A Single-center, Retrospective Study of Focal Segmental Glomerulosclerosis after Kidney Transplantation: Evolutive Analysis

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ABSTRACT

Background: Focal segmental glomerulosclerosis (FSGS) has a high recurrence rate after renal transplantation, which significantly impacts renal graft survival. However, the factors related to recurrence remain unclear.

Objective: This study aimed to analyze focal segmental recurrence and evolution of glomerulosclerosis after renal transplantation.

Methods: This was a descriptive, retrospective study involving 88 adults who underwent renal transplantation within a 15-year period. Demographic and clinical characteristics, as well as the occurrence of graft loss, were analyzed. Over the study period, 88 patients with a diagnosis of FSGS after transplantation were identified.

Results: The mean age of the patients (n=54, males) was 29.1 years. Transplants with deceased donors predominated (60.9%). Calcineurin and prednisone inhibitors were present in 96.4% of the initial immunosuppression regimens. The mean time of onset of proteinuria greater than 0.5 g/g was 20.51 days. At 60 months after transplantation, 44.16% of the patients had partial remission, 25.97% had complete remission, and 29.87% had no remission. However, 50.60% of the patients developed graft loss throughout the analyzed period. Eight patients (9.4%) died within 60 months, of which five (62.5%) were attributed to infection.

Conclusion: Our results indicate that FSGS after renal transplantation is a disease of high recurrence that is commonly precocious, and the histological alterations in light microscopy are not simultaneous to the appearance of proteinuria. Hypertension is considered a risk factor causing progression and recurrence. Thus, prospective studies are required to better evaluate progression and recurrence factors.

KEYWORDS: Focal segmental glomerulosclerosis; Transplantation; Graft loss; Systemic arterial hypertension

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is characterized by histological findings that may be common to the evolution of different glomerular lesions but not to a specific nosological entity [1-3]. FSGS has a high rate of progression to renal disease [1] and presents high recurrence rates after renal transplantation [2].

After transplantation, the disease may recur in >60% of cases and, if left untreated, causes early graft loss in >50% of those affected [2,4]. However, in cases of second transplantation, the probability of recurrence can reach 100% in situations where there was graft loss by FSGS in the first transplant. [5]. The occurrence of proteinuria is an independent pre-

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dictor of patient and graft survival that also acts as a cardiovascular risk marker [5-7].

The distinction between recurrent and de novo FSGS is complicated. First, native kidney biopsies in the vast majority of the transplanted population are low, and histological confirmation of the disease is also low. Second, another glomerular disease different from that affecting the native kidney may cause glomerulopathy in the transplanted kidney. Third, due to the absence of periodic and systematic biopsies in the transplanted kidney, in the absence of graft dysfunction or significant proteinuria, underdiagnosis of glomerulopathy may occur and result in subclinical recurrence. Fourth, the failure to perform routine immunofluorescence biopsy and electron microscopy testing on transplanted kidney specimens makes the diagnosis of glomerulopathies difficult. Fifth, more than one renal finding may be identified in graft histology, resulting in confounding evidence, such as the presence of interstitial fibrosis and tubular atrophy in varying degrees (or chronic graft nephropathy), signs of toxicity by calcineurin inhibitors, and acute or chronic rejection. Lastly, the glomerulonephritis may have originated from the kidney donor [8]. The risk factors for the recurrence of FSGS are childhood onset of FSGS, use of cyclosporine in the initial treatment of FSGS in native kidneys, white race, previous graft loss due to FSGS, time of evolution from FSGS diagnosis to end-stage renal failure, presence of mesangial proliferation in the native kidney biopsy [8-11].

This study aimed to evaluate the occurrence of post-transplant FSGS within a 15-year follow-up period in terms of diagnosis and evolution of the disease based on demographic and histological characteristics, clinical and laboratory evolution, response to treatment, and potential factors involved in the prognosis and progression to graft loss.

MATERIALS AND METHODS

Study Design

This retrospective, descriptive study from a single center included adolescent and adult patients who received kidney transplants from live and deceased donors between January 1999 and September 2014. The study was approved by the Ethics Committee of Universidade Federal de São Paulo, Brazil (No. 623.096).

The study population consisted of renal transplant recipients with renal graft biopsy who were diagnosed with post-transplant FSGS. Cases of pancreas-kidney transplantation and cases of post-transplant secondary FSGS were excluded from the study.

Definitions

An expanded criterion donor (ECD) was defined as any donor aged >60 years, or donors aged 50–60 years, who presented at least two of the following characteristics: death by cerebrovascular etiology, history of hypertension, or final serum creatinine >1.5 mg/dL [11].

Delayed graft function was defined as the need for dialysis within 1 week after renal transplantation [7]. Proteinuria was defined as >0.5 g/g with the measurement standardized by the protein/creatinine ratio in an isolated urine sample.

Renal function was determined by serum creatinine (using isotope dilution mass spectrometry) and estimated glomerular filtration using the Modification of Diet in Renal Disease formula [12].

FSGS after kidney transplantation was defined as the presence of proteinuria after renal transplantation with no histological antecedent of other glomerulonephritis or based on renal biopsy findings compatible with FSGS [10,11].

Partial remission of FSGS was defined as creatinine stabilization at 25% of basal creatinine, associated with a 50% reduction of proteinuria compared to pre-treatment levels and <3.0 g/g with nephrotic values. Remission was defined as proteinuria with <0.3 g/g creatinine stability at baseline or <25% of baseline.

Table 1: Demographic characteristics of the recipients.

Variables	Statistics
Age (years), mean ± SD	29.1 ± 13.3
BMI (kg/m^2), mean ± SD	21.62 ± 4.85
Sex, male, no. (%)	54 (61.4%)
Race, no. (%)	
White	59 (67.8%)
Brown	16 (18.4%)
Black	11 (12.6%)
Yellow	1 (1.1%)
Etiology CKD, no. (%)	
Chronic glomerulonephritis	5 (5.7%)
FSGS	53 (60.9%)
Undetermined	29 (33.3%)
Treatment prior to transplantation, no. (%)	
Hemodialysis	65 (75.6%)
Peritoneal dialysis	10 (11.6%)
Hemodialysis – peritoneal dialysis	4 (4.7%)
Conservative (preemptive)	5 (5.8%)
Time on dialysis (months), mean ± SD	33.23 ± 36.08
Re-transplant, no. (%)	16 (18.4%)
Systemic arterial hypertension, no. (%)	72 (83.7%)
Non-diabetics, no. (%)	86 (100%)
Anti-HCV positive, no. (%)	3 (3.5%)

CKD: chronic kidney disease; FSGS: focal segmental glomerulosclerosis; HCV: hepatitis C virus.

Statistical Analysis

Continuous variables were presented as mean±standard deviation (SD) or median. Statistical analysis was performed in two steps. A preliminary step, based on the analysis of each variable, identifies information with the greatest potential to relate to the response. Thus, categorical variables were treated using the log-rank test and categorical variables with the adjustment of a Cox proportional hazards model with a single independent variable. In the final analysis, the variables selected in the preliminary analysis and which did not show multicollinearity participated in the adjustment process of the Cox proportional hazards model. Categorical variables were summarized as frequencies and proportions. Univariate and multivariate analyses were performed to define risk factors for renal graft loss.

RESULTS

We identified 88 patients with a diagnosis of post-transplant FSGS. The demographic and clinical characteristics of the recipients are shown in Table 1.

A notable number of patients (64.3%) underwent native kidney biopsy, with a diagnosis of FSGS in 60.9%. The etiology of chronic kidney disease was FSGS in 60.9% of cases. Most patients exhibited systemic arterial hypertension (83.7%).

Five patients (5.8%) underwent preemptive renal transplantation, and 75.6% underwent dialysis as renal replacement therapy prior to transplantation. The mean (SD) dialysis duration (hemodialysis or peritoneal dialysis) was 33.23 ± 36.08months. Sixteen (18.4%) patients underwent re-transplantation. The kidney

Table 2: Characteristics of the transplantations.

Variables	Statistics
Transplantation time (yrs), mean ± SD	6.8 ± 3.12
ARP (antibody reactivity panel), mean ± SD	11 ± 24.1
Family history of glomerulopathies, no. (%)	1 (1.2%)
Donor type, no. (%)	
HLA1	12 (13.8%)
HLA2	18 (20.7%)
HLA3	4 (4.6%)
Deceased donor	53 (60.9%)
Biopsy of the native kidney, no. (%)	
No	30 (35.7%)
FSGS	52 (61.9%)
Others	2 (2.4%)
Expanded criterion donor, no. (%)	21 (25.6%)
Induction immunosuppression, no. (%)	
Thymoglobulin	27 (32.5%)
Anti-IL2	22 (26.5%)
Initial immunosuppression, no. (%)	
Tacrolimus + prednisone + azathioprine	33 (39.3%)
Tacrolimus + prednisone + mycophenolate	29 (34.5%)
Cyclosporine + prednisone + azathioprine	17 (20.2%)
Everolimus + prednisone + mycophenolate	1 (1.2%)
Tacrolimus + prednisone + everolimus	2 (2.4%)
Everolimus + prednisone + mycophenolate	2 (2.4%)
DGF, no. (%)	40 (47.6%)
DGF time (days), mean ± SD	22.85 ± 22.87
Hospitalization time (days), mean ± SD	10.88 ± 19.38
Time of onset of proteinuria >500 mg (days), mean ± SD	20.51 ± 20.88

ARP: antibody reactivity panel.; HLA: human leucocyte antigen; FSGS: focal segmental glomerulosclerosis; Anti-IL2: anti-interleucin-2; DGF: delayed graft function.

transplant characteristics are shown in Table 2.

The mean (SD) duration of hospitalization for transplantation was 10.88±19.38 days and the time of onset of proteinuria >0.5 g/g was on average 20.51±20.88 days (Tables 1 and 2).

Indication for renal graft biopsy due to suspected FSGS occurred, on average, 99.57±349.54 days after renal transplantation, or a median of 79 days, with the mean time conflicting with the mean time of onset of proteinuria. Histological characteristics of FSGS were mostly verified by subsequent biopsies, with a mean (SD) time of onset of histological changes of 164.56±375.89 days. Only 21.5% of the patients had FSGS histological characteristics at the first graft biopsy. Treatment data are summarized in Table 3.

At 60 months post-transplantation, 44.16% of patients exhibited partial remission, 25.97% had complete remission, and 29.87% showed no remission of glomerular disease. However, considering the entire period analyzed, 50.60% of patients evolved with loss of graft, with 77.27% of cases secondary to FSGS.

The main treatment complication was infec-

Table 3: Characteristics of post-transplant FEBD throughout the evolution.

Variables	Statistics
Time for the first post-transplant renal biopsy, mean±SD*	99.57 ± 349.54
FSGS – first biopsy, no. (%)	17 (21.50%)
Time to obtain confirmatory sampling of FSGS in biopsy (days), mean±SD	164.56 ± 375.89
FSGS post-transplantation treatment, no. (%)	
Plasmapheresis	61 (70.10%)
Rituximab	10 (11.49%)
Methylprednisolone	79 (90.80%)
Plasmapheresis start time (days), mean±SD	85.90 ± 132.54
Remission after 5 years, no. (%)	
Partial	34 (44.16%)
Complete	20 (25.97%)
No remission	23 (29.87%)
Loss of graft, no. (%)	44 (50.60%)
Serum creatinine 12 months after transplantation (mg/dL), mean±SD	1.94±1.02
Infection during treatment, no. (%)	52 (67.50%)
Death, no. (%)	8 (9.4%)

FSGS: focal segmental glomerulosclerosis

*Time for the first post-transplant renal biopsy was indicated by suspicion of FSGS.

tion/sepsis (67.5%). Eight patients (9.4%) died over the 60-month period, with five (62.5%) deaths attributed to infection (Table 3).

The associations between renal graft loss and the variables of interest were assessed using the log-rank test (for categorical variables) and the Cox proportional hazards model (for numerical variables). The results obtained are shown in Table 4.

Results acquired from the fitting of the Cox proportional hazards model are shown in Table 5.

DISCUSSION

FSGS is one of the main glomerulopathies that most frequently recurs after renal transplantation. The estimated recurrence rate ranges from 30% to 60% [8,13].

The pathophysiology of FSGS is not fully known. The presence of early recurrence post-transplantation suggests that circulating factors are responsible for the loss of the structural integrity of podocytes, with consequent destruction of the filtration barrier and proteinuria [14,15].

In this study, 88 patients from the transplant population exhibited FSGS as a recurrence or de novo. The recurrence rate was 59% considering the first transplant, and it reached 100% in cases of re-transplantation. The present study identified the presence of arterial hypertension as a progression factor for graft loss. Approximately 84% of the patients in the sample had arterial hypertension, with 65% taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, which were more predominant among those with graft loss.

Other risk factors previously related to graft loss include the occurrence of acute rejection episodes, delayed graft function (DGF), serum creatinine >1.5 mg/dL at 1 year post-transplant, black kidney recipients, longer dialysis duration, ECD, and deceased donor [9,11,17].

There was a predominance of deceased donors (60.9%). This finding appears to reflect only the composition of the overall population studied and the recent increased trend in the number of deceased donors at our institution.

Table 4: Univariate analysis of risk factors for development of renal graft loss.

Variables	P-value
Transplant time (years)	0.294
Age at time of transplantation (years)	0.970
BMI - kg/m2	0.883
Dialysis time (months)	0.833
ARP (%)	0.997
Cold ischemia time (hours)	0.650
Delayed graft function time (days)	0.250
Length of hospital stay (days)	0.073
Proteinuria onset time >500 mg/g	0.696
Date of first biopsy (days)	0.440
Time of biopsy with FSGS sampling	0.087
Treatment start time (days)	0.089
Plasmapheresis onset time (days)	0.039
Number of plasmapheresis sessions	0.278
Serum creatinine (mg/dL) at 1 year	0.003
Dialysis mode	0.427
Serology for hepatitis C	0.533
Systemic arterial hypertension	0.227
Type of donor	0.587
Family history of glomerulonephritis	0.999
Expanded criterion donor	0.845
Initial immunosuppression	0.436
Delayed graft function	0.595
Plasmapheresis	0.254
Rituximab	0.233
Methylprednisolone	0.019
Partial remission	0.093
Complete remission	0.245
Death	0.628
Infection during treatment	0.857

BMI: body mass index; ARP: antibody reactivity panel.; FSGS: focal segmental glomerulosclerosis

It should be emphasized that a family history of glomerulopathy was documented in only 1.2% of cases. Recurrence has not been reported to occur or rarely occurs in patients with familial FSGS [9]. In the present study, the lower frequency of familial cases of FSGS possibly contributed to the higher recurrence rate.

We observed that proteinuria >500 mg/day appeared at a relatively early time point during the course of the post-transplantation period, within an average of 20 days. There are two possible clinical presentations of FSGS after renal transplantation: an early, more frequent form with massive proteinuria appearing hours or days after transplantation, and a more insidious late form that develops months or years after renal graft implantation [9]. Early proteinuria may also originate from the native kidney when there is residual diuresis.

Table 5: Multivariate analysis and adjustment of the Cox proportional hazards model to the data.

	Variables	P-value	Coefficient	Relative risk	95% CI Confidence interval	
	Systemic arterial hypertension	0.025	10.87	52679.67	4.00	694469787.06
	Serum creatinine (mg/dL) at 1 year	0.066	3.62	37.32	0.78	1778.57
	Number of plasmapheresis sessions[a]	0.702	0.16	1.17	0.52	2.65
	Treatment start time[b]	0.058	1.15	3.15	0.96	10.36
	Number of plasmapheresis sessions, treatment start date	0.038	-1.27	0.28	0.09	0.93
Interactions	Systemic arterial hypertension, serum creatinine at 1 year	0.999	—	—	—	—
	Systemic arterial hypertension, number of plasmapheresis sessions	0.999	—	—	—	—
	Systemic arterial hypertension, treatment start time	0.999	—	—	—	—
	Serum creatinine at 1 year, number of plasmapheresis sessions	0.770	—	—	—	—
	Serum creatinine at 1 year, treatment start time	0.233	—	—	—	—
	Plasmapheresis	0.146	—	—	—	—
	Transplant time	0.392	—	—	—	—
	Partial remission	0.633	—	—	—	—
	Length of hospital stay (days)	0.831	—	—	—	—

a) For better interpretation of the results, in the calculations of this step, the variable values were divided by 10.
b) For better interpretation of the results, in the calculations of this step, the variable values were divided by 30.

In a case-control study [17] evaluating 34 patients with primary FSGS who underwent kidney transplantation between 1988 and 2008, the diagnosis of FSGS was made, on average, 113 months prior to transplantation. Seven patients had FSGS recurrence and 58% evolved with graft loss; however, the overall graft survival was 60% in 10 years for the entire group.

Hemodialysis was the predominant pre-transplant treatment among the patients included in this study [18]. The mean time on dialysis before transplant was 33 months. An Italian study evaluating 34 patients transplanted with primary FSGS reported a mean duration of dialysis of 40.9 months [19].

Notably, only 5.8% of patients with post-transplant FSGS in our study had undergone preemptive transplantation. Considering the importance attributed to circulating factors in some forms of FSGS, transplantation performed without a transitional period in dialysis could be a cause for concern [19].

In the present study, it was possible to observe that the indication for renal biopsy on suspicion of FSGS occurred late, on average 99.6 days after transplantation, contrasting with the high frequency of proteinuria >500 mg/day, which presented on average 20.5 days after renal transplantation, detected from the day of transplantation up to 180 days post-transplantation. This finding is explained by the absence of systematic protocols for graft biopsy and the indication for biopsy only in the presence of graft dysfunction or significant proteinuria, generally >1 g/day [8]. Furthermore, early biopsies are not commonly able to confirm the diagnosis of post-transplant FSGS. Only 21.50% of renal graft biopsies performed for the first time post-transplantation showed histologically proven FSGS, which may depend on sampling errors, disparities between clinical manifestation and visible histological lesions in light microscopy, and systematic non-performance of electron microscopy [20]; and the underlying indication for biopsy of the graft was predominantly graft dysfunction.

On average, plasmapheresis was initiated 2.5 months post-transplantation, which was justified by waiting for the response to another treatment, delayed indication of the procedure due to lack of experience in the management of this therapeutic strategy, or local difficulties in performing plasmapheresis.

Although 90.8% of patients received pulses of methylprednisolone prior to plasmapheresis, the efficacy of corticosteroids in the treatment of recurrent or de novo FSGS has never been evaluated in randomized trials [20]. High-dose corticosteroids associated with cyclosporine and plasmapheresis have been proposed to induce higher remission rates than corticosteroids alone [21]. However, plasmapheresis is considered the heart of the treatment [15]. Complete or partial remission occurred in 63% of adult patients with recurrence of FSGS undergoing plasmapheresis [13]. Plasmapheresis has been indicated as first-line treatment for FSGS. The best results are achieved when treatment is started early after renal transplantation [14].

Rituximab has been indicated as a treatment option for post-transplant FSGS in cases of incomplete remission and plasmapheresis dependence since 2006, with successful partial or total remission in 64% of cases [22]. The impact of post-transplant FSGS treatment with rituximab could not be fully assessed in this sample because it was administered in only 11.5% of patients and became available only recently.

Of note, at the 12-month follow-up post-transplantation, patients who had lost their graft had serum creatinine levels averaging 1.94 mg/dL. The serum creatinine level at this time point may be considered a risk factor for graft loss, which was only marginally significant (p=0.066) in the multivariate statistical analysis, but its value in clinical practice is indisputable.

In this study, 44.16% of patients presented a partial response to treatment and 25.97% presented a complete response. Overall, 70.13% had partial or total response, which is close to that of similar reports in literature. The treatment for post-transplant FSGS in this study was based mainly on increasing the dose of corticosteroids administered orally and the addition of intravenous pulse therapy with methylprednisolone (91% of cases) with or without plasmapheresis (70% of cases). Moroni et al. [17] showed 80% partial or total remission rates in FSGS cases treated with plasmapheresis plus ACE inhibitors (enalapril 20 mg, twice a day). In a systematic review covering 39 cases of recurrent FSGS treated with rituximab, partial or complete remission occurred in 67% of cases [23].

Another important factor associated with graft loss is the post-transplantation immunosuppressive regimen chosen. The initial immunosuppression in our sample was chosen based on immunological risk and donor type, with no influence based on previous occurrence of glomerulopathy. In this study, 74% of patients received tacrolimus, associated with prednisone and mycophenolate or azathioprine, while 20% received cyclosporine, prednisone, and azathioprine as their initial immunosuppression treatment. The immunosuppressive regimen did not appear to have influenced the episodes of infection, in contrast with the use of plasma and immunosuppressants for the treatment of FSGS.

The infection episodes had an impact on the morbidity and mortality of transplanted patients due to immunosuppression [24]. A study on 190 renal transplant patients conducted at our institution [24], including patients hospitalized in the intensive care unit for septic shock, showed that the lung and urinary tract were the most affected sites. The 1-year total mortality rate was 42.6% [24]. Nevertheless, the high rate of infection (67,5%) subsequent to pulses with methylprednisolone and plasmapheresis appeared to be associated with immunosuppression intensification for FSGS treatment.

In a meta-analysis [25] of six studies including a total of 117 patients, graft loss due to recurrence was lower in patients undergoing plasmapheresis [25].

Thirteen patients with recurrence of FSGS showed benefit in terms of graft survival when plasmapheresis was initiated within 14 days after recurrence in 85% of the patients [26]. Graft loss in untreated patients ranged from 58% to 68% in adults [26]. A study evaluating 33 adult transplanted patients with FSGS reported 73% graft survival in 5 years, which was significantly lower than that of patients without FSGS recurrence [9].

The sample studied included ECD in 25.6% of cases. Although ECD was associated with a higher prevalence of DGF and longer hospitalization time (47.6% and 10.88 days, respectively), ECD did not impact change in graft or recipient survival in a review study [27].

Over the 5-year study period, 9.4% of patients with recurrent FSGS died. Deaths were generally attributed to infections likely associated with immunosuppression intensification for the treatment of post-transplant FSGS. High mortality rates have also been associated with infection [11, 24].

FSGS showed a high rate of recurrence in post-transplantation patients and was determinant for the loss of the renal graft in 50% of patients. Among the possible risk factors for graft loss were systemic arterial hypertension and longer time to treatment initiation directed at the control of post-transplant FSGS. This type of glomerulopathy manifests early as proteinuria, before histological lesions confirm diagnosis. Treatment directed at the control of post-transplant FSGS is more successful if it is not delayed waiting for histological confirmation of FSGS diagnosis. Considering the therapeutic resources available at the time of this study, plasmapheresis was associated with higher remission. Further prospective studies are required to further explore the factors of progression and recurrence.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of the following to this study: CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior/Coordination of Improvement of Higher Level Personnel, members of the Discipline of Nephrology, members of the Nefritis group, the Renal Post-transplant Ambulatory at the Kidney Hospital, and the Director of the Kidney Hospital and all its collaborators.

CONFLICTS OF INTEREST: None declared.

FINANCIAL SUPPORT: None.

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