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Renal allograft survival in transplant recipients with focal segmental glomerulosclerosis

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ABSTRACT

Introduction: The frequency that idiopathic focal segmental glomerulosclerosis (FSGS) recurs in renal allografts is reportedly 20-50%, but the epidemiology of secondary FSGS in this setting has scarcely been addressed.

Objectives: The aim of this study was to examine the incidence, etiology, and subtypes of FSGS in renal allograft recipients and allograft survival in recipients with FSGS.

Patients and Methods: As a retrospective review, we examined medical records of 359 consecutive renal allograft recipients (living donors, 329; cadaveric donors, 30). In 121 of these patients, allograft dysfunction or proteinuria prompted biopsies. We compared allograft survival in recipients with and without FSGS. We then determined histologic subtypes of FSGS using the Columbia classification and categorized FSGS as recurrent or *de novo*, and idiopathic or secondary.

Results: Of 121 subjects who were biopsied, six with inadequate specimens (<10 glomeruli) were excluded. Only 17 of those remaining (n=115) were diagnosed as secondary FSGS. Renal allograft survival did not differ significantly in patients with or without FSGS ($P=0.953$). Subtypes of FSGS were as follows; not otherwise specified (NOS; n=8), collapsing (n=5), cellular (n=2), and perihilar (n=2).

Conclusion: Secondary FSGS was observed in 14.5% of biopsies of renal allograft recipients and seemed no significant impact on allograft survival.

Implication for health policy/practice/research/medical education:

Focal segmental glomerulosclerosis (FSGS) was observed in 14.5% of biopsies of renal allograft recipients and subtypes of FSGS were as follows; not otherwise specified (47.1%), collapsing (29.4%), cellular (11.8%), and perihilar (11.8%). Secondary FSGS develops in renal allograft due to various etiology including rejection and calcineurin inhibitor nephrotoxicity in addition to glomerular hyperfiltration but seemed no significant impact on allograft survival.

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Introduction

Focal segmental glomerulosclerosis (FSGS) may develop in renal allografts for various reasons. It may recur or arise *de novo* and may be idiopathic or secondary. The incidence of recurring idiopathic FSGS in renal allografts is reportedly 20%-50% (1-6), with a 2.6% incidence of related allograft loss over 2.96 years (mean interval; 8.2% lost to follow-up) (4) or 12.7% loss in 10 years (95% confidence interval; 7.3-21.6) (7).

Secondary FSGS is rooted in a multiplicity of disorders, such as hyperfiltration (8), reduced renal mass (9),

reflux nephropathy (10), obesity (11-16), drugs (17-24), viruses (25-28), or glomerular disease [immunoglobulin A nephropathy (IgAN) (29) and lupus nephritis (30-32) in particular]. Renal allografts may be similarly affected, in conjunction with rejection (33-34), although the epidemiology of secondary FSGS has scarcely been addressed in this regard.

Objectives

The present efforts were focused on the following; 1) incidence and subtypes of FSGS in renal allograft

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recipients, 2) allograft survival in recipients with FSGS, and 3) nature of FSGS (recurrent or *de novo*, idiopathic or secondary).

Patients and Methods

Study design

Medical records of 359 consecutive renal allograft recipients (living donors, 329; cadaveric donors, 30) were reviewed in retrospect, all transplantations taking place at Jichi Medical University Hospital between January 2001 to December 2018. A total of 121 biopsies were performed, prompted by allograft dysfunction or proteinuria. Specimens with <10 glomeruli were grounds for exclusion. Qualifying recipients were grouped by FSGS status (presence or absence) to compare renal allograft survival.

Light microscopy served to identify FSGS subtypes (based on the Columbia classification) (35) and subsequently categorize FSGS as recurrent or *de novo* and idiopathic or secondary. In the absence of pathologic changes or clinical conditions predisposing to FSGS, we presumed FSGS was idiopathic. Otherwise, FSGS was considered secondary.

Obesity was defined as a body mass index (BMI) >25 kg/m², in accord with the Japanese Society for the Study of Obesity. Estimated glomerular filtration rate (eGFR) was calculated as follows; eGFR = 194 × creatinine (Cr) (mg/dL)^{-1.094} × age (years)^{-0.287} (× 0.739, if female) (mL/min/1.73 m²) (36). Urinary protein excretion was assessed by protein-to-Cr ratios (g/g Cr) of spot urine samples. Banff criteria were the benchmarks for rejection (37).

Histologic studies

We used standard techniques to prepare tissues for light, immunofluorescence, and electron microscopic examinations. For light microscopy, formalin-fixed samples were processed routinely, embedded in paraffin, cut at 1 μm, and variably stained (hematoxylin & eosin, periodic Acid-Schiff, silver methenamine-Masson trichrome, and Elastica van Gieson methods). Paraffin-embedded sections were also immunostained for deposition of C4d, as previously described (38). Frozen sections (3 μm) were obtained for immunofluorescence microscopy, using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, and fibrinogen.

Ethical approval

Informed consent was obtained from each patient enrolled in this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. This research was approved by the ethical committee of Jichi Medical University Hospital (IRB approval number RINDAI 16-066).

Statistical analysis

All data were expressed accordingly as mean ± SD or median (range). Chi-square test was applied to categorical variables, using Student's *t*-test or Mann-Whitney U test to assess continuous variables. Renal allograft survival was analyzed by Kaplan-Meier method, with log-rank test. The impact of FSGS on death-censored graft survival was gauged via Cox proportional hazards model, adjusting for baseline imbalances in recipient groups with or without FSGS. EZR freeware (v1.35; R Foundation for Statistical Computing, Vienna, Austria) (39) was invoked for all computations, setting significance at *P*<0.05.

Results

Of renal allograft recipients (n=121) who were biopsied, six with inadequate specimens (<10 glomeruli) were excluded. However, changes of FSGS were absent in all six. In the remaining 115 patients, a diagnosis of FSGS was established for 17.

Characteristics of allograft recipient groups, with or without FSGS at biopsy, are shown in Table 1. Although urinary protein excretion at biopsy and transplant-to-biopsy interval were significantly greater in patients with (vs without) FSGS (*P*=0.00146 and *P*=0.00151, respectively), the presence or absence of FSGS had no significant impact on renal function at biopsy (*P*=0.287) or death-censored graft survival (*P*=0.953) (Figure 1). Once adjusted for transplant-to-biopsy interval and urinary protein excretion (in Cox proportional hazards analysis), death-censored graft survival proved similar, regardless of FSGS status (adjusted hazard ratio for death-censored graft loss in recipients with FSGS=3.70, 95% confidence interval: 0.733-18.7; *P*=0.113).

Characteristics of the 17 recipients with FSGS are shown in Table 2. Histologic subtypes of FSGS were as follows; not otherwise specified (NOS; n=8), collapsing (n=5), cellular (n=2), and perihilar (n=2) (Figure 2). No allograft recipient with FSGS had known native kidney involvement. However, the status of native kidneys was lacking in eight. On the other hand, there were signs of diabetic nephropathy (n=4), IgAN (n=2), polycystic kidney disease (n=2), or Henoch-Schönlein purpura nephropathy (HSPN; n=1). FSGS was presumed secondary in all 17 patients, based on associated pathologic findings or clinical features. Likely precipitating events or conditions were calcineurin inhibitor (CNI) toxicity (n=10), chronic active antibody-mediated rejection (ABMR; n=8), obesity (n=7), arteriosclerosis (n=3), reflux nephropathy (n=2), recurrent IgAN (n=2), or recurrent HSPN (n=1).

Discussion

During the course of this study, FSGS was identified in 14.5% of renal allograft recipients who required biopsies.

Table 1. Characteristics of recipient groups with or without FSGS at biopsy

	FSGS (n=17)	non-FSGS (n=98)	P value
Sex, male (%)	70.6	59.2	0.535
Age (y)	46.9±13.2	48.7±13.8	0.606
BMI (kg/m ²)	23.1 (17.5-30.3)	21.9 (15.1-40.3)	0.595
Living donor (%)	94.1	90.8	1.000
Hypertension (%)	88.2	71.4	0.274
Diabetes mellitus (%)	29.4	28.6	1.000
ARB or ACE-I (%)	58.8	32.7	0.0725
Transplant-to-biopsy interval (days)	2249 (96-5391)	356 (5-6032)	0.00151
Serum creatinine (mg/dL)	2.78±1.36	2.35±1.53	0.287
Urinary protein excretion (g/g Cr)	1.52 (0.31-7.68)	0.48 (0-6.43)	0.00146
Microhematuria (%)	35.3	24.5	0.376

FSGS, focal segmental glomerulosclerosis; BMI, body mass index; ARB, angiotensin receptor blockers; ACE-I angiotensin-converting enzyme inhibitor.

Categorical variables expressed as percentages (%); continuous variables as mean ± SD or median (range).

Groups comparisons achieved by chi-square test (percentages of males, living donors, hypertensive disease, diabetes mellitus, ARB/ACE-I use, and microhematuria), Student's t-test (age and serum creatinine), or Mann-Whitney U test (BMI, transplant-to-biopsy interval, and urinary protein excretion).

Allograft survival did not differ significantly ($P=0.953$) as a result; and in all 17 recipients with FSGS, it was considered a secondary manifestation. Although we cannot state this with certainty, no decisive evidence of idiopathic FSGS emerged. Instead, CNI toxicity (58.8%), chronic active ABMR (47.1%), obesity (41.2%), arteriosclerosis (17.6%), reflux nephropathy (11.8%), recurrent IgAN (11.8%), and recurrent HSPN (5.9%) were variably implicated. Such findings are presumptive but are well corroborated by earlier probes into pathologic or clinical underpinnings of secondary FSGS.

As the leading cause of secondary FSGS herein, CNI toxicity may inflict hyperfiltration injury and subsequent arteriolar hyalinosis, with global glomerulosclerosis (40) or glomerular ischemia (17,41). Indeed, severe arteriolar

hyalinosis was visible in all 10 of our patients with overt CNI toxicity. Others (33,34) have also reported FSGS following rejection, although the inherent mechanism is still unclear. Immunologic injury to endothelium and podocytes may be involved. Obesity may contribute to glomerular hyperfiltration, heightening filtration pressures of proximal glomerular capillaries to result in sclerosis near

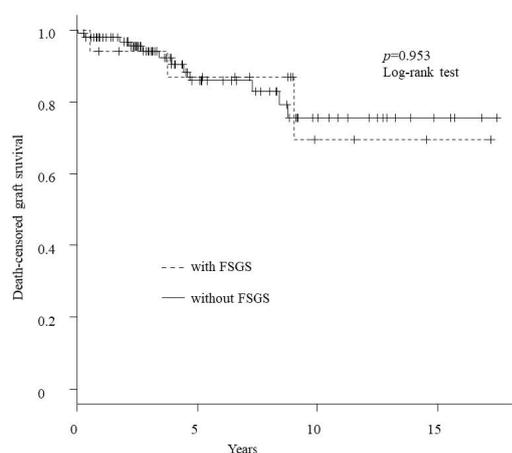
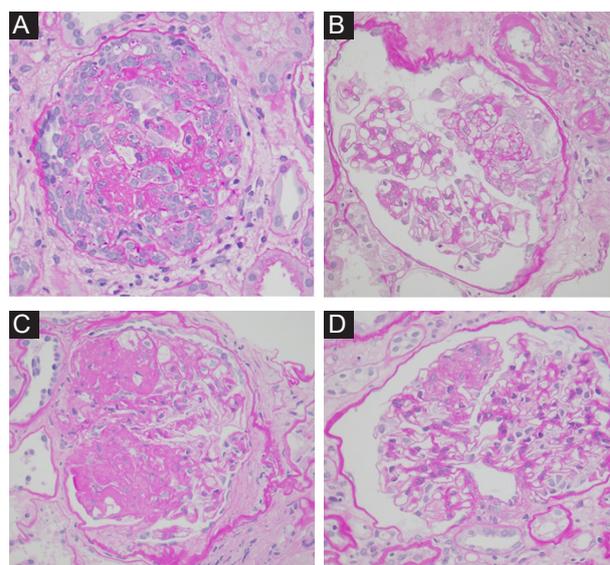
**Figure 1.** Kaplan-Meier analysis of death-censored graft survival. FSGS, focal segmental glomerulosclerosis.**Figure 2.** Renal allograft biopsies (Periodic acid-Schiff stain, original magnification × 400): (a) Collapsing variant (Case 6) showing capillary collapse and prominent epithelial cell hypertrophy and hyperplasia; (b) Cellular variant (Case 4), marked by segmental expansion of glomerular tuft and endocapillary foam cells; (c) Perihilar variant (Case 10) with segmental hyalinosis and sclerosis near vascular pole; and (d) NOS (Case 17) demonstrating segmental capillary obliteration by extracellular matrix. NOS, not otherwise specified.

Table 2. Characteristics of recipients with FSGS

Case	Transplant-to-biopsy interval (days)	BMI (kg/m ²)	Native kidney disease	Immunosuppressant regimen	Serum creatinine (mg/dl)	Urinary protein excretion (g/g Cr)	FSGS subtype	Coexisting pathologic findings or clinical features suggesting etiology of secondary FSGS
1	5391	30.3	DMN	CyA MMF MP	2.25	1.95	NOS	Rejection, CNI toxicity, obesity
2	3376	22.9	IgAN	TAC MMF MP	1.55	1.04	NSO	Recurrent IgAN, CNI toxicity
3	3165	19.7	Unknown	TAC MZR MP	2.72	1.54	Collapsing	CNI toxicity, arteriosclerosis
4	2980	27.5	Unknown	CyA MMF	2.27	0.45	Cellular	CNI toxicity, obesity, Reflux nephropathy
5	2875	23.8	Unknown	TAC MMF MP	2.18	(3+)	NOS	CNI toxicity
6	2725	17.5	IgAN	TAC MZR MP	2.3	1.88	Collapsing	Recurrent IgAN, CNI toxicity
7	2267	26.8	HSPN	TAC AZA MP	2.59	1.5	Collapsing	Recurrent HSPN, CNI toxicity, obesity
8	2249	27.0	PKD	TAC MMF MP	3.71	3.32	Perihilar	Rejection, CNI toxicity, obesity
9	2221	18.2	Unknown	TAC MMF MP	2.09	1.52	Cellular	Rejection, CNI toxicity
10	2119	28.7	Unknown	TAC MMF MP	2.59	(3+)	perihilar	Obesity
11	1721	23.1	DMN	TAC MMF	1.72	0.64	NOS	Rejection, CNI toxicity, arteriosclerosis
12	1147	25.2	DMN	TAC MMF EVR	1.97	1.67	NOS	Rejection, obesity
13	1099	22.9	Unknown	TAC EVR MP	2.79	(2+)	Collapsing	Rejection
14	447	29.6	DMN	TAC MMF MP	3.6	7.68	Collapsing	Rejection, obesity
15	201	18.4	Unknown	TAC MMF MP	6.76	0.65	NOS	Arteriosclerosis
16	133	18.1	PKD	TAC MMF EVR	1.64	0.37	NOS	Reflux nephropathy
17	96	19.7	Unknown	TAC MMF MP	2	0.31	NOS	Rejection

FSGS, focal segmental glomerulosclerosis; BMI, body mass index; DMN, diabetic nephropathy; CyA, cyclosporine A; MMF, mycophenolate mofetil; MP, methylprednisolone; NOS, not otherwise specified; CNI, calcineurin inhibitor; IgAN, immunoglobulin A nephropathy; TAC, tacrolimus; MZR, mizoribine; HSPN, Henoch-Schonlein purpura nephropathy; AZA, azathioprine; PKD, polycystic kidney disease; EVR, everolimus.

Chronic active antibody-mediated rejection evident in all patients with rejection.

Dipstick urinalysis only in cases 5, 10, and 13 (urinary protein excretion unavailable).

vascular poles (11,42). Changes of FSGS have similarly been noted in many (101/128) cases of IgAN, again linked to podocyte injury (29). FSGS in reflux nephropathy likely results from nephron loss, imposing hyperfiltration on those left intact (10). Unilateral kidney recipients seem prone to glomerular hyperfiltration as well. A critical factor may be the duration of these conditions, because transplant-to-biopsy intervals proved significantly longer in our patients with FSGS.

There are data to indicate that graft survival is significantly worse in recipients with (vs without) *de novo* FSGS (43). Unfortunately, further categorization as idiopathic or secondary is lacking at the source, therefore the cited outcomes may in part reflect idiopathic *de novo* FSGS, the prognosis of which is poor. In our patients,

FSGS was largely presumed to be secondary and whether present or not had no significant impact on renal allograft survival. Hence, the prognosis of renal allograft recipients is seemingly unaltered by secondary FSGS.

Conclusion

According to our data, only 14.5% of renal allograft recipients undergoing biopsies for allograft dysfunction or proteinuria showed evidence of FSGS which was considered secondary in all instances. Secondary FSGS was seemed to have no significant impact on allograft survival.

Limitation of the study

This study has several acknowledged limitations. The

status of native kidneys in a segment of allograft recipients was unknown, prohibiting FSGS designation as recurrent or *de novo*. In addition, our method of separating idiopathic and secondary FSGS (based pathologic changes or clinical features) was not foolproof. Finally, biopsies were not obtained from every patient with renal allograft dysfunction or proteinuria, therefore the incidence of FSGS we have determined may be inaccurate.

Authors' contribution

TaS participated in research design, performance of the research, and writing the paper. KN participated in research design, performance of the research, and writing the paper. YK participated in research design, performance of the research, and writing the paper. TK participated in research design, performance of the research, and writing the paper. ToS participated in research design, performance of the research, and writing the paper. TY participated in research design, performance of the research, and writing the paper.

Conflicts of interest

The authors have declared that no conflict of interest exists.

Ethical considerations

Ethical issues have been completely observed by the authors.

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