidney from CAA progression and interstitial fibrosis. Anti-aldosterone agents are also expected to work renoprotectively in humans (21, 22). In our case, the combination treatment of ARB and eplerenone seemed to show a beneficial effect on proteinuria because of de novo FSGS lesions associated with CAA.

We report here an intriguing case that showed two distinct FSGS lesions between pre- and post-transplantation. The combination therapy of ARB and eplerenone successfully reduced urine protein derived from FSGS lesions.

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