Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants

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Histologic variants of idiopathic focal segmental glomerulosclerosis (FSGS) may have prognostic value. A recent working classification system has distinguished five FSGS variants. We evaluated a cohort of adult patients with biopsy-proven FSGS diagnosed between March 1982 and July 2001 to determine if subtypes were associated with renal outcome. Renal biopsies were reviewed by two pathologists. Demographic and clinical data were obtained from charts. Outcomes were partial and complete remission of the nephrotic syndrome, and renal failure. The frequency of FSGS variants was: 3% cellular ($N=6$), 11% collapsing ($N=22$), 17% tip lesion ($N=34$), 26% perihilar ($N=52$), and 42% not otherwise specified (NOS) ($N=83$). Collapsing FSGS affected younger and more often black patients. Black race was uncommon in tip variant. Collapsing and tip variants had higher proteinuria and lower serum albumin than perihilar and NOS variants. Better renal function and less severe tubulointerstitial injury were observed in patients with tip variant. These patients were more likely to receive steroids and more often achieved complete remission (50%). After a median follow-up of 1.8 years, 23% of patients were on dialysis and 28% had renal failure. Collapsing FSGS had worse 1-year (74%) and 3-year (33%) renal survival compared to other variants (overall cohort renal survival at 1 and 3 years: 86 and 67%). Different histologic variants of FSGS have substantial differences in clinical features at the time of biopsy diagnosis and substantial differences in renal outcomes.

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The term focal segmental glomerulosclerosis (FSGS) is applied to a pathologically diverse group of glomerular lesions with heterogeneous clinical manifestations. FSGS shares overlapping patterns of injury with segmental consolidation and obliteration of glomerular architecture by accumulation of collagenous extracellular matrix or by increased cellularity or both. Different studies report a broad range of estimates for progression to renal failure, remission rates of the nephrotic syndrome, and response to therapy of patients with FSGS.[1–3]

Differences in study populations, such as racial profile or therapy, may explain some of the discrepancies in outcomes between different clinical studies. However, the differences can be, in part, the result of the failure to recognize the structural variants of FSGS and to stratify the data accordingly. Recognition of unique subtypes of FSGS may be required because the histopathologic variants of FSGS could be etiologically and pathogenetically distinct, and therefore have different prognoses and optimum therapies. For example, the tip lesion variant of FSGS (tip lesion FSGS), initially described by Howie *et al.* in 1984, may have a more benign course and a better response to corticosteroid therapy compared to other structural variants of FSGS.[4–9] Conversely, the collapsing variant of FSGS (collapsing FSGS) is known for an aggressive course, often with decreased renal function at presentation and rapid progression to renal failure.[10,11] The perihilar variant of FSGS (perihilar FSGS) usually is accompanied by glomerulomegaly and often is seen in association with obesity or reduced functional renal mass.[12] Most studies of the clinical features and outcomes of FSGS have not taken these morphologic variants of FSGS into consideration.

Studies that attempted to determine the clinical importance of different structural variants of FSGS are complicated by the lack of standardized definitions for these pathologic variants. Recently, a group of renal pathologists proposed a standardized pathologic classification system for FSGS.[13,14] Five categories were defined: collapsing variant of FSGS (collapsing FSGS), tip lesion variant of FSGS (tip lesion FSGS), cellular variant of FSGS (cellular FSGS), perihilar variant of FSGS (perihilar FSGS), and FSGS not otherwise specified (FSGS NOS) (Figure 1).

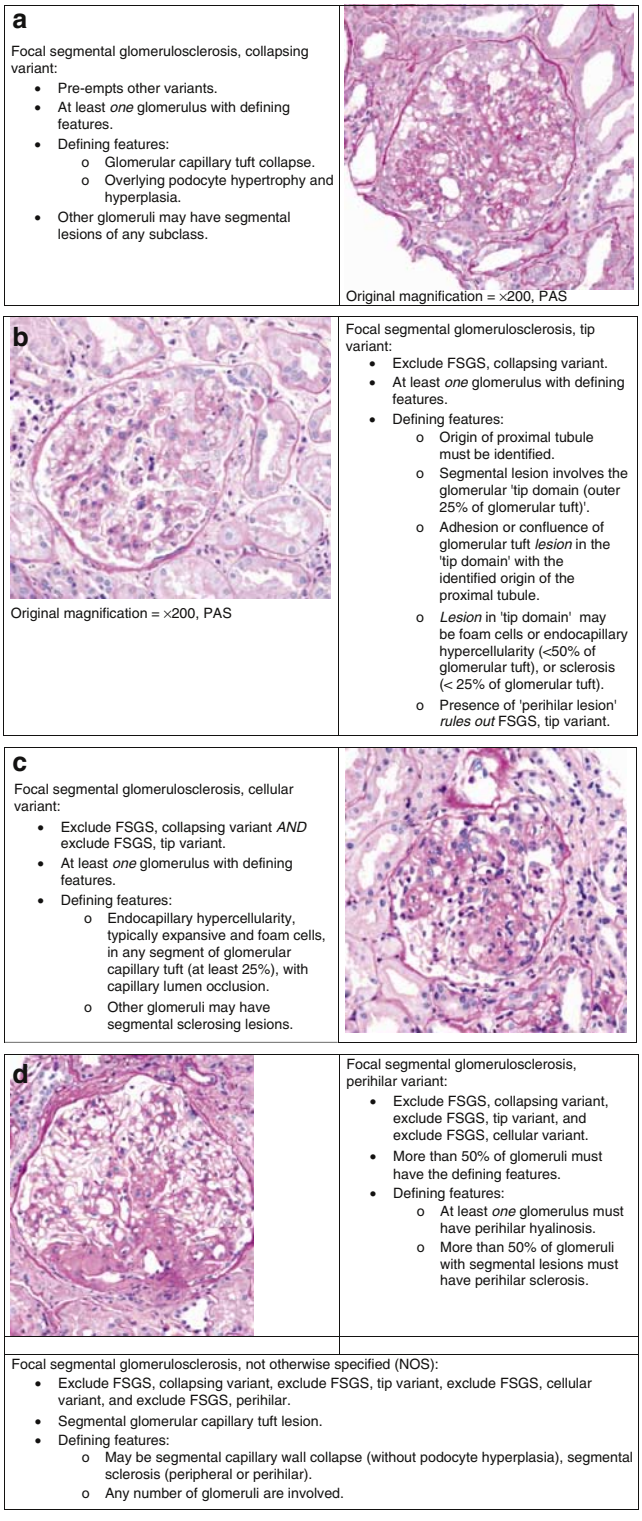


Figure 1 | Columbia FSGS classification system. Pictures are representative images of FSGS variants: (**a**) collapsing FSGS, (**b**) tip FSGS, (**c**) cellular FSGS, and (**d**) perihilar FSGS.

Two recent studies have described the clinical characteristics and renal outcomes of patients with FSGS using the new pathologic classification.[8,15] These studies compared some but not all five of the FSGS variants. The current study utilized a large cohort of FSGS patients to determine if the pathologic variants defined by the Columbia proposal[14] are distinct clinical and pathologic entities. Pathologic specimens and clinical data from the Glomerular Disease Collaborative Network patient registry were reviewed and the clinical outcomes and response to treatment were compared across the FSGS subtypes.

RESULTS

A total of 282 patients were enrolled into the registry. Eighty-five patients were not eligible for this evaluation owing to age less than 21 years ($N=39$) or presence of less than 5 glomeruli per level of section on biopsy or missing slides ($N=46$). In the remaining 197 patients, the frequency of the variants was: 3% cellular FSGS ($N=6$), 11% collapsing FSGS ($N=22$), 17% tip lesion FSGS ($N=34$), 42% NOS FSGS ($N=83$), and 26% perihilar FSGS ($N=52$). As so few patients were identified with cellular FSGS, data for this group are presented but not included in the statistical comparisons among variants.

As expected, nephrotic syndrome, hypertension, and renal insufficiency were commonly seen in all variants at presentation (Table 1). After a median follow-up of 1.8 years (range 0–16 years), 45 (23%) patients were on dialysis and 56 (28%) were either on dialysis or had doubled their serum creatinine. Thirty-eight patients (19%) had a complete remission and nine (5%) had partial remission of the nephrotic syndrome at follow-up (Table 1). Partial remission was achieved in one patient with collapsing FSGS, two patients with FSGS NOS, five patients with perihilar FSGS, and one patient with tip lesion FSGS.

One hundred and thirty-nine patients (71%) were treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers during follow-up. Treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers was not associated with remission of the nephrotic syndrome ($P=0.11$). Sixty-seven patients (34%) received corticosteroid treatment at a mean prednisone-equivalent dose of 63 ± 17 mg/day for an average of 8.6 ± 7 months. Patients with the tip lesion FSGS were more often treated with corticosteroids and those with the collapsing variant were less likely compared to other variants (62% tip lesion, 14% collapsing, 35% perihilar, 37% NOS, $P=0.003$). Overall, treatment with corticosteroids was significantly associated with remission ($P=0.007$). Complete remission was seen in 20 of 67 (30%) patients taking corticosteroids and seven of 58 (14%) of those not treated with corticosteroids. After adjusting for corticosteroid exposure, complete remission was still significantly higher for tip FSGS compared to other variants ($P<0.001$). However, use of corticosteroid therapy was not associated with better renal survival ($P=0.10$). Only 8% of the patients received additional immunosuppressive therapy: six received cyclophosphamide, 10 cyclosporine, two either mycophenolate mofetil or azathioprine, and one fish oil.

Table 1 | Demographics, clinical presentation, and outcomes of focal segmental glomerulosclerosis variants

		Focal segmental glomerulosclerosis variants					
	Total cohort (*N*=197)	Cellular (*N*=6)	Collapsing (*N*=22)	Tip (*N*=34)	Perihilar (*N*=52)	NOS (*N*=83)	*P*-value
Age	49±15	45±13	38±12[a]	54±13	50±16	50±15	0.0009
(range)	(23–89)	(30–61)	(24–73)	(28–73)	(23–89)	(23–81)	
Male (%)	55	67	45	50	56	58	0.70
Black (%)	40	33	91[b]	15[b]	29	43	<0.001
Nephrotic syndrome (%)	70	75	83	88	55[c]	67	0.01
Hypertension (%)	74	75	67	54	80	80	0.05
MAP (mmHg)	107±14	110±10	106±13	111±16	105±14	107±13	0.30
Serum creatinine (mg/dl)	2.1±2.0	2.5±1.7	3.1±3.8	1.5±0.9[d]	2.0±1.4	2.1±1.8	0.02
Serum albumin (g/dl)	3.1±0.9	2.8±0.9	2.5±1.0[b]	2.5±0.9[b]	3.7±0.6	3.2±0.8	<0.0001
Cholesterol (mg/dl)	289±127	278±184	280±132	359±141	242±68	283±130	0.14
Proteinuria (g/day)	6.8±4.9	16±15	10.0±5.3[b]	9.7±7.0[b]	4.4±3.3	5.5±4.6	<0.001
Median (inter-quartile range)	5(3–9)	14 (7–26)	12 (4–15)	7(5–12)	4 (2–6)	5 (3–7)	
Complete remission[e] (%)	19	33	14	50[f]	10	13	<0.0001
Partial or complete remission[e] (%)	24	33	18	53[f]	19	16	<0.0001
1-year renal survival (%)	86	83	74	88	89	86	—[g]
3-year renal survival (%)	67	NA	33	76	75	65	—[g]

MAP=mean arterial pressure; NA=not available; NOS=not otherwise specified.
Note: Test does not include cellular FSGS variant.
Numbers are mean±s.d. or percentages, unless stated.
[a]Collapsing vs others.
[b]Collapsing, Tip vs Perihilar, NOS.
[c]Perihilar vs tip and collapsing.
[d]Tip vs Collapsing.
[e]Patients with less than 0.5 mg/dl increase in serum creatinine at follow-up.
[f]Tip vs others.
[g]See survival analysis (figure).

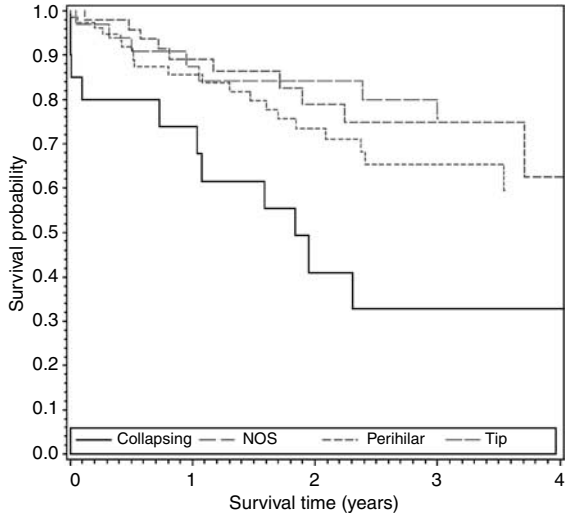
The sociodemographic, clinical presentation, and pathologic findings across the different variants of FSGS are discussed below.

Collapsing FSGS

Collapsing FSGS had a striking pre-dilection for African-Americans and typically presented with severe nephrotic syndrome (mean proteinuria >10 g/day) and substantial renal insufficiency, as has been reported in earlier studies[10,11,15] (Table 1). There was no sex pre-dilection. These patients were on average younger than patients with the other FSGS variants, although all variants had a wide age range. Collapsing FSGS patients had the worst 1-year (74%) and 3-year (33%) renal survival (Figure 2), and only 14% of patients were in complete remission at the end of follow-up. Pathologically, collapsing FSGS had the highest total injury score with the highest levels of injury in glomeruli, tubules, and interstitium, but this was not statistically significant (Table 2). Thus, differences in the histologic severity of injury in collapsing FSGS did not explain the markedly worse prognosis and supports the possibility that the nature of the injury was inherently different.

Tip lesion FSGS

Tip lesion FSGS patients had a disproportionately low percentage of African-Americans (15%), which is in striking contrast to the increased proportions of African-Americans with collapsing FSGS (91%). Tip lesion FSGS patients usually presented with severe nephrotic syndrome with a mean 24 h urine protein of 9.7 g, mean serum albumin of 2.5 g/dl, and mean serum cholesterol of 359 mg/dl (Table 1). Although both tip lesion FSGS and collapsing FSGS presented with more frequent and more severe nephrotic syndrome than other variants of FSGS, the initial and final renal function was least impaired in tip lesion FSGS patients and most severely



Patients at risk					
Collapsing	20	12	5	3	3
NOS	78	47	33	17	6
Perihilar	50	35	21	12	4
Tip	34	26	22	19	11

Figure 2 | Renal survival of patients with focal segmental glomerulosclerosis by variant subtype. $P=0.0016$ by the log-rank test. Numbers below the table represent patients at risk at each time point.

Table 2 | Pathologic findings in renal biopsy of focal segmental glomerulosclerosis variants

Pathology findings	Focal segmental glomerulosclerosis variants (*N*=197)					
	Cellular (*N*=6)	Collapsing (*N*=22)	Tip (*N*=34)	Perihilar (*N*=52)	NOS (*N*=83)	*P*-value
Glomerular sclerosis/consolidation (0–4)	1.3±1.0	2.0±1.0	0.8±0.5[a]	1.9±1.0	1.8±1.0	<0.0001
Interstitial fibrosis (0–4)	1.9±1.0	2.1±0.9	0.9±0.7[a]	2.0±0.9	2.0±1.0	<0.0001
Tubular atrophy/injury (0–4)	1.9±1.0	2.2±0.9	0.9±0.7[a]	2.0±0.9	1.9±1.0	<0.0001
Interstitial leukocytes infiltration (0–4)	0.8±0.3	1.5±0.8	0.5±0.5[a]	1.2±0.8	1.2±0.8	<0.0001
Arteriosclerosis (0–4)	1.4±1.1	1.2±1.2[b]	0.8±0.9[b]	1.8±1.0	1.9±1.1	<0.0001
Total injury score (0–16)[c]	5.2±2.8	6.3±2.7	2.5±1.5[a]	5.9±2.6	5.6±2.9	<0.0001

NA=not available; NOS=not otherwise specified.
Note: A minimum of five glomeruli was required for inclusion in the study. Cellular variant not included in analysis.
[a]Tip compared to others.
[b]Collapsing and Tip vs Perihilar and NOS.
[c]Sum of the scores for arteriolar, glomerular and interstitial sclerosis, and tubular atrophy.

impaired in collapsing FSGS patients. Of all FSGS variants, tip lesion FSGS patients had the highest rate of complete remission (50%) and the highest rate of renal survival at 3 years (76%) and 5 years (76%) (Figure 2). After adjusting for corticosteroid exposure, complete remission was still significantly higher for tip lesion FSGS compared to other variants ($P<0.001$). In accord with the better preservation of renal function, pathologic evaluation revealed the least severe tubulointerstitial injury and total injury score in patients with tip lesion FSGS (Table 2). Tip lesion patients also had the least severe arteriosclerosis even though these patients were on average older than the other groups. This finding is in line with the clinical observation that tip lesion FSGS patients had the lowest frequency of hypertension.

Perihilar FSGS

Patients with perihilar FSGS had the lowest frequency of nephrotic syndrome (55%) and the highest frequency of hypertension (80%) (Table 1). At presentation, they had slightly lower mean serum albumin (3.7 g/dl), lowest mean serum cholesterol (242 mg/dl), and lowest mean 24 h urine protein (4.4 g). These patients had the lowest serum creatinine at presentation and a low rate of complete and partial remission (around 10% for each); they had good renal survival at 1 year (89%) and 3 years (75%) (Figure 2). Perihilar FSGS did not have a pre-dilection for African-Americans.

Cellular FSGS

Given the low frequency of the cellular FSGS as defined by the Columbia system, no conclusions could be reached about its typical clinical features or outcomes.

NOS FSGS

Patients with FSGS NOS tended to have clinical and pathologic parameters that were intermediate with respect to the spectrum of findings in the other distinctive variants, although this group was most similar to the perihilar FSGS group (Tables 1 and 2). Hypertension (80%) and nephrotic syndrome (67%) were common. Complete remission was low at 13%, and renal survival at 3 years was 65% (Figure 2). Pathologic evaluations indicated that this variant probably is not merely an advanced phase of the other distinctive variants because glomerular sclerosis and chronic tubulointerstitial injury were not particularly severe.

DISCUSSION

The data on idiopathic FSGS in adults encompass a pathologically diverse group of diseases with different demographic characteristics, clinical manifestations, and outcomes. The most striking demographic finding was the markedly increased proportion of African-Americans with collapsing FSGS (91%) and substantially lower proportion of African-Americans with tip lesion FSGS (15%). At presentation, collapsing FSGS and tip lesion FSGS usually had severe nephrotic syndrome with mean 24 h protein excretions of 10.0 and 9.7 g/day, respectively, whereas perihilar FSGS and FSGS NOS had less proteinuria with mean 24 h protein excretions of 4.4 and 5.5 g/day, respectively. Although collapsing FSGS and tip lesion FSGS presented with similarly severe proteinuria, the outcomes were dramatically different. Collapsing FSGS had a low complete remission rate (14%) and low 3-year renal survival (33%), whereas tip lesion FSGS had the highest complete remission rate (50%) and the best 3-year renal survival (76%). In addition to less severe nephrotic syndrome, perihilar FSGS and FSGS NOS tended to have more hypertension clinically and more arteriosclerosis pathologically.

Two recent papers studied clinical–pathologic correlates of patients with FSGS utilizing this working proposal of the morphologic classification of FSGS.[8,15] An analysis of 47 patients with tip lesion FSGS showed that patients were predominantly Caucasians and often had nephrotic syndrome and severe proteinuria at presentation, similarly to patients in our study.[8] In addition, patients often had mild histologic features and preserved renal function. Of 29 patients with follow-up, 59% achieved complete remission of nephrotic syndrome at a mean follow-up of 21.5 months and one lost renal function.[8] The study by Chung *et al.* compared three FSGS variants, but only two of the variants were defined using the Columbia working proposal criteria.[15] Similar to our results, these patients with tip lesion FSGS and 'cellular

FSGS' (that we call collapsing FSGS) more often had nephrotic syndrome and low serum albumin at presentation than those with 'classic FSGS'. However, the degree of interstitial fibrosis and glomerulosclerosis in their study was not different among their three groups of patients. Five of 11 patients with tip lesion FSGS achieved complete remission and three of 11 progressed to end-stage renal disease at a mean of 99 months of follow-up.[15]

Our study showed complete remission in 50% of patients with tip lesion FSGS, similar to the above studies. These patients had mild chronic histologic features compared to other variants. However, we were not able to show a renal survival advantage comparing patients with tip lesion FSGS and those with perihilar FSGS and FSGS NOS.

The current study does not define the relative frequency of various FSGS categories because of sampling techniques used that caused a selection bias in favor of patients with collapsing and tip lesion FSGS. These patients more often present with nephrotic syndrome or increased creatinine, and, therefore, they are more likely to have a kidney biopsy, an inclusion criterion for our study. However, the low frequency of cellular FSGS as defined by the Columbia classification system in our study and others[15] raises the issue of whether or not this is a distinctive category of FSGS. The hallmark of the cellular lesion as defined by the Columbia classification, endocapillary foam cells, can be seen in the other variants of FSGS and are particularly conspicuous in many examples of tip lesion FSGS. One possibility is that some lesions that would fulfill the criteria for cellular FSGS are, in fact, advanced stages of tip lesion FSGS in which the cellular consolidation has spread from the tip to involve a greater portion of the glomerular tuft.

The argument has been raised that the various structural appearances observed in FSGS are merely random patterns of injury that do not define distinct subsets of patients with different disease processes. The data in this study do not support this argument because of the significant differences in demographics, clinical presentation, and outcomes that correlate with the different patterns of injury. In addition, the pathologic findings on the initial renal biopsy specimens do not support the concept that these different histologic appearances represent different temporal phases in the evolution of the injury because there was no clear progression of chronicity among the groups.

Further support for the distinctiveness of the pathologic variants and for the possibility that they result from different etiologies and pathogenic mechanisms is provided by the correlation of these variants with specific forms of secondary FSGS. For example, known secondary causes of FSGS including human immunodeficiency virus-associated FSGS[16] and most FSGS caused by pamidronate[17] manifest as collapsing FSGS and not as tip lesion FSGS or perihilar FSGS. Likewise, perihilar FSGS is the typical glomerular injury caused by obesity[18] or reduced renal mass.[19,20] Thus, recognized causes of FSGS usually produce specific patterns of injury that correspond to histologic variants in patients with idiopathic FSGS, which supports the concept that these variants are not random variations caused by a common pathogenic mechanism, but rather are the result of different etiologies.

The recognition of distinctive variants of disease that are subsumed under the imprecise term FSGS is only a first step toward recognizing etiologically and pathogenetically distinct variants of FSGS, so that appropriate prevention and treatment can be identified.

MATERIALS AND METHODS

Study design and population

A cohort of adult patients with biopsy-proven idiopathic FSGS diagnosed between March 1982 and July 2001 within the Glomerular Disease Collaborative Network (GDCN) was evaluated. The GDCN is a consortium of over 200 nephrologists from throughout the southeastern United States who submit renal biopsy specimens to the University of North Carolina Nephropathology Laboratory. Since 1998, the GDCN has been actively recruiting both prospective and retrospective diagnoses for an ongoing FSGS registry. Clinical data is prospectively gathered from the time of renal biopsy diagnosis until the patient reaches end-stage renal disease or dies. Patients were eligible for the current study if they were older than 21 at the time of renal biopsy and signed an informed consent for participation in the registry.

Patients with sickle cell disease, reflux nephropathy, single kidney, human immunodeficiency virus infection, and a documented history of sleep apnea were excluded by review of the medical records. Obesity was not an exclusion criterion in this study because patient weights were most often measured at disease presentation when patients frequently had nephrotic syndrome with significant edema, which prevented reliable estimates of body mass index. Patients with FSGS in renal transplant biopsies were also excluded. Renal biopsies containing less than five glomeruli per level of section in light microscopy were excluded. The study was approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina.

Kidney biopsy methods

Kidney biopsy specimens were evaluated by (1) light microscopy on formalin–fixed, paraffin-embedded tissue using hematoxylin and eosin, periodic acid Schiff, and Masson trichrome staining; (2) immunofluorescence microscopy on frozen tissue using fluoresceinated antibodies to immunoglobulin (Ig)G, IgA, IgM, kappa light chains, lambda light chains, C3, C1q, and fibrin; and (3) transmission electron microscopy on tissue fixed in 2.5% gluteraldehyde and plastic embedded. Patients with any of the structural expressions of FSGS were entered into the registry. Pathologic findings in the vascular, glomerular, and interstitial compartments, including arteriosclerosis, glomerular sclerosis, interstitial fibrosis, interstitial leukocyte infiltrate, and tubular injury or atrophy, were scored using a semiquantitive scale of 0 = normal, 1 = mild, 2 = moderate, 3 = moderately severe, and 4 = severe. A global chronicity score was calculated by the sum of the individual scores for arteriosclerosis, glomerular sclerosis, interstitial fibrosis, and tubular atrophy with a maximum score of 16.

The renal biopsy materials were categorized according to the Columbia FSGS classification system[13] independently by the study

pathologists, DBT and JCJ. A summary of the classification system is included in Table 1. Renal biopsy review was carried out without the knowledge of clinical outcomes. Agreement in diagnosis was 97%. In the remaining 3% of cases ($N=6$), agreement was reached by a second review of the slides.

Classification of FSGS

Major histologic criteria for the five FSGS variants are summarized below and representative images provided in Figure 1. All variants had segmental consolidation of some glomeruli that was either predominantly sclerotic or cellular. Glomerular sclerosis was defined as the extracellular accumulation or condensation of matrix that impinged on or obliterated capillary lumens.

'Cellular' variants of FSGS have been recognized for decades.[21] However, the term 'cellular FSGS' has been used for distinctly different patterns of glomerular injury. This likely has led to the description of different clinical presentations and outcomes in the literature.[15,21] In the current study, we use the Columbia classification system in which the two variants of FSGS with the most conspicuous 'cellularity' are divided into 'cellular' variant of FSGS and 'collapsing' variant of FSGS. The increased cellularity in cellular variant of FSGS as defined by the Columbia system is caused by endocapillary hypercellularity (inside the glomerular basement membrane) usually with foam cells (Figure 1c). Whereas in the collapsing variant of FSGS, the increased cellularity is caused by extracapillary hypercellularity outside the glomerular basement membrane caused by epithelial hypertrophy and hyperplasia (Figure 1a). The tip lesion variant of FSGS also often but not always has segmental increased cellularity caused by a combination of endocapillary foam cells and hypertrophied epithelial cells that are in segments contiguous with the proximal tubular epithelial cells (Figure 1b). Perihilar FSGS is characterized not only by the perihilar location of lesions but also by the presence of hyalinosis (Figure 1d). The NOS FSGS category is a nonspecific category that may include unrecognizable stages of the other variants as well as other unrelated disease processes that fulfill the general pathologic definition of FSGS.

Clinical data and definitions

Medical records were reviewed for demographics and clinical findings at renal biopsy and at 3-month (± 1 month) intervals of follow-up. Data were collected on disease presentation, co-morbidities, medications, and findings by physical examination. Information was also recorded on FSGS treatment, use of antihypertensive agents, and renal and patient outcomes including the outcome of the nephrotic syndrome, initiation of dialysis, receiving a kidney transplant, or death. Serum creatinine, albumin and cholesterol, and urinary protein excretion were recorded when available.

Nephrotic syndrome was defined as urinary protein excretion higher or equal to 3.5 g/day associated with serum albumin of less than 3.5 g/dl. Complete remission was considered as a reduction in proteinuria to less than or equal to 0.6 g/24 h with stable serum creatinine (not more than 25% increase in serum level between biopsy diagnosis and each proteinuria evaluation). Partial remission was defined as a reduction in proteinuria to less than 3.5 g and higher than 0.6 g/24 h, and stable renal function in patients presenting with nephrotic syndrome. Renal failure was defined as a sustained doubling of the serum creatinine, or by initiation of chronic dialysis or kidney transplantation.[22] Hypertension was defined as a blood pressure of 130/90 mmHg or higher or the use of antihypertensive drugs.

Statistical analysis

Demographics, pathologic parameters, and clinical and laboratory findings at renal biopsy and follow-up were evaluated across FSGS subtypes using a continuity adjusted χ^2 test or Fisher exact test, as required by the available sample size and frequency distribution. Continuous variables were compared between subgroups of FSGS using analysis of variance or a log-rank test for variables, if assumptions for analysis of variance were not met. As this was considered an exploratory hypothesis generating analysis and not a hypothesis testing analysis, an adjustment for multiple testing was not carried out and a P-value of <0.05 was considered statistically significant. Results are reported as means $\pm$ standard deviation (s.d.). Kaplan–Meier renal survival estimates were calculated and a log-rank test was used to compute a non-parametric test for inequality of survival curves between groups. Analysis was performed using SAS version 8.1 statistical software (SAS Institute, Cary, NC, USA).

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