Journal of Nephropathology

De novo focal segmental glomerulosclerosis and kidney hypertrophy associated with progressive obesity after kidney transplantation

Tomo Suzuki[1*] , Masahiko Yazawa[1], Masataka Hasegawa[1], Daisuke Ichikawa[1], Naohiko Imai[1],
Hideo Sasaki[2], Tatsuya Chikaraishi[2], Junki Koike[3], Yugo Shibagaki[1]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan
[2]Division of Urology, Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan
[3]Department of Diagnostic Pathology, St. Marianna University School of Medicine, Kanagawa, Japan

ABSTRACT

Background: Obesity is an important problem associated with worsening cardiovascular disease and the progression of proteinuria in kidney transplant recipients. We describe a case of de novo focal segmental glomerulosclerosis (FSGS) associated with progressive obesity after kidney transplantation (KTx).
Case Presentation: A 41-year-old male patient underwent an allograft kidney biopsy because of nephrotic range proteinuria. The donor was his father who was aged 70 years at transplantation. In addition, there was a substantial difference in body weight (BW) between the recipient and donor. At 56 months after kidney transplantation, the patient's BW increased from 83.1 kg (BMI, 29.3 kg/m²) before kidney transplantation to 93.9 kg (BMI, 33.1 kg/m²). An allograft biopsy showed glomerular hypertrophy and focal segmental sclerotic lesions with partial epithelial cell hyperplasia. The histologic diagnosis was FSGS, not otherwise specified (NOS) variant. A comparison between the kidney volume before and after kidney transplantation, evaluated using volumetric computed tomography, revealed prominent kidney hypertrophy (1.77 times).
Conclusions: Our case demonstrated that de novo FSGS after kidney transplantation is induced by progressive obesity, as manifested by glomerular hypertrophy as well as kidney hypertrophy. This is a hyperdynamic state contributed to the pathogenesis of de novo FSGS. Our report is important to understand the pathogenesis of FSGS.

1. Background

Focal segmental glomerulosclerosis (FSGS) is an important cause of proteinuria and a quintessential podocyte disease (1). Primary FSGS often occurs in the early phase after kidney transplantation (KTx) because of a circulating factor in the recipient. In contrast, adaptive FSGS, also known as non-nephrotic syndrome, is associated with a hyperhemodynamic state, such as a single kidney, podocytopenia due to low birth weight, hypertension, and obesity (1- 4). De novo FSGS after kidney transplantation occurs in the chronic phase (5). Proteinuria among transplant recipients is one of the most important factors for allograft and patient survival (6). The causes of proteinuria related to an allograft

Corresponding author: Tomo Suzuki, M.D., PhD; Email address: t2suzuki@marianna-u.ac.jp

kidney include hypertension, recurrent kidney disease, and transplant glomerulopathy. The rate of graft survival in kidney transplantation has increased since the 2000s because of the use of immunosuppressive agents, such as basiliximab and mycophenolate mofetil, in addition to low dosing of a calcineurin inhibitor (CNI) (7). Therefore, the problem with allograft survival after kidney transplantation changed from acute rejection to chronic diseases, such as interstitial fibrosis/tubular atrophy and arteriosclerotic disease in obesity due to lifestyle, corticosteroid use, and CNI.

The body weight (BW) of recipients after kidney transplantation often increases due to use of immunosuppressive agents, including corticosteroids, and relaxed diet restrictions (8). Obesity is associated with the progression of proteinuria in kidney transplantation recipients (9). Furthermore, the allograft kidney, due to a single functional kidney, is susceptible to a hyperdynamic state. One of the characteristics of obesity-related glomerulopathy (ORG) is glomerular hypertrophy due to hyperfiltration (4). Subsequently, ORG transitions from glomerular hypertrophy to adaptive FSGS. After kidney transplantation, both kidney and glomerular hypertrophy occur (10).

We describe a case of de novo FSGS, not otherwise specified (NOS) variant with glomerular hypertrophy associated with progressive obesity after kidney transplantation. This case demonstrated both glomerular and prominent kidney hypertrophy based on volumetric computed tomography (CT). The present case suggests the pathogenesis of de novo FSGS to be a hyperdynamic state.

2. Case Presentation

A 41-year-old Japanese man with end-stage kidney disease (ESKD), who was on hemodialysis for one year, received an ABO-compatible living kidney transplant. The cause of ESKD was suspected as immunoglobulin (Ig)-A glomerulonephritis because of his history of tonsillitis. Furthermore, he had never developed edema. His birth history was unremarkable. His BW at discharge after kidney transplantation was 83.1 kg, and his body mass index (BMI) was 29.3 kg/m². (The BMI of the living-donor to permit kidney transplantation is 30 kg/m² or less in our facilities.) The donor was his 70-year-old father. The donor's BW was 65 kg (BMI, 23.0 kg/m²). The difference between the recipient and donor's BW was substantial. The patient did not have proteinuria at the 1-year protocol biopsy. Eighteen months after kidney transplantation, he showed mild proteinuria and no hypoalbuminemia. Therefore, we prescribed

Table 1. Main laboratory data at kidney biopsy of 56 months after KTx

Peripheral blood	
White blood cell (/μL)	7700
Hemoglobin (g/dL)	13.8
Platelet (×10⁴/μL)	23.9
Blood chemistry	
Total-Protein (g/dL)	6.4
Albumin (g/dL)	4.2
AST (IU/L)	16
ALT (IU/L)	18
BUN (mg/dL)	14.8
Cr (mg/dL)	1.96
eGFR (mL/min/1.73 m²)	32.2
Total-cholesterol (mg/dL)	202
Triglyceride (mg/dL)	167
Glucose (mg/dL)	93
HbA1C (%)	4.9
Urine tests	
Pro/OB	+/±
UPCR (g/g.cre)	2.12
Urinary sediment	
Red blood cell	Absent

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Pro, protein; occult blood; UPCR, urine protein to creatinine ratio.

an angiotensin II receptor blocker (ARB). However, proteinuria increased gradually, and kidney biopsy was performed 56 months after kidney transplantation. Laboratory test results are summarized in Table 1. The primary data revealed proteinuria (urinary protein level, 2.1 g/g creatinine) and mild renal dysfunction (serum creatinine level, 1.96 mg/dL) but no hypoalbuminemia (serum albumin level, 4.2 g/dL). Dyslipidemia was well controlled using two drugs, a statin and cholesterol transporter inhibitor (low-density lipid cholesterol level, 113 mg/dL). The area under the curve (0-12 hours) of tacrolimus was slightly low at 70.1 ng.h/mL (target concentration, 100-150 ng.h/mL). The patient's BW increased to 93.9 kg (BMI, 33.1 kg/m²). His systolic blood pressure at home was 120-130 mm Hg, which was well controlled with the ARB and calcium channel blocker. The lower extremities did not show edema.

In the 0-hour biopsy, glomerular hypertrophy and interstitial fibrosis (Figure 1A) were absent. The 1-year protocol biopsy showed glomerular hypertrophy, with a glomerular size >250 μm (Figure 1B). The episode biopsy performed 56 months after kidney transplantation showed glomerular hypertrophy and focal segmental sclerotic lesions with partial epithelial cell hyperplasia (Figure 1C). Endothelial cell proliferation and glomerular basement membrane thickening were subtle. Global
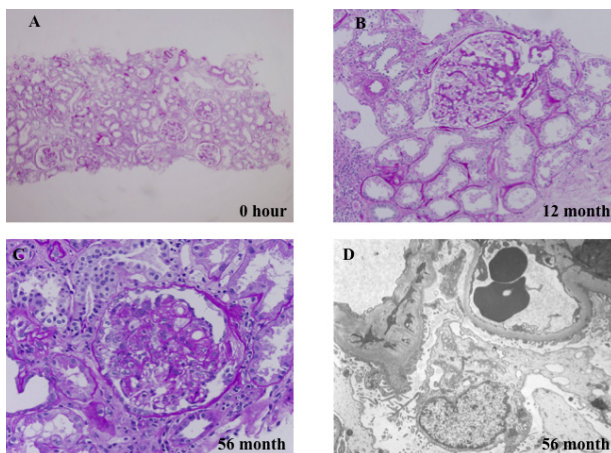
Figure 1. Kidney biopsy specimen. (A) Periodic acid-Schiff (PAS) staining shows no glomerular hypertrophy at the 0-hour biopsy; (B) PAS staining of the glomeruli shows glomerular hypertrophy at the 1-year protocol biopsy; (C) PAS staining of the glomeruli shows segmental sclerotic lesions with epithelial cell hyperplasia at the 56-month episode biopsy; and (D) electron microscopy of the glomeruli shows focal foot process effacement and focal podocyte detachment at the 56-month episode biopsy.

Figure 2. Volumetric computed tomography before and after transplantation. (A) Volume of the donor right kidney before transplantation is 123 541.1 mm^3, and (B) volume of the donor right kidney after transplantation is 153 847.7 mm^3. (C) Volume of the donor left kidney before transplantation is 132 322.3 mm^3, and (D) volume of the donor kidney after transplantation is 234 328.6 mm^3.

sclerosis included hyalinosis. However, hyalinosis of the arteriosclerosis was not observed. Immunofluorescence staining demonstrated positive results for IgM and C3 in the sclerotic lesions and negative results for IgG, IgA, and C1q. Electron microscopy revealed focal foot process effacement. Furthermore, focal podocyte detachment and non-electron dense deposit area were apparent (Figure 1D). The histologic diagnosis was FSGS, NOS variant. According to the clinical data, BW increased remarkably by 10.8 kg (BMI increased from 29.3 to 33.1 kg/m^2) after kidney transplantation. In addition, he did not develop hypoalbuminemia. Thus, the cause of FSGS was determined as progressive obesity. We compared the kidney size before and after transplantation using volumetric CT. The volume of the donor right kidney was 1.16 times greater: the kidney volumes before and after transplantation were 123 541.1 mm^3 and 153 847.7 mm^3, respectively (Figure 2A, 2B). In contrast, there was remarkable kidney hypertrophy, and the volume of the recipient kidney was 1.77 times greater. Volumes of the donor left kidney before and after transplantation were 132 322.3 mm^3 and 234 328.6 mm^3, respectively (Figure 2C, 2D). Therefore, we diagnosed the patient as having de novo FSGS and kidney hypertrophy associated with progressive obesity after kidney transplantation.

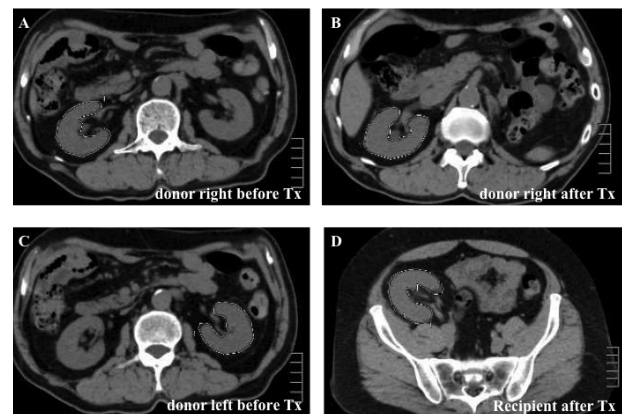After the diagnosis, the urinary protein level fluctuated from 2 to 5 g/g creatinine, and kidney function was gradually exacerbated. With the support of the transplant coordinator, we created an educational program that included nutritional education, and we lent the patient a pedometer for exercise. After participation in the education program, the patient's BW decreased by 2 to 3 kg; thus, we will continue this program.

3. Discussion

The present case demonstrated FSGS in a mildly obese patient after kidney transplantation. The patient's history did not include edema, and we suspected that the cause of ESKD was IgA glomerulonephritis. In addition, he did not develop hypoalbuminemia after kidney transplantation, and glomerular hypertrophy with FSGS over time and kidney hypertrophy were demonstrated by volumetric CT. Therefore, we considered that FSGS in this case was a secondary form of FSGS instead of primary recurrent FSGS.

FSGS is recognized as a podocyte disease. Recently, experimental studies have demonstrated the disruption of cross-talk between podocytes and endothelial cells, representing progressive glomerulosclerosis via podocyte loss (11). In humans, endothelial injury due to malignant hypertension induces FSGS in a remnant kidney after kidney donation (12). In transplant patients, the characteristic of de novo FSGS was marked hyaline arteriolosclerosis and appearance 2 years post-kidney transplantation (5). Additionally, de novo FSGS occurred 1.5 years after kidney transplantation and was induced by a calcineurin inhibitor, which was one of the causes of endothelial cell injury (13). However, arteriolosclerosis and endothelial injury in the present

case were unremarkable. Thus, the main cause of FSGS in the current case was not endothelial injury.

The primary characteristic of ORG is glomerular hypertrophy due to hyperfiltration. Early histological change in the kidneys of morbidly obese individuals revealed glomerular hypertrophy before the appearance of albuminuria (14). We observed glomerular hypertrophy before proteinuria in the present case. A recent case report mentioned that the kidney volume increased approximately 1.23 times after transplantation from one male patient to another male patient (10). The increased kidney volume is consistent with the fact that the estimated glomerular filtration rate (eGFR) after kidney donation was approximately 60% of the pre-transplant eGFR (15). Surprisingly, kidney volume after transplantation was 1.77 times in this case. The remarkable increase in kidney volume indicated the patient's hyperdynamic state. The mean BMI in ORG is reported as 41.7 kg/m² (4). Our patient was mildly obese (BMI 33.1 kg/m²). One of the reasons for this was only the one functional kidney. Glomerular hypertrophy could occur in moderately obese individuals with two kidneys (16). We considered that a mild increase of BW was susceptible to inducing a hyperdynamic state after kidney transplantation. The other reason for the mild obesity was the body size mismatch between the patient and donor. Previous reports have shown that kidney graft survival is associated with body size mismatch (17). Body size mismatch was probably associated with hyperfiltration. The present case involved a body size mismatch; the difference between the recipient and donor's BWs was 22 kg. Therefore, even mild obesity after kidney transplantation may be a risk factor for de novo FSGS, especially in the case of kidney transplantation with body size mismatch.

The use of selective marginal living donors has been increasing and achieved acceptable outcomes for donor renal function. However, recipient renal function may have a negative effect (18). A current case involved a 70-year-old non-marginal donor from Japan and conversely, a marginal donor from the Amsterdam Forum. Glomerular hypertrophy and FSGS were induced by podocyte loss because podocytes are highly differentiated cells with a minimum capacity to regenerate. Hodgin et al reported that the number of podocytes decreases with age (19). A normal allograft reduced the density of podocytes in more than two normal kidneys, and an allograft with transplant glomerulopathy reduced the density of podocytes in more than one normal allograft. Further, a low density of podocytes was associated with a reduced eGFR, glomerulosclerosis, and proteinuria (20). We did not calculate the number and density of podocytes in our case. However, we speculated that the number and density of podocytes might be insufficient. A marginal donor might be a risk factor of de novo FSGS due to podocytopenia.

We often evaluate FSGS using the Columbia classification, which has five variants (1). The variant of ORG is perihilar, that is, glomerulosclerosis around a vascular pole (1, 4). However, FSGS in our case was of NOS variant. Gupta et al reported that the rate of FSGS of NOS variant after kidney transplantation was high (70.3%) and associated with severe arteriolosclerosis (5). The detachment of podocytes around a urinary pole is caused by increased mechanical distending and shear forces (21). In our case, podocytes, except the vascular pole, may have been detached because the allograft kidney was prominently in a hyperdynamic state under non-physiological conditions.

4. Conclusions

The present case indicated that de novo FSGS after kidney transplantation is induced by progressive obesity, as manifested by glomerular hypertrophy as well as kidney hypertrophy. Not only an increasing BW but also a marginal donor and body size mismatch are important risk factors for FSGS after kidney transplantation. Therefore, mild obesity after kidney transplantation should be considered as a potential risk factor for de novo FSGS when these conditions exist.

Authors' contribution

TS wrote the manuscript. YM, MH, NI, HS, TC and YS were the patient's treating physicians. TS, DI and JK contributed histological interpretation. YM, NI and YS contributed by reviewing and revising the manuscript.

Conflicts of interest

The authors of this manuscript have no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication,

double publication) have been completely observed by the authors. The patient has given his informed consent regarding this case report.

Funding/Support

None.

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