Focal Segmental Glomerulosclerosis in Nephrotic Adults: Presentation, Prognosis, and Response to Therapy of the Histologic Variants

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Abstract. The histopathologic diagnosis of primary focal segmental glomerulosclerosis (FSGS) has come to include a number of histologic lesions (variants), but the prognostic significance of these discrete lesions is controversial because published information regarding the presentation, course, and response to treatment is limited. A retrospective analysis was conducted of 87 nephrotic adult patients with biopsy-proven primary FSGS. Patients were categorized on the basis of histologic criteria into those with a classic scar (36 patients), the cellular or collapsing lesion (40 patients), or the tip lesion (11 patients) of FSGS to evaluate differences in presentation, response to therapy, and clinical outcomes. The clinical features at biopsy were similar among the three groups with the exception that patients with the tip lesion were older and patients with the collapsing lesion had more severe proteinuria. Over the course of follow-up, 63% of patients treated attained remission and the response to steroid therapy was similar among the groups (classic scar 53% *versus* collapsing lesion 64% *versus* tip lesion 78%; $P = 0.45$). The overall renal survival was significantly better for patients who entered remission compared with patients who did not enter remission (92% *versus* 33% at 10 yr; $P < 0.0001$). The renal survival at 10 yr for patients who entered remission was similar among the three groups (classic scar 100% *versus* tip lesion 100% *versus* collapsing lesion 80%; $P = 0.61$). In patients who did not enter remission, the renal survival at 10 yr was significantly worse for patients with collapsing lesion and tip lesion (classic scar 49% *versus* tip lesion 25% *versus* collapsing lesion 21%; $P = 0.002$). In conclusion, the prognosis for nephrotic FSGS patients who enter remission is excellent regardless of the histologic lesion. Because the remission rate after treatment is similar among patients with the histologic variants, response to therapy cannot be predicted on the basis of histology alone. Thus, nephrotic patients with primary FSGS should receive a trial of therapy irrespective of the histologic lesion when not contraindicated.

Focal segmental glomerulosclerosis (FSGS) is a pattern of injury defined by a segmental scar, which involves some but not all glomeruli. When all of the secondary causes of this pattern of injury are eliminated, the remaining patients receive a diagnosis of primary FSGS. Although patients with primary FSGS may present with any level of proteinuria, clinical concern is greatest for those who present with nephrotic-range proteinuria because without treatment, they have an extremely poor prognosis, progressing to ESRD over the course of 3 to 6 yr (1,2). However, it is widely recognized that the prognosis in nephrotic patients with primary FSGS is significantly improved when remission of proteinuria is achieved. Because >50% of nephrotic adult patients with FSGS respond to an aggressive course of steroids, a trial of therapy has been recommended (1,3–5).

Received April 14, 2004. Accepted May 29, 2004.

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1046-6673/1508-2169
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000135051.62500.97

Over the last 20 yr, in addition to the "classic" segmental scar, a number of histologic lesions or variants have been included in the diagnosis of primary FSGS, most notably the cellular or collapsing lesion and the tip lesion (6–10). The importance of recognizing these variants is the putative difference in prognosis and therapeutic response associated with the different lesions. Recently, a pathologic classification of FSGS has been proposed (7,9), but the prognostic and therapeutic utility of such a classification remains controversial (11,12), largely because studies that have assessed the clinical relevance of the histologic variants of primary FSGS in nephrotic patients are few and conflicting (6,13–17).

We previously published our experience with the cellular lesion in adults with primary FSGS, which found that the response to therapy and outcome for patients in remission were similar to patients with the classic scars of FSGS (16). We now present our enlarging experience in nephrotic adults with primary FSGS, with increased follow-up, to evaluate the importance of the tip and cellular or collapsing lesions of FSGS.

Materials and Methods

We conducted a retrospective, clinicopathologic analysis of adult patients (>15 yr of age at presentation) who had primary FSGS and nephrotic-range proteinuria (>3 g/d) and were seen by the Renal

Pathology Service and followed by the Section of Nephrology at Rush University Medical Center (Chicago, IL) between 1975 and 2001. The diagnosis of primary FSGS was established when there was no immunopathologic or ultrastructural evidence for another primary glomerular disease or a systemic disease associated with secondary segmental glomerular sclerosis and when review of the medical records of each patient revealed no evidence of systemic disease, other diseases associated with glomerulopathy, morbid obesity, reflux, HIV infection, nephrectomy, solitary kidney, intravenous drug abuse, or a family history of renal disease. On the basis of these criteria, we identified a total of 117 patients with primary FSGS; nephrotic-range proteinuria was present in 87 of these patients, and they form the basis of this study.

Definition of FSGS and Pathology Studies

Inclusion in this study required a minimum of five glomeruli in the light microscopic section. The pathologic diagnosis of FSGS was established by the finding of at least one glomerulus with a segmental lesion, and some of the remaining glomeruli were relatively normal. Although the segmental nature of this lesion was usually obvious, we accepted a lesion as segmental when at least one unscarred lobule with patent capillaries was present in the involved glomerulus. Three morphologic forms of FSGS were included: the classic scar (Figure 1), the cellular or collapsing lesion (Figure 2), and the tip lesion (Figure 3).

The classic scar is defined by a segmental scar that is located either at the hilum or in the glomerular periphery. The scar comprises either the obliteration of the glomerular architecture and replacement by collagen or segmental glomerular collapse without a "cellular" lesion. The overlying parietal and visceral epithelium may be prominent, especially when associated with an adhesion, but it is not stratified. This lesion is frequently associated with hyalinosis and adhesions. The finding of a cellular or a tip lesion (see below) excludes the biopsy from the classic scar category.

We use the term "cellular" lesion as we originally defined it in 1985 (18), and it is identical to collapsing lesion (12,19) described by Weiss *et al.* (20), Detwiler *et al.* (13), and Valeri *et al.* (17). The diagnosis of "cellular" FSGS requires at least one glomerulus with segmental or global glomerular collapse with hypertrophy and hyperplasia of the overlying visceral epithelium. Collapse means that the glomerular capillaries are obliterated with loss of endothelium, wrinkling, and folding of the glomerular basement membranes without destruction or replacement with excess collagen. The hypertrophic epithelial cells have vesicular nuclei with prominent nucleoli and copious, basophilic cytoplasm with vacuoles, and periodic acid-Schiff (PAS)–positive droplets. Epithelial hyperplasia is evidenced by stratification of often poorly cohesive cells that have occasional mitoses. Involved glomeruli may show segmental endocapillary hypercellularity with foam cells and macrophages, and adhesions are occasionally

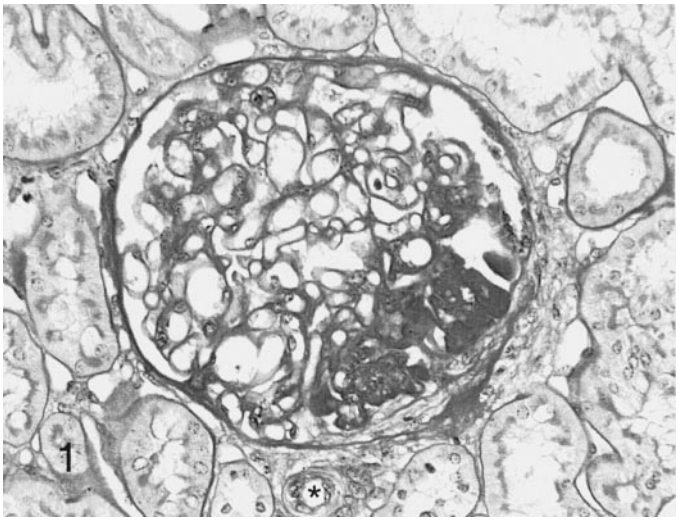


Figure 1. Classic focal segmental glomerulosclerosis (FSGS). A segmental scar with an adhesion to Bowman's capsule and hyalinosis is present in the perihilar region of the glomerulus. Hilar arteriole (*). Magnification, ×66, periodic acid-Schiff (PAS) stain.

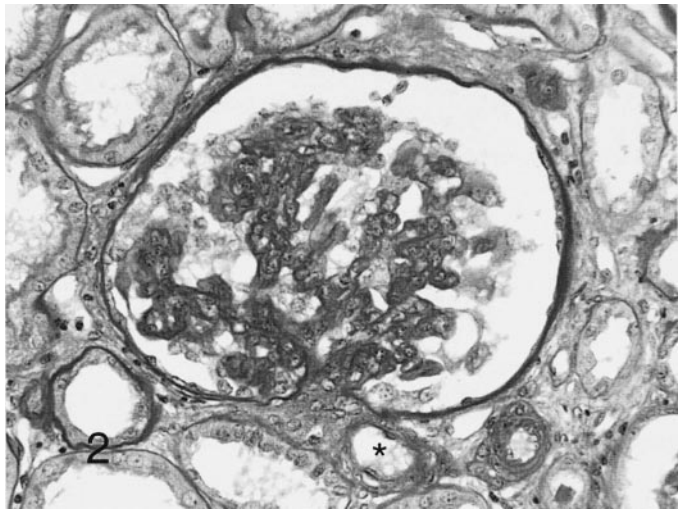


Figure 2. The cellular lesion of FSGS. The entire glomerular tuft shows collapse of capillaries and proliferation, hypertrophy, and vacuolization of the visceral epithelium. Afferent arteriole at the juxtaglomerular apparatus (*). Magnification, ×66, PAS stain.

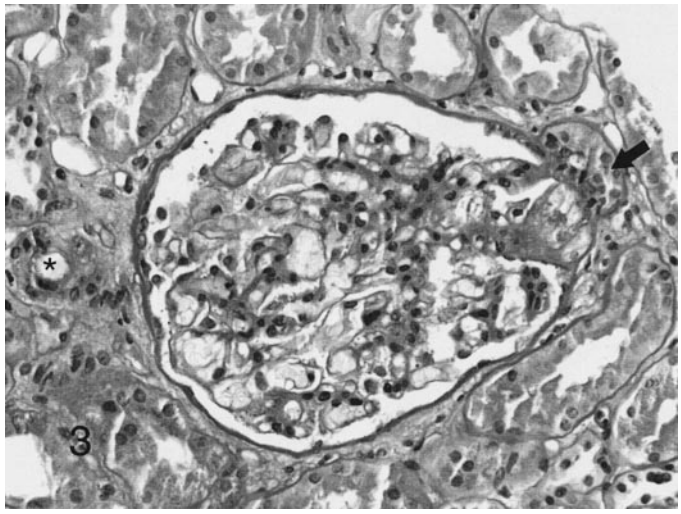


Figure 3. The tip lesion of FSGS. A single glomerular lobule is adherent to Bowman's capsule at the origin of the proximal tubule (➡). The involved capillaries are occluded by foamy macrophages, and the uninvolved glomerulus has patent capillaries and normal mesangial matrix and cellularity. Hilar arterioles (*). Magnification, ×66, PAS stain.

present. In contrast, D'Agati *et al.* (7–9) defined the cellular lesion as a glomerulus with a segmental endocapillary hypercellularity in the absence of hypertrophy and hyperplasia of the overlying epithelial cells. We (S.M.K. and M.M.S.) reviewed the slides of every patient in this series and found none that would be classified as a cellular lesion by the recently proposed classification (7,9). Thus, for the remainder of this article, the cellular and collapsing lesions are considered to be synonymous. Classic scars and global sclerosis are frequently seen along with the cellular/collapsing lesion of FSGS.

The "tip lesion" variant of FSGS is defined by segmental glomerular pathology that involves the tubular pole of Bowman's capsule (the origin of the proximal tubule must be present in at least one involved glomerulus). As originally described by Howie *et al.* (21), the lesion is small, involving only one glomerular lobule or a few capillaries, and there is an adhesion between the involved, distal tuft and the parietal epithelium or the underlying stroma at the tubular pole of the glomerulus. The segmental glomerular pathology includes capillary collapse, infiltration with foam cells and macrophages, and proliferation and hypertrophy of the overlying podocytes. As defined, there is overlap of the pathologic features seen in the tip and the cellular lesions, but the tip lesion is distinguished by its small size and location. Global sclerosis and classic lesions may occur in cases of the tip lesion, but a cellular lesion excludes the biopsy from this category.

Renal biopsy tissue was divided and processed for light, fluorescence, and electron microscopy. Fluorescence and electron microscopy was used to exclude nonprimary causes of FSGS, but the light microscopic examination of slides stained with hematoxylin and eosin, Masson's trichrome, PAS, and methenamine silver–PAS (Jones stain) provided the diagnosis of FSGS and categorization into one of the three groups. The percentage of interstitial fibrosis was calculated using an ocular grid and point-counting on trichrome stained sections of renal cortex. The renal pathologist (M.M.S.), who was blinded to the clinical data, performed the histologic evaluation. The pathologic classification of the 87 nephrotic adults was as follows: classic scars, 36 patients (41%); cellular lesion, 40 patients (46%); and tip lesion, 11 patients (13%).

Clinical Studies and Laboratory Examination

Demographic, clinical, and laboratory information at the time of renal biopsy and at follow-up was obtained on each patient. Clinical records were reviewed to determine the patients' race, gender, age, BP, level of protein excretion, serum creatinine, and serum albumin at the time of biopsy. Presentation was defined as the time when proteinuria was first detected. Renal insufficiency was defined as a serum creatinine >1.3 mg/dl. ESRD was defined as a serum creatinine ≥ 5 mg/dl or the need for renal replacement therapy. The level of proteinuria at the time of biopsy was categorized as (*1*) nephrotic-range proteinuria defined as >3 g/d protein and (*2*) massive proteinuria defined as >10 g/d protein. Nephrotic syndrome was defined as nephrotic-range proteinuria and hypoalbuminemia (≤ 3.5 g/dl). Hypertension was defined as a systolic BP >140 mmHg and a diastolic BP >90 mmHg. In patients with nephrotic proteinuria, complete remission was defined as a urine protein of ≤ 0.3 g/d, and partial remission was defined as a urine protein between 0.31 and 2.5 g/d.

Treatment

The decision to treat patients with immunosuppressive therapy, including corticosteroids, was based solely on physician discretion. A total of 51 (59%) patients received treatment. From 1975 to 1994 50% (31 of 62) of patients received treatment. In 1994, we reviewed the response to therapy in primary FSGS (22) and thereafter recommended a trial of steroid therapy in nephrotic patients with primary FSGS in whom renal function is well preserved (serum creatinine <3 mg/dl) and in whom it is not contraindicated (*e.g.*, morbid obesity, diabetes). From 1994 to 2001, 80% (20 of 25) of patients seen received treatment. Although no specific therapeutic regimen was used, we proposed a more aggressive approach to the treatment of nephrotic adults with primary FSGS. This comprises an initial course of prednisone given at a dose of 1 mg/kg per day (up to 80 mg) for 3 to 4 mo. In patients who demonstrated complete or partial remission, the dose of prednisone was then tapered slowly over 2 to 3 mo. Patients who were unresponsive to the initial therapy were tapered off prednisone more rapidly, over 4 to 6 wks. To minimize toxicity in the elderly, an alternate-day prednisone regimen (1 to 2 mg/kg up to 120 mg) was used for 4 to 5 mo.

Statistical Analyses

Categorical data were analyzed using the χ^2 test. Mann-Whitney and ANOVA using Dunn multiple comparison tests were used for evaluating the continuous data. Renal survival time from the date of biopsy to ESRD was determined by product-limit life-table distributions and compared using a log-rank test. Data are reported as a mean $\pm$ SD. $P < 0.05$ is considered significant.

Results

Clinical Characteristics

The clinical characteristics at biopsy of the 87 nephrotic patients, based on their histologic classification (classic scars, 36 [41%] patients; cellular lesion, 40 [46%] patients; and tip lesion, 11 [13%] patients), are shown in Table 1. The demographic features (race and gender) were similar among the three groups with the exception that patients with the tip lesion were older at biopsy. The level of proteinuria, the proportion of patients with proteinuria >10 g/d, and the degree of hypoalbuminemia were significantly greater in patients with the cellular lesion compared with those patients with the classic scar. Patients with the tip lesion had more hypoalbuminemia than patients with the classic scar, but the severity of proteinuria was not significantly different. The time from presentation to biopsy was shortest in patients with the tip lesion, but this was not significantly different from patients with classic scars or cellular lesions.

Pathology Studies

The pathologic features are shown in Table 2. The overall average number of glomeruli for evaluation by light microscopy was 25 ± 17 (in 90% of biopsies, there were ≥ 10 glomeruli), and this was similar among the three groups of patients. The proportion of glomeruli with classic segmental scars was significantly larger in patients with classic FSGS compared with patients with cellular (19 patients had classic segmental scars) or tip lesions (one patient had classic segmental scars). In patients with classic FSGS, classic segmental scars involved $<20\%$ ($12 \pm 5\%$; median, 12%) of glomeruli in 27 (75%) patients and $\geq 20\%$ ($27 \pm 4\%$; median, 26%) of glomeruli in nine (25%) patients. In patients with the cellular lesion, the overall proportion of glomeruli with segmental or global cellular lesions was $22 \pm 18\%$. In the majority of patients (24 patients [60%]) with the cellular lesion, the pro-

Table 1. Baseline characteristics at biopsy[a]

Characteristics	Classic FSGS	Cellular Lesion	Tip Lesion	*P*
n	36	40	11	
Black	23 (64%)	29 (73%)	6 (55%)	NS
Male	23 (64%)	23 (58%)	5 (45%)	NS
Age (yr)	40 ± 17	38 ± 16	53 ± 17[c,d]	<0.05
Hypertension	18 (50%)	18 (45%)	8 (73%)	NS
Creatinine (mg/dl)	1.7 ± 0.8	2.5 ± 2.1	1.6 ± 0.7	NS
Renal insufficiency	19 (53%)	27 (68%)	6 (55%)	NS
Proteinuria (g/d)	6.6 ± 3.5	12.5 ± 9.9[b]	8.6 ± 4.0	<0.05
Proteinuria >10 g/d	6 (17%)	17 (43%)[b]	3 (27%)	<0.05
Albumin (g/dl)	3.2 ± 1.0	2.7 ± 0.8[b]	2.5 ± 0.7[c]	<0.05
Nephrotic syndrome	21 (58%)	32 (80%)[b]	10 (91%)[e]	<0.05
Presentation to biopsy (mo)	13 ± 29	9 ± 19	3 ± 5	NS

[a] Results are given as mean ± SD. FSGS, focal segmental glomerulosclerosis.
[b] $P < 0.05$ cellular *versus* classic.
[c] $P < 0.05$ tip *versus* classic.
[d] $P < 0.05$ tip *versus* cellular.
[e] $P = 0.06$ tip *versus* classic.

Table 2. Pathology studies[a]

Characteristics	Classic FSGS	Cellular Lesion	Tip Lesion	*P*
n	36	40	11	
Total glomeruli	22 ± 14	27 ± 22	21 ± 8	NS
Classic segmental scar (%)	16 ± 8[c,d]	4 ± 6	4 ± 13	<0.001
Global sclerosis (%)	21 ± 23	18 ± 21	8 ± 11	NS
Segmental cellular lesion (%)	—	12 ± 12	—	—
Global cellular lesion (%)	—	10 ± 11	—	—
Total cellular lesions (%)	—	22 ± 18	—	—
Tip lesions	—	—	12 ± 6	—
Total involvement (%)[b]	37 ± 24	43 ± 23[e]	24 ± 17	<0.05
Interstitial fibrosis (%)	21 ± 13	23 ± 14	18 ± 8	NS

[a] Results are given as mean ± SD.
[b] Percentage of glomeruli with any glomerular lesion.
[c] $P < 0.001$ classic *versus* cellular.
[d] $P < 0.001$ classic *versus* tip.
[e] $P < 0.05$ cellular *versus* tip.

portion of glomeruli with cellular lesions (segmental plus global) was <20% (10.6 ± 4%; median, 11%) of glomeruli. Segmental and global cellular lesions involving ≥20% (39 ± 17%; median, 33%) of glomeruli was observed in 16 (40%) patients. The percentage of cortical interstitial fibrosis was similar among the three groups. There was no significant difference in the percentage of interstitial fibrosis among patients with classic or cellular lesion on the basis of the degree of involvement (<20% *versus* ≥20% classic or cellular lesions).

Clinical Course and Outcome

A total of 51 (59%) patients were treated with steroids (Table 3). On average, patients received high-dose prednisone therapy (60 mg/d) for 3.18 ± 1.49 mo (mean ± SD; median, 3.00), and the total course of therapy, including the steroid taper was 8.99 ± 9.93 mo (mean ± SD; median, 6.00 mo). Although the proportion of patients who were treated was not significantly different among the groups ($P = 0.1$), a larger proportion of patients with the tip lesion were treated compared with patients with classic FSGS or the cellular lesion. The duration of high-dose prednisone therapy was not significantly different among the three groups: classic scar, 3.26 ± 2.04 mo (median, 3.00); cellular lesion, 3.35 ± 1.16 mo (median, 3.00); and tip lesion, 2.57 ± 1.00 mo (median 3.00). The total therapeutic course also was not significantly different among the three groups: the classic scar, 12.03 ± 14.54 mo (median, 9.00); the cellular lesion, 6.83 ± 3.21 mo (median, 6.5); tip lesion, 9.00 ± 10.85 mo (median 5.00). In addition to steroids, 11 patients received cyclophosphamide or cyclosporin as part

Table 3. Outcome[a]

Characteristics	Classic FSGS	Cellular Lesion	Tip Lesion	*P*
n	36	40	11	
Treated	17 (47%)	25 (63%)	9 (82%)	NS
remission	9 (53%)[c]	16 (64%)	7 (78%)	NS
complete	6	6	5	
partial	3	10	2	
No treatment	19	15	2	
remission[b]	2	2	0	NS
Total remission	11	18	7	NS
No remission	25	22	4	
Follow-up from biopsy (mo)	73 ± 94	52 ± 45	99 ± 94	NS
ESRD	9 (25%)	17 (43%)	3 (27%)	NS
remission	1	1	0	
no remission	8	16	3	
treated	4	6	2	
no treatment	5	11	1	

[a] Results are given as mean ± SD.
[b] Partial remissions.
[c] Percentage of patients treated.

of the initial course of therapy. The proportion of patients who received these agents was not significantly different among the three groups (four patients with classic FSGS, six with the cellular lesion, and one with the tip lesion; $P = 0.7$).

Clinical and pathologic features of the treated patients are shown in Tables 4 and 5. There were no significant differences among the groups in the clinical features at biopsy in treated patients (Table 4). The degree of interstitial fibrosis and global sclerosis was similar among the groups, but the proportion of glomeruli with classic segmental scars was highest in patients with classic FSGS, and patients with cellular FSGS had a greater proportion of glomeruli with any glomerular lesion compared with patients with tip lesions (Table 5).

The duration of follow-up was similar among the three groups (Table 3). Remission (complete or partial) was attained in 32 (63%) patients treated (Table 3). The overall response to treatment among the three groups was not different; however, a larger proportion of patients with the tip lesion attained complete remission (five patients [55%]) compared with patients with classic FSGS (six patients [35%]) or the cellular lesion (six patients [24%]). The remission rate in patients who had classic FSGS with segmental scars involving ≥20% of glomeruli was 50% (two of four treated patients) compared with 54% (seven of 13 treated patients) for patients with <20% involvement with classic segmental scars (NS). The remission rate in patients with the cellular lesion involving ≥20% of glomeruli was 33% (four of 12 treated patients) compared with 92% (12/13 treated patients) for patients with <20% involvement with cellular lesions ($P = 0.008$). Of the 36 patients who were not treated, remission (spontaneous) was observed in only

Table 4. Baseline characteristics at biopsy in treated patients[a]

Characteristics	Classic FSGS	Cellular Lesion	Tip Lesion	*P*
n	17	25	9	
Black	8 (47%)	18 (72%)	4 (44%)	NS
Male	9 (53%)	14 (56%)	4 (44%)	NS
Age (yr)	40 ± 18	36 ± 17	50 ± 16	NS
Hypertension	8 (47%)	11 (44%)	6 (67%)	NS
Creatinine (mg/dl)	1.4 ± 0.5	1.9 ± 1.4	1.6 ± 0.8	NS
Renal insufficiency	7 (41%)	15 (60%)	5 (56%)	NS
Proteinuria (g/d)	7.6 ± 3.7	15.2 ± 11.3	8.6 ± 3.6	NS
Proteinuria ≥10 g/d	4 (24%)	13 (52%)	2 (22%)	NS
Albumin (g/dl)	2.8 ± 0.9	2.6 ± 0.8	2.3 ± 0.5	NS
Nephrotic syndrome	12 (75%)	21 (84%)	9 (100%)	NS
Presentation to biopsy (mo)	7 ± 11	4 ± 10	2 ± 3	NS

[a] Results are given as mean ± SD.

Table 5. Pathology studies in treated patients[a]

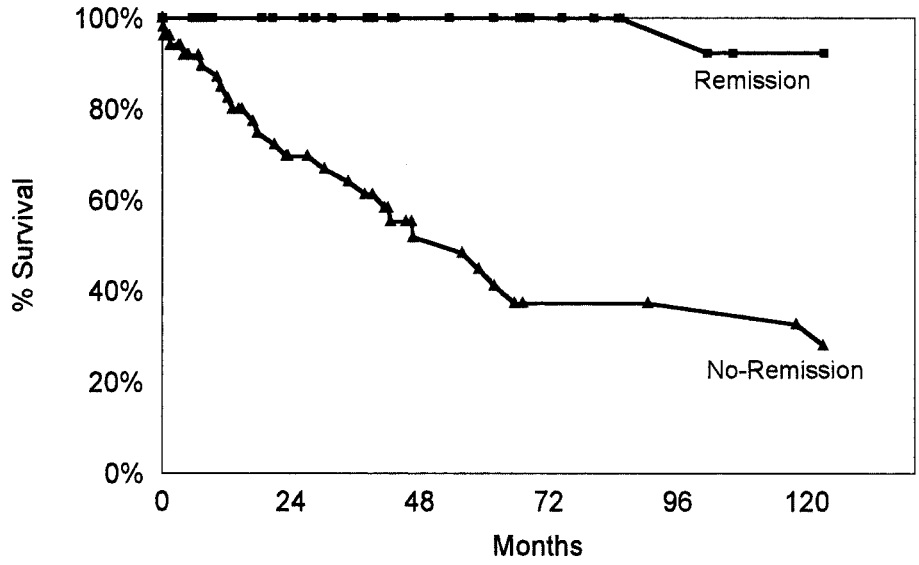
Characteristics	Classic FSGS	Cellular Lesion	Tip Lesion	*P*
n	17	25	9	
Total glomeruli	23 ± 11	22 ± 11	22 ± 8	NS
Classic segmental scar (%)	15 ± 8[c,d]	3 ± 6	5 ± 15	<0.001
Global sclerosis (%)	12 ± 12	8 ± 11	6 ± 11	NS
Segmental cellular lesion (%)	—	14 ± 13	—	—
Global cellular lesion (%)	—	10 ± 11	—	—
Total cellular lesions (%)	—	24 ± 16	—	—
Tip lesions (%)	—	—	12 ± 4	—
Total involvement (%)[b]	26 ± 15	35 ± 18[e]	23 ± 18	<0.05
Interstitial fibrosis (%)	18 ± 10	19 ± 11	17 ± 9	NS

[a] Results are given as mean ± SD.
[b] Percentage of glomeruli with any glomerular lesion.
[c] $P < 0.001$ classic *versus* cellular.
[d] $P < 0.001$ classic *versus* tip.
[e] $P < 0.05$ cellular *versus* tip.

four (11%) patients, and in all cases, these were partial remissions (63% remission rate for treated *versus* 11% for untreated patients; $P = 0.0001$).

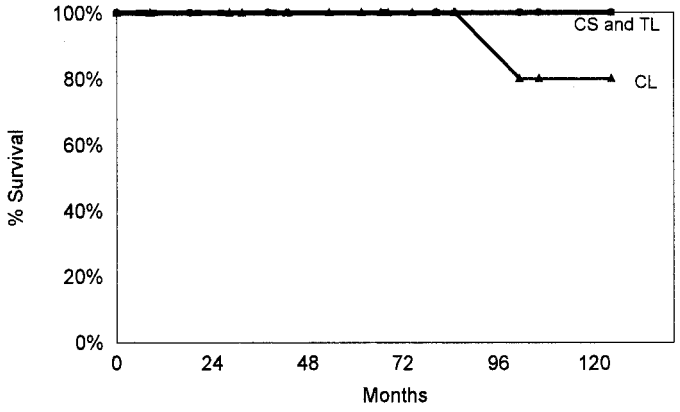
Progression to ESRD was observed in a total of 29 (33%) patients, and the proportion of patients who progressed to ESRD was greatest in patients with the cellular lesion. Overall, progression to ESRD was significantly greater in patients who did not attain remission compared with patients who attained remission (53% [27 of 51] *versus* 6% [2 of 36]; $P < 0.0001$), and this was a consistent finding irrespective of the lesion (Table 3). The proportion who progressed to ESRD for patients in remission compared with those who were not in remission was 9 *versus* 32% ($P = 0.2$) for patients with the classic lesion, 6 *versus* 73% ($P < 0.0001$) for patients with cellular lesions, and 0 *versus* 75% ($P < 0.05$) for patients with tip lesions. Progression to ESRD was significantly higher in the 36 patients who did not receive treatment (17 of 36 patients [47%]) compared with those who received a course of therapy (12 of 51 patients [24%]; $P < 0.05$; Table 3).

The overall renal survival at 5 and 10 yr in patients who attained remission was 100% and 92%, respectively (Figure 4). In patients who attained remission, the renal survival at 5 and 10 yr was 100% in patients with classic FSGS and the tip lesion and 100% and 80%, respectively, for patients with the cellular lesion (Figure 5). In patients who did not attain remission, the overall renal survival at 5 and 10 yr was significantly poorer,



Month	0	12	24	36	48	60	72	84	96	108	120
Remission	36	33	30	27	23	22	18	16	14	12	12
No-Remission	51	37	27	24	16	13	10	10	9	9	8

Figure 4. Renal survival in nephrotic FSGS patients based on remission status ($P < 0.0001$). Numbers in the table represent patients at risk at each time point.



Month	0	12	24	36	48	60	72	84	96	108	120
CS	11	9	7	6	5	5	4	4	4	4	4
CL	18	18	18	16	14	13	10	8	6	4	4
TL	7	7	7	7	6	6	6	6	6	6	6

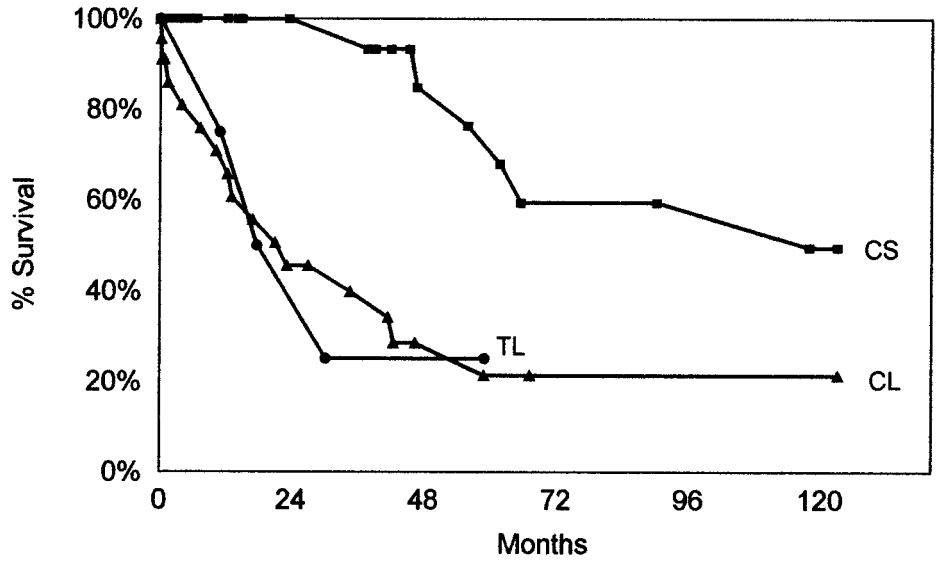
Figure 5. Renal survival in nephrotic patients who attain remission ($P = 0.61$). CS (■), classic lesion; CL (▲), cellular lesion; TL (●), tip lesion. Numbers in the table represent patients at risk at each time point.

at 45% and 33%, respectively ($P < 0.0001$; Figure 4). The renal survival at 5 and 10 yr in patients who did not attain remission was 76% and 49% in patients with classic FSGS, 21% each for patients with cellular lesions, and 25% (5 yr) for patients with tip lesions ($P = 0.002$; Figure 6). The poorer renal survivals observed for nonremitting patients with cellular and tip lesions persisted even when adjusted for the level of proteinuria at baseline. Of the four patients who had tip lesion and did not enter remission, three progressed to ESRD at 11, 18, and 30 mo. The remaining patient had good renal function at last follow-up at 59 mo.

Discussion

We reviewed the presentation and clinical course of nephrotic adults with primary FSGS to determine the significance of the classic scar and the cellular and the tip lesions. We conclude that there was no significant difference in the response to steroid treatment among the three groups, with a remission rate of >50% in all patients who received steroid therapy. In patients who entered remission, we continue to observe a significantly improved renal survival compared with patients who did not enter remission, irrespective of the histologic lesion. However, the renal survival among nephrotic patients who did not enter remission was significantly poorer for patients with cellular and tip lesions compared with patients with classic scars. Thus, in nephrotic adults with primary FSGS, the response to therapy remains the best prognostic indicator of outcome irrespective of the histologic subclassification.

In 1985, Schwartz and Lewis (18) recognized that patients with the cellular lesion had more severe proteinuria and were more often nephrotic at presentation than patients with classic segmental scars. Shortly after this, Weiss *et al.* (20), Detwiler *et al.* (13), and Valeri *et al.* (17) reported their experience in patients with an identical pathologic lesion but chose the term "collapsing" FSGS, thus emphasizing the microvascular rather than the glomerular epithelial cell features of the lesion. They confirmed that patients with this lesion had more severe proteinuria than patients with classic lesions; in addition, they found that the lesion was more commonly seen in black individuals and was associated with a poor prognosis with more



Month	0	12	24	36	48	60	72	84	96	108	120
CS	25	20	16	16	11	10	8	8	7	7	6
CL	22	15	10	8	5	4	3	3	3	3	3
TL	4	4	3	2	2	1					

Figure 6. Renal survival in nephrotic patients who did not attain remission. $P = 0.002$ by the log-rank test. CS (■), classic lesion; CL (▲), cellular lesion; TL (●), tip lesion. Numbers in the table represent patients at risk at each time point.

rapid progression to ESRD compared with patients with classic scars. As pointed out by Meyrier (12,19), although the nomenclature differs among the various reports, the histologic features of the "cellular" and "collapsing" lesions of FSGS are identical.

Our present study confirms our original observations, which is in contrast to the experience of Detwiler *et al.* (13) and Valeri *et al.* (17), who found remission rates of <20% and overall progression to ESRD in 50% of patients over 2 to 3 yr. The reason for the poorer response rate in these studies is not clear but may be due to differences in therapeutic approach and to the presence of more advanced renal disease as the level of renal insufficiency and degree of tubulointerstitial injury were greater and the involvement with cellular lesions was more widespread in the experience of Detwiler *et al.* (13) and Valeri *et al.* (17) compared with our patients. Consistent with this hypothesis is our observation that remission rates were significantly worse in patients with ≥20% cellular lesions. Thus, early recognition and treatment of patients with the cellular lesion may improve both the likelihood of a therapeutic response and the prognosis.

Initial reports in nephrotic patients with the tip lesion suggested an excellent response to steroids and favorable course similar to that of minimal-change disease rather than FSGS (14,21,23,24). Subsequent reports found that the response and course in patients with the tip lesion was similar to that of patients with FSGS and thus questioned the clinical significance of this feature (6,10,25,26). In 1985, Howie *et al.* (14) reported the clinical course in 31 patients with the tip lesion. They found that 48% of patients attained remission with steroids, and this resulted in an excellent prognosis with a 10-yr renal survival of 90%. However, in the 52% of patients who were unresponsive to treatment, the 10-yr renal survival was 30%. Thus, their experience with the tip lesion was similar to that reported in patients with classic FSGS. Recently, however, Stokes *et al.* (27) published their experience in 29 patients with he tip lesion, in whom they found the presentation and course more similar to that of minimal-change disease than FSGS. Patients with the tip lesion had a sudden onset of the nephrotic syndrome with the time from presentation to biopsy of 2.4 mo and an overall remission rate of 72% with a complete remission rate of 58%. Of the eight patients who did not attain remission, only one progressed to ESRD; however, the follow-up was only 21.6 mo overall. Our experience with the presentation and response to treatment in patients with the tip lesion reflects that of Stokes *et al.* (27). However, unlike Stokes *et al.*, we found that the prognosis in patients who did not attain remission remains poor (with an overall follow-up of 99 mo), similar to that of FSGS rather than minimal-change disease. Finally, it is of interest that Stokes *et al.* (27) found that 74% of patients with the tip lesion had coexisting segmental lesions that would preclude a diagnosis of minimal-change disease. Thus, although the prognosis is good for patients with the tip lesion given their high rate of response to therapy, the question of whether the tip lesion should be considered a variant of minimal-change disease rather than FSGS remains unresolved.

The best predictor of outcome in nephrotic patients with primary FSGS, irrespective of histologic variant, is a remission in proteinuria (1,4,5,16,28). Because spontaneous remissions are rare and the use of conservative management alone rarely leads to remission in nephrotic patients with FSGS, a trial of steroids has been recommended (2–5). In cases in which there is concern regarding the use of steroids as initial therapy, such as the obese patient or patients with diabetes, the use of cyclosporine may be a beneficial alternative, but it also has risk (1,29–31). Previous attempts to determine which patients are most likely to benefit from a trial of therapy have failed to demonstrate any clinical or histologic features at biopsy that reliably predict response (3,5,16). Recently, Bazzi *et al.* (32) showed that the fractional excretion of IgG, a measure of protein selectivity, is highly predictive of response to steroid and immunosuppressive therapy in their patients with FSGS. This observation must be confirmed in larger numbers of patients with primary FSGS (including the histologic variants). Until then, patients who have primary FSGS and remain nephrotic despite conservative treatment should receive a trial of steroids or immunosuppressive therapy.

Acknowlegments

Results of this study were presented at the 35th Annual Meeting of the American Society of Nephrology, October 2002 in Philadelphia, PA.

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