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Idiopathic collapsing focal segmental glomerulosclerosis: A clinicopathologic study

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Idiopathic collapsing focal segmental glomerulosclerosis: A clinicopathologic study. A review of all native kidney biopsies at our center from 1974 to 1993 identified 43 cases of idiopathic focal segmental glomerulosclerosis (FSGS) with predominantly collapsing features and lacking evidence of HIV-1 infection or intravenous drug use. No case was identified before 1979 and the incidence of this entity has progressively increased over the past two decades. Compared to 50 age-matched controls of idiopathic FSGS with typical perihilar scars, the group of idiopathic collapsing FSGS displayed black racial predominance, a higher serum creatinine and more severe features of nephrotic syndrome at biopsy. Morphologic features of visceral epithelial cell hypertrophy and hyperplasia, tubular microcysts, tubular epithelial degenerative and regenerative features and interstitial edema were more prevalent and severe in collapsing FSGS. Median time to ESRD was rapid in collapsing FSGS versus controls (13.0 months vs. 62.5 months, $P < 0.05$). Correlates of progression to ESRD included a higher initial serum creatinine and failure to undergo remission of proteinuria. Both glomerulosclerosis and certain features of tubular damage were independent predictors of the level of renal function at time of biopsy, but not of the rate of progression of renal insufficiency. Although three patients had partial or complete spontaneous remissions, none of 26 patients treated with steroids alone responded. Idiopathic collapsing FSGS is a variant of FSGS with increasing incidence, distinct clinicopathologic features, black racial predominance, a rapidly progressive course and relative steroid resistance.

Focal segmental glomerulosclerosis (FSGS) is a common pattern of glomerular injury comprising up to 20% of all cases of idiopathic nephrotic syndrome in adults [1]. Several independent investigators have documented the increasing frequency of both idiopathic and secondary forms of FSGS in renal biopsies in recent years [2, 3]. Although both the course of idiopathic FSGS and the response to immunosuppressive therapy may vary, many patients progress to renal failure. In an attempt to predict the prognosis and account for the heterogeneous course of patients with FSGS, a number of histopathologic patterns of FSGS have been defined including FSGS with diffuse mesangial hypercellularity, a cellular variant, and the glomerular "tip lesion" [4–7]. The prognostic importance of these histologic subsets remains controversial [8]. In 1986, Weiss and co-workers described a small group of patients with a rapidly progressive form of FSGS characterized by unusual histologic features of focal segmental and global "collapse" of the glomerular capillary walls accompanied by marked visceral cell hypertrophy [9]. All six patients had very heavy proteinuria and a rapid course to renal failure over 0.5 to 48 months. Only one of these patients was later found to have the Acquired Immunodeficiency Syndrome (AIDS), although data regarding HIV-1 infection were not reported for the other patients. Subsequently, Detwiler et al reported sixteen patients with a similar "collapsing" pattern of idiopathic FSGS in the absence of evidence of HIV-1 infection or intravenous drug use [10]. Their patients had similar clinical features to those described by Weiss et al with more rapid progression to renal failure than seen in other patients with FSGS. These reports suggest a distinct subset of idiopathic FSGS with unusually rapid progression to renal failure.

At Columbia-Presbyterian Medical Center, we have also noted an increasing incidence of all cases of FSGS among biopsies submitted to our renal pathology division over the last two decades [3]. There has also been a striking increase in idiopathic FSGS with collapsing morphologic features among patients lacking clinical or serologic evidence of HIV-1 infection or risk factors for HIV-1 infection. A retrospective review of 240 cases of idiopathic FSGS accessioned by the Columbia-Presbyterian Nephropathology Laboratory over the past 20 years identified our first case of idiopathic collapsing FSGS in 1979 [3]. Since that time the incidence of this entity has increased from 11% of all idiopathic FSGS from 1979 to 1985, to 20% of all idiopathic FSGS from 1986 to 1989, to 24% from 1990 to 1993 [3].

To better characterize the clinical and morphologic features of this variant of FSGS and to determine which epidemiologic, clinical and histologic features may be of prognostic significance, we performed a detailed evaluation of 43 patients with idiopathic collapsing FSGS. Their features were compared to 50 age-matched controls with the classic histologic form of idiopathic FSGS.

Methods

All biopsies of idiopathic FSGS accessioned by the Renal Pathology Laboratory at Columbia-Presbyterian Medical Center from 1974 to 1993 were re-reviewed for proper classification. Among 4073 native kidney biopsies, there were 394 cases of FSGS, of which 240 were idiopathic FSGS. Of these, 43 cases (18%) manifested predominantly collapsing features and lacked evidence of HIV-1 infection or intravenous drug use. Morphologic criteria for inclusion were the demonstration in histologic sections of focal glomerulosclerosis characterized by segmental or

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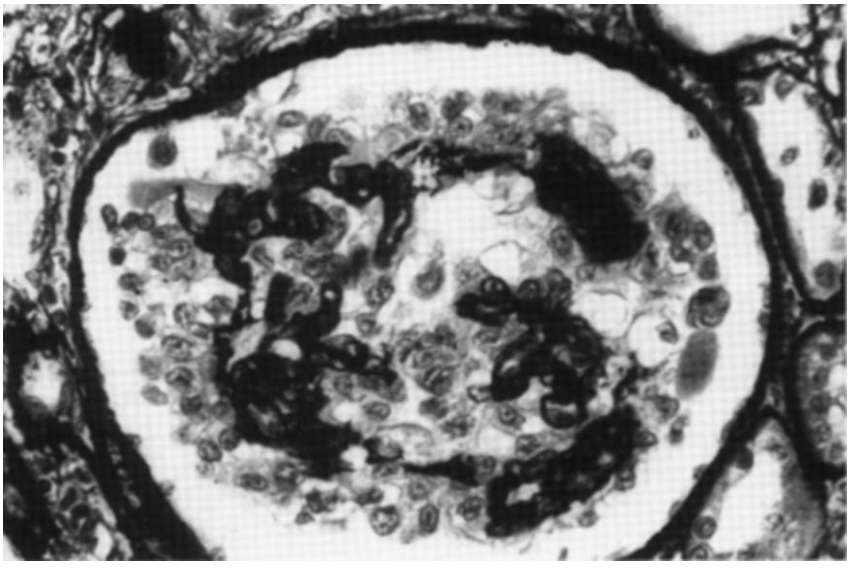

Fig. 1. *There is global collapse of the glomerular capillaries without increased intracapillary matrix.* Visceral epithelial cells are markedly hypertrophied. (Jones methenamine silver, ×500).

global wrinkling and "collapse" of the glomerular capillary walls with prominent hypertrophy and hyperplasia of the overlying visceral epithelial cells, often accompanied by intracytoplasmic protein resorption droplets, as illustrated in Figure 1. Biopsies with any glomeruli demonstrating global collapse and/or over 20% of glomeruli with segmental collapse qualified as meeting pathologic entry criteria for collapsing FSGS. The number of glomeruli exhibiting collapsing features and the degree of tubulointerstitial damage were variable.

None of the 43 cases had any known risk factor for HIV-1 exposure and none developed signs or symptoms of HIV-1 infection during the follow-up period which ranged up to 135 months (mean 32.2 months). In 33 cases, serologic testing for antibody to HIV-1 by ELISA was available and was negative in every case. No patient had clinical evidence of any secondary cause of FSGS such as heroin abuse, reflux nephropathy, sickle cell disease, obesity or reduced renal mass.

Case histories were reviewed for demographic and clinical data including presenting features at the time of biopsy, course, treatment and outcome. Renal biopsies were processed according to standard techniques for light microscopy, fluorescence microscopy and electron microscopy. At least 12 histologic levels were stained with hematoxylin-eosin, periodic acid-Schiff (PAS), Masson's trichrome and Jones methenamine-silver stains. Histologic features were graded by calculating the percentage of glomeruli exhibiting a particular histologic finding (global or segmental collapse, or global or segmental glomerulosclerosis) and by semiquantitative analysis (using a scale of 0 to 3+) for the following features: visceral epithelial cell hypertrophy and hyperplasia, tubular microcysts, tubular epithelial degenerative and regenerative changes, tubular atrophy, interstitial edema, inflammation and fibrosis. In the case of tubulointerstitial features, these were accorded 0 for absent, 1 for $< 20\%$, 2 for 20 to 50% and 3 for $> 50\%$ of the biopsy surface affected.

Partial remission of proteinuria was defined as a reduction in proteinuria to less than 2 grams daily and a full remission as less than 1 gram daily. End-stage renal disease (ESRD) was defined as the time point at which renal replacement therapy was initiated. All clinical and pathologic features were compared to those of a control group of 50 patients with idiopathic FSGS and classic biopsy features of FSGS defined as segmental scars with increased matrix and variable hyalinosis without global glomerular basement membrane collapse. Controls were matched for age and year of renal biopsy.

Statistical analysis was performed using standard *t*-testing, X^2-analysis, Wilcoxon rank sum analysis, linear regression analysis, life table analysis and one-way ANOVA, as appropriate. Statistical significance was assumed at P value < 0.05, with correction for multiple comparisons by the method of Bonferroni.

Rate of progression of renal insufficiency was defined as the slope of the best fit-linear regression analysis of the inverse creatinine-time curve (using 4 or more time points for each patient starting from the time of biopsy). A multiple regression analysis was performed for predictors/correlates of: (1) rate of progression of renal insufficiency, and (2) serum creatinine at biopsy, for both the collapsing and control FSGS groups. Demographic (age, race/ethnicity, gender), clinical (degree of proteinuria, hypertension, remission of proteinuria) and all histologic variables were added to the model. Variables which appeared to correlate best were carried through succeeding models until the best correlation could be obtained.

Results

Clinical features at presentation

The mean age of patients with idiopathic collapsing FSGS at the time of renal biopsy was 32.2 years (range of 1.5 to 72 years). There were 10 pediatric patients (23%) of which only four (9%) were 12 years or younger, and only seven (16%) were over 50 years old. The male-to-female ratio of 1.38 in the collapsing FSGS group was not significantly different from controls (Table 1). There was a strong and significant black racial predominance (61%) among the collapsing FSGS patients compared to controls (22%; $P < 0.025$).

Thirty-five of the 43 cases (82%) presented with the nephrotic syndrome, 4 (9%) with the nephrotic syndrome and uremia and 4

Table 1. Demographics of idiopathic collapsing FSGS

	Collapsing FSGS (N = 43)	Control FSGS (N = 50)	P value
Age *years*	32.2	32.8	NS
mean (range)	(1.5–72)	(1–67)	
Race/ethnicity			
White	17%	54%	
Black	61%	22%	<0.025
Hispanic	22%	24%	
Gender % *male*	58%	50%	NS

Table 2. Clinical features at biopsy of idiopathic collapsing FSGS

	Collapsing FSGS (N = 43)	Control FSGS (N = 50)	P value
Creatinine *mg%*	4.2 (0.8–24)	2.0 (0.4–14)	NS
% Creatinine < 2.0	54%	76%	
Time to biopsy *months*	7.9 (1–72)	48.6 (1–360)	<0.025
$UV_{protein}$ *g/day*	10.2 (2.2–36.6)	6.9 (0.4–24.4)	NS
% $UV_{protein}$ > 3.0	91%	75%	
$U_{protein}/U_{creatinine}$	11.0 (1.6–44.4)	5.4 (1.0–25.9)	NS
% U_{Prot}/U_{Cr} > 3.0	87%	58%	
Albumin *g/dl*	2.4 (1.0–4.1)	2.9 (1.0–4.5)	NS
% Albumin < 3.5	91%	53%	
Cholesterol *mg/dl*	404 (154–993)	335 (165–873)	NS
% Chol. > 240	74%	65%	
% Chol. > 300	65%	44%	
Nephrotic syndrome	91%	60%	<0.025
Hypertension	65%	56%	NS

Data are: mean (range). Abbreviations are: $UV_{protein}$, 24-hour urinary protein excretion; $U_{protein}/U_{creatinine}$ (or U_{Prot}/U_{Cr}), spot urinary protein-to-creatinine ratio.

(9%) with uremia alone. One patient had a history of Sjögren's syndrome and one had serologic evidence of systemic lupus erythematosus (ANA positive at 1:320, elevated double-stranded anti-DNA antibody titer and reduced serum complement) without clinical features fulfilling American Rheumatology Association (ARA) criteria for the diagnosis of SLE. Only four patients (9%) had constitutional symptoms or signs at presentation not explained by nephrotic syndrome or uremia, including: (1) one patient with fever, headache, nonspecific rash, myalgias, anorexia and weight loss; (2) one patient with fever, alopecia and abnormal liver function tests; (3) one patient with non-infectious diarrhea and weight loss; and (4) one patient with a non-bacterial pharyngitis. No patients were receiving potentially nephrotoxic medications at the time of disease onset.

When clinical features at the time of biopsy were compared (Table 2), patients with collapsing FSGS had a higher serum creatinine (4.2 vs. 2.0 mg/dl) despite a much shorter period of time from onset of renal disease to biopsy (7.9 vs. 48.6 months, $P < 0.025$), suggestive of a more rapidly progressive form of renal disease and not a delay in recognition. Ninety-one percent of patients with collapsing FSGS manifested nephrotic syndrome compared to 60% of controls ($P < 0.025$). All markers of the nephrotic syndrome were more prevalent and severe in the collapsing FSGS group, including more severe proteinuria (10.2 vs. 6.9 g/day), a lower serum albumin (2.4 vs. 2.9 g/dl) and edema (74% vs. 50%) though none reached statistical significance. There was no difference in serum cholesterol levels (404 mg/dl vs. 335 mg/dl, P = NS) or the prevalence of hypertension (65% vs. 56%, P = NS) in collapsing FSGS versus classic FSGS controls.

Table 3. Histology of idiopathic collapsing FSGS—Glomerular

	Collapsing FSGS (N = 43)	Control FSGS (N = 50)	P value
Of all glomeruli			
Global collapse %	18%	0%	<0.025[a]
Global + segmental collapse %	52%	1.3%	<0.025[a]
Global sclerosis %	17%	18%	NS[a]
Global + segmental sclerosis %	23%	43%	<0.025[a]
2+ Or greater on semiquantitative analysis			
Glomerulomegaly	5%	10%	NS[b]
VEC hypertrophy	67%	18%	<0.025[b]
VEC hyperplasia	84%	38%	<0.025[b]

Abbreviation is VEC, visceral epithelial cell. The semiquantitative scale is 0 to 3+.
[a] by Wilcoxon Rank Sum Analysis
[b] by χ^2 analysis

Renal biopsy findings

The defining histologic feature of this form of FSGS was a global or segmental "collapse" of the glomerular capillary walls characterized by a distinctive wrinkling and retraction of the glomerular basement membranes resulting in obliteration of the glomerular capillary lumen with marked visceral cell hypertrophy and hyperplasia (Fig. 1). This process was best appreciated in PAS or silver stained sections and was sometimes associated with loss of endothelial and mesangial cells in the involved segments. Typically, there was little or no increase in endocapillary or mesangial matrix and both hyalinosis and endocapillary foam cells were rarely if ever identified. Glomerular involvement by collapse could be either segmental or global without obvious predilection for the perihilar region. A mean 18% of glomeruli (range 0 to 55%) exhibited global collapse and a mean 34% (range 0 to 92%) segmental collapse, so that a mean 52% (range 6 to 100%) of all glomeruli demonstrated collapsing features (Table 3). The visceral epithelial cells were often so hypertrophied as to form pseudo-crescents which could be differentiated from true crescents by their lack of spindled cellular morphology, intercellular matrix or attachment to Bowman's capsule (Fig. 2). These visceral epithelial cells often demonstrated extremely swollen cytoplasm containing hyaline protein resorption droplets that stained pink with the PAS stain and red with the trichrome stain. Their nuclei were typically enlarged with a vesicular chromatin pattern, increased number of nucleoli and focal mitotic figures (Fig. 3). Synechiae were rarely observed between the tuft and Bowman's capsule. Glomeruli unaffected by tuft collapse either appeared histologically normal (except for some visceral cell swelling) or demonstrated more classic lesions of segmental or global sclerosis characterized by increased matrix, hyalinosis and Bowman's capsular adhesions. Glomerular hypertrophy was not recognized as a feature of this condition.

A characteristic finding in this variant of FSGS was the presence of severe tubulointerstitial disease that often appeared out of proportion to the degree of glomerulosclerosis (Table 4). In addition to tubular atrophy, interstitial fibrosis, edema and inflammation there were frequent tubular degenerative and regenerative changes. The latter included simplification of the epithelial lining

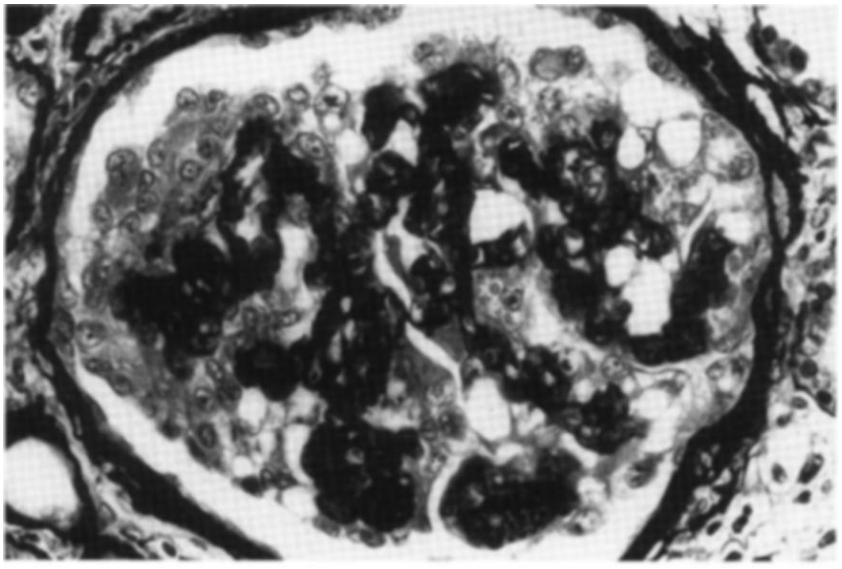

Fig. 2. *Glomerular capillaries are occluded by collapse of the glomerular basement membranes.* Visceral epithelial cells are hypercellular, forming pseudocrescents. Podocytes contain many intracytoplasmic vacuoles and protein resorption droplets. (Jones methenamine silver, ×500).

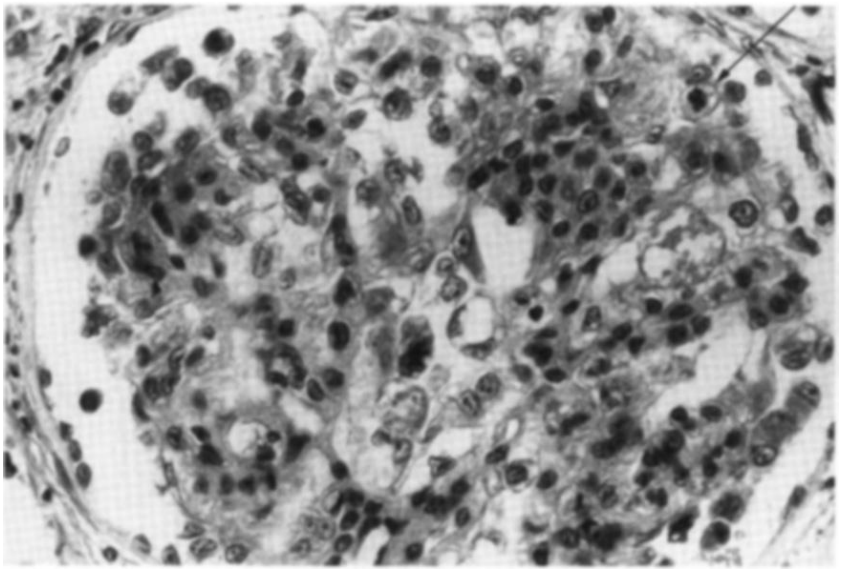

Fig. 3. *With the hematoxylin-eosin stain, the glomerulus appears hypercellular due to severe visceral cell proliferation.* One visceral epithelial cell is in mitosis (arrow) (Hematoxylin-eosin, ×500).

of proximal tubules, enlarged vesicular nuclei with frequent nucleoli and mitoses, focal apoptosis and shedding of desquamated epithelial cells into the tubular lumen (Fig. 4). Eighteen of 43 cases (42%) demonstrated tubular microcysts, which contained loose proteinaceous casts (Fig. 5). Arteriosclerosis was present in 27 of 43 cases (63%).

By immunofluorescence microscopy, there was focal segmental or global staining of the glomerular tuft with antisera to IgM (95%), C_3 (93%) and C_1 (49%) (Fig. 6). Visceral epithelial cell protein resorption droplets often stained for IgG, IgA and albumin, with similar staining in the tubular epithelial protein droplets (Fig. 7).

Electron microscopy disclosed prominent wrinkling and generally little or no thickening of glomerular basement membranes in the affected lobules. The overlying visceral cells were generally markedly hypertrophied and capped with complete effacement of foot processes, focal detachment and increased number of protein resorption droplets, clear transport vesicles and abundant rough endoplasmic reticulum (Figs. 8 and 9). Adjacent glomerular capillaries unaffected by collapse were notable for extensive

Table 4. Histology of idiopathic collapsing FSGS—Tubulointerstitial

	Collapsing FSGS (N = 43)	Control FSGS (N = 50)	P value
2+ Or greater on semiquantitative analysis			
Tubular microcysts	12%	0%	<0.025
Tubular degeneration	14%	0%	<0.025
Tubular regeneration	21%	4%	<0.025
Tubular atrophy	51%	32%	NS
Interstitial edema	26%	0%	<0.025
Interstitial inflammation	44%	18%	NS
Interstitial fibrosis	62%	30%	NS

The semiquantitative scale is 0 to 3+. All comparisons are by χ^2 analysis.

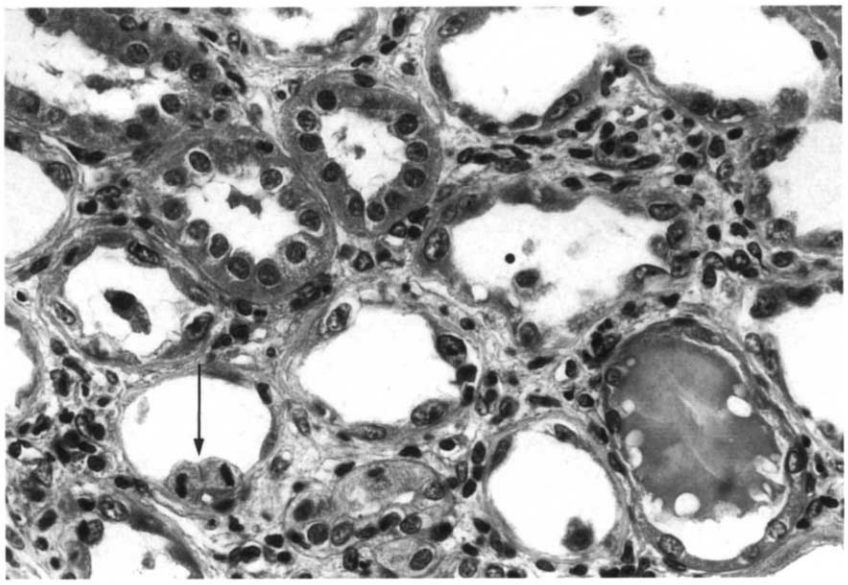

Fig. 4. *The tubules show widespread epithelial simplification with regenerative nuclear atypia and focal mitotic figures (arrow).* There is interstitial edema and inflammation (Hematoxylin-eosin, ×500).

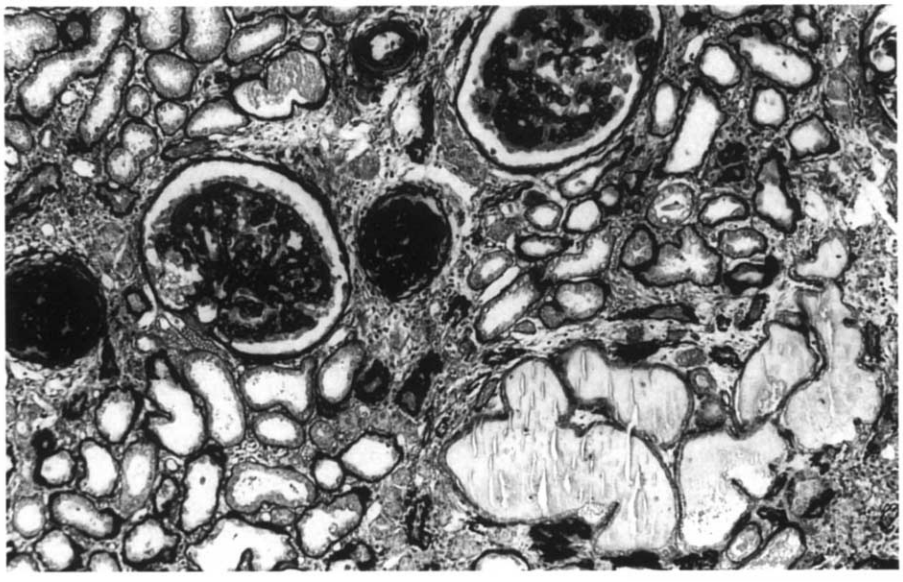

Fig. 5. *Low power view showing global glomerulosclerosis and global glomerular collapse.* There are focal tubular microcysts as well as patchy tubular atrophy and interstitial fibrosis (Jones methenamine silver, ×125).

(mean 80%) effacement of foot processes. In contrast to their frequent occurrence in biopsies of HIV-1-infected patients, tubulo-reticular inclusions were found within the cytoplasm of a single glomerular endothelial cell in only 2 of the 43 cases.

Comparative morphologic data

Comparative morphologic data between renal biopsies of patients with idiopathic collapsing FSGS and idiopathic classic FSGS controls are presented in Tables 3 and 4. For the collapsing group, a mean of over half (52%) of glomeruli had either global or segmental collapse with nearly one-fifth (mean 18%) exhibiting global collapsing features. Conventional lesions of segmental sclerosis defined as discrete foci of increased intracellular matrix, with or without hyalinosis, and Bowman's capsular adhesion were identified in only 5% (mean) of glomeruli. This is in contrast to 25% of glomeruli demonstrating classic lesions of segmental glomerulosclerosis among controls ($P < 0.025$). There was significantly greater visceral cell hypertrophy and hyperplasia among the collapsing group (both $P < 0.025$). All histologic markers of tubulointerstitial injury were greater in collapsing FSGS than control FSGS biopsies, and these reached statistical significance for the parameters of tubular microcysts, tubular degenerative and regenerative changes and interstitial edema, but not tubular atrophy, interstitial inflammation or fibrosis.

Treatment and outcome

Of the 43 patients with collapsing FSGS, 26 (60%) received immunosuppressive treatment for their renal disease (Table 5). These 26 patients were all first given a trial of prednisone. Ten pediatric cases received prednisone 60 to 80 mg/day. Of the 16 adult patients, half received prednisone 1 mg/kg/day and the other half received 2 mg/kg on alternate days. All received at least a

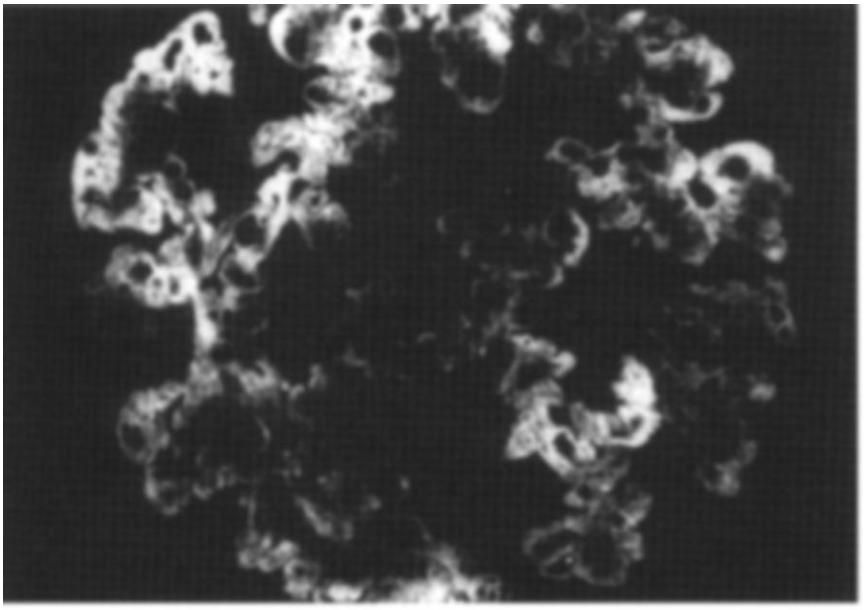

Fig. 6. *By fluorescence microscopy there is global staining of the collapsed glomerular lobules with antisera to IgM (×500).*

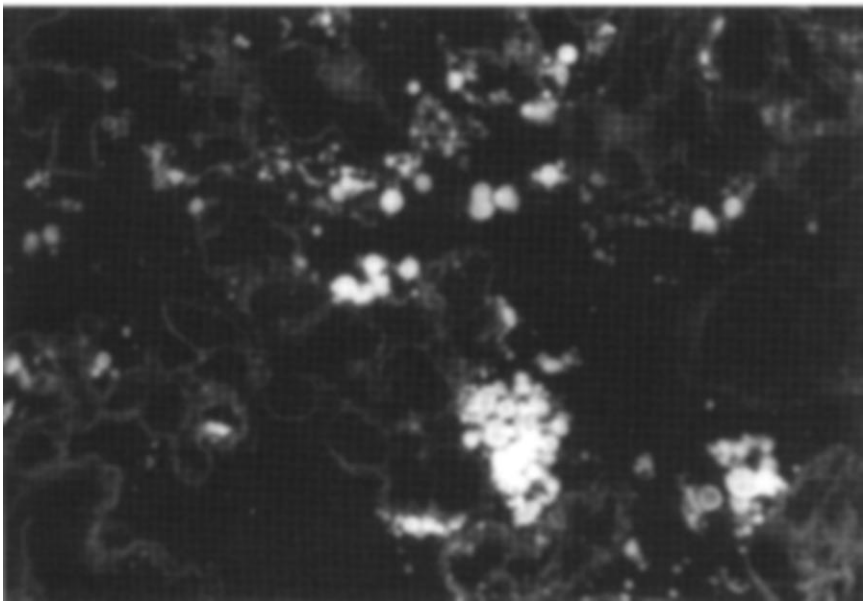

Fig. 7. *Visceral epithelial cells contain intracytoplasmic protein resorption droplets which are highlighted with antisera to albumin (×500).*

two-month trial of steroid therapy but only five patients (3 adults on daily prednisone and 2 adults on an alternate day regimen) received at least a six-month course of corticosteroids. Six patients also received cyclophosphamide (3 pediatric and 2 adult cases who received oral cyclophosphamide for 5 to 12 weeks and 1 adult case who received a six-month course of intravenous pulse cyclophosphamide of 1 g/M^2/month). Three patients received a trial of cyclosporine A (4 to 5 mg/kg/day for 8 to 26 weeks). There were no complete or partial remissions of proteinuria in the 26 steroid-treated patients. One partial remission was obtained among the 6 cyclophosphamide-treated patients (17%), and 2 remissions (one complete and one partial) among the three cyclosporine A-treated patients. Three untreated patients experienced a spontaneous remission of proteinuria (2 full, 1 partial). Therefore, there was a total 14% remission rate among the collapsing FSGS patients, compared to a 36% remission rate (16 full, 2 partial) among the control FSGS group (Table 5). These remissions in the collapsing FSGS group have been followed for a mean of 53 months (range 21 to 135 months). One patient has relapsed and progressed to ESRD. There was no difference in steroid treatment rate between the collapsing FSGS group and the historical control FSGS group (60% vs. 78%, P = NS), although the collapsing FSGS were much less likely to have received a full six-month trial of prednisone (5 out of 26 or 19% vs. 19 out of 39 or 49%). There was no difference in the treatment rates with cyclophosphamide (14% vs. 20%, P = NS); however, the collapsing FSGS group were less likely to be treated with cyclosporine A (7% vs. 24%), perhaps as a reflection of the more

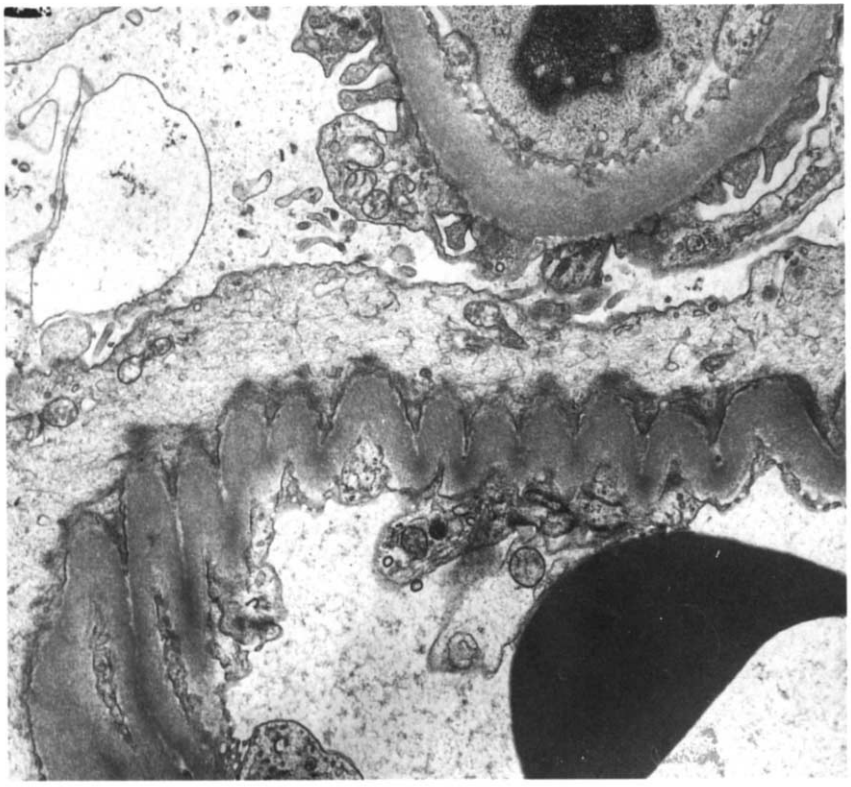

Fig. 8. *Electron micrograph showing early collapse with segmental wrinkling and pleating of the glomerular basement membrane.* There is extensive foot process fusion of the overlying podocyte. There are no endothelial tubuloreticular inclusions (uranyl acetate, lead citrate, ×3500).

advanced renal insufficiency at biopsy in the collapsing FSGS group.

Patients with idiopathic collapsing FSGS were followed for a mean of 32.2 months (range 6 to 135 months). At last follow-up, 51% of these patients reached ESRD. By life table analysis, the median renal survival measured from the time of biopsy to ESRD was significantly shorter in the collapsing versus the control group (13.0 months vs. 62.5 months, $P < 0.05$, Table 6 and Fig. 10). Three patients underwent a second renal biopsy. All three demonstrated a progression from a predominantly focal and segmental to a more diffuse and global glomerular collapse on repeat biopsy. Among patients with collapsing FSGS, 7 received a renal transplant, including one living-related and 6 cadaveric grafts. Two grafts were lost to rejection and none developed evidence of recurrent disease.

Evaluation of the demographic and clinical features which might be predictive of outcome in idiopathic collapsing FSGS was first analyzed by dichotomizing patients using ESRD as end-point. Comparative analysis of those who progressed to ESRD versus those who did not progress to ESRD uncovered no significant differences with respect to age, race or gender (data not shown). Clinical predictors of outcome included the serum creatinine at biopsy ($P < 0.05$) and lack of remission of proteinuria ($P < 0.025$). However, there was no correlation between outcome and the severity of proteinuria or other features of the nephrotic syndrome (Table 7).

There were no histologic features which were found to distinguish those with rapid progression to ESRD from those with no or slow progression. Of note, the percentage of glomeruli with segmental or global collapse, severity of visceral cell hypertrophy or hyperplasia, tubular microcysts, degenerative or regenerative tubular changes and interstitial edema, inflammation or fibrosis did not correlate with outcome (data not shown).

Predictors of progression were also analyzed using the rate of decline of renal function expressed as the slope of the best fit-linear regression model of the inverse creatinine-versus-time curve, calculated from the time of biopsy to either ESRD or last available follow-up. The rate of progression did not correlate with the severity of the nephrotic syndrome as defined by the level of urinary protein excretion or serum albumin for the collapsing FSGS group, but did correlate for the control FSGS group (Table 8). The rate of progression in the collapsing FSGS group correlated highly with the severity of tubular degenerative and regenerative changes by ANOVA ($P < 0.02$, data not shown), but not with any other tubulointerstitial parameter nor with the degree of glomerular collapse or sclerosis.

In the collapsing FSGS patients, the serum creatinine at biopsy correlated weakly but significantly with the percent of globally sclerotic glomeruli ($r = 0.51$, $P < 0.02$) but no other histologic feature. This is in contrast to the control FSGS group for which multiple significant histologic correlations were found with serum creatinine, including the percent of sclerotic glomeruli, degree of tubular regenerative changes and interstitial inflammation (all $P < 0.02$, data not shown).

By multiple regression analysis, the serum creatinine at biopsy in collapsing FSGS patients correlated significantly with male gender (higher creatinines), global glomerulosclerosis, tubular regenerative features and tubular atrophy but not race, degree (percent) of glomerular collapse or interstitial disease (Table 9). Similarly, global glomerulosclerosis and tubular regenerative features (the latter rare in control FSGS) were significant correlates of the serum creatinine at biopsy in control FSGS (Table 9). By

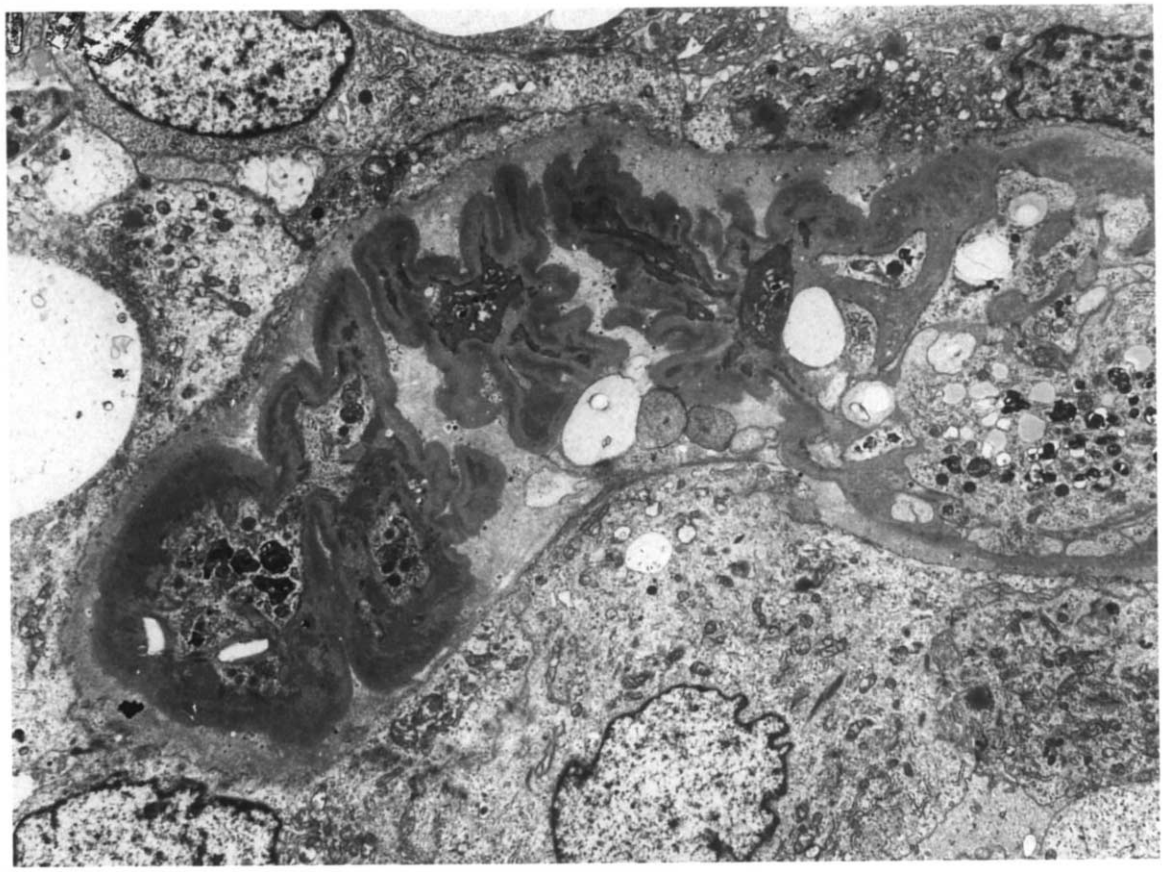

Fig. 9. *Electron micrograph illustrating an advanced stage of glomerular basement membrane collapse with obliteration of the capillary lumen and detachment and hypertrophy of the visceral epithelial cells forming a cellular cap (uranyl acetate, lead citrate, ×2500).*

Table 5. Treatment response of idiopathic collapsing FSGS

	Full remission < 1 g/day	Partial remission < 2 g/day
Spontaneous	2/43 (5%)	1/43 (2%)
Steroids	0/26 (0%)	0/26 (0%)
Cytotoxics	0/6 (0%)	1/6 (17%)
Cyclosporine A	1/3 (33%)	1/2 (33%)

Cytotoxics are principally oral cyclophosphamide.

Table 6. Outcome of idiopathic collapsing FSGS

	Collapsing FSGS (N = 43)	Control FSGS (N = 50)	P value
ESRD (over time of follow-up)	51%	42%	NS[a]
Follow-up time *months*	32.2	61.4	NS[b]
Median renal Survival time *months* (from biopsy)	13.0	62.5	<0.05[c]

[a] By χ^2 analysis
[b] By unpaired t testing
[c] By life table analysis

multiple regression analysis (Table 10), including all demographic, clinical and histologic features, the rate of progression of renal dysfunction in collapsing FSGS correlated best only with male gender as a predictor of faster progression (P = 0.076). In comparison, the rate of progression in control FSGS correlated significantly with hypoalbuminemia, segmental collapse of glomeruli (by definition, there was no global glomerular collapse in control FSGS) and total glomerulosclerosis (Table 10).

Discussion

Focal segmental glomerulosclerosis (FSGS) is a heterogenous group of disorders with respect to etiology, morphology, clinical course and response to treatment [8–11]. Primary or idiopathic FSGS must be differentiated from secondary forms of FSGS including those associated with remnant kidneys and hyperfiltration, sickle cell disease, obesity, heroin nephropathy and other disorders [8, 11–17]. Within the last decade, HIV-associated nephropathy (HIVAN), an entirely new form of secondary FSGS with a unique clinical picture, morphology and a rapid course to renal failure has been defined [18, 19]. Most recently, a number of reports have described small series of patients without evidence of HIV-1 infection but with a similar collapsing variant of FSGS and a rapid progression to ESRD [9, 10]. Weiss et al in 1986 first described six patients with a new glomerulopathy characterized by prominent glomerular tuft collapse, heavy proteinuria and the rapid development of ESRD [9]. In the three year follow-up, only one of these patients developed overt AIDS. More recently, Detwiler et al reported 16 patients with collapsing FSGS and no serologic or clinical evidence of concurrent HIV-1 infection [10].

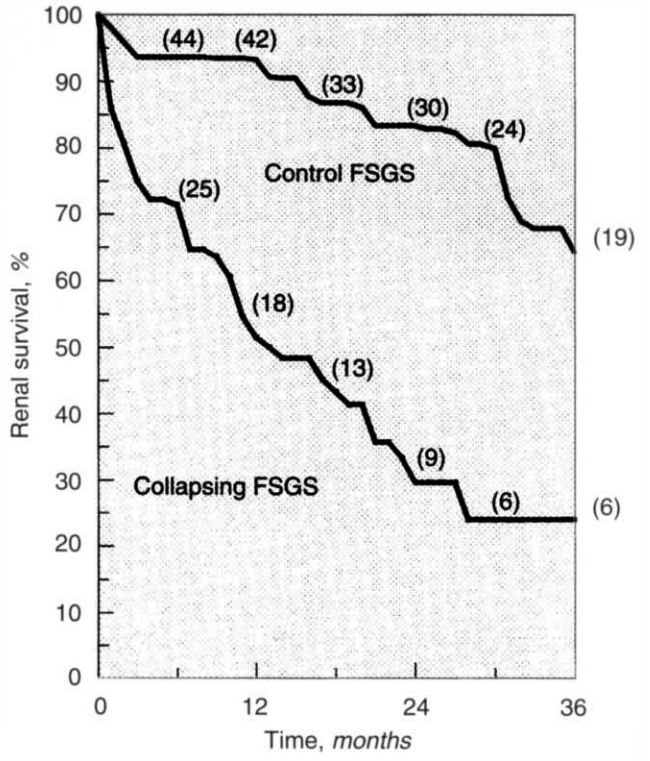

Fig. 10. *Life table analysis of renal survival (free of ESRD) in idiopathic collapsing versus control FSGS (X^2 analysis; $P < 0.05$).*

Table 7. Predictors of progression in idiopathic collapsing FSGS (clinical features at biopsy)

	ESRD ($N = 22$)	Not ESRD ($N = 14$)	P value
Serum creatinine *mg/dl*	6.7	1.4	<0.05
Time to biopsy *months*	9.5	8.6	NS
$UV_{protein}$ *g/day*	9.4	9.7	NS
$U_{protein}/U_{creatinine}$	9.4	12.2	NS
Serum albumin *g/dl*	2.5	2.4	NS
Serum cholesterol *mg/dl*	386	417	NS
Hypertension	82%	43%	NS
Remission of proteinuria	0%	43%	<0.025

$UV_{protein}$ is 24-hour urinary protein excretion; $U_{protein}/U_{creatinine}$ is the spot urinary protein-to-creatinine ratio.

These patients manifested heavy proteinuria (mean of over 13 gms daily) and a rapid progression to renal failure. These 16 patients were culled from a total of 849 biopsies performed from 1988 to 1990 by the North Carolina Collaborative Glomerular Study Group. Both reports describe idiopathic collapsing FSGS as a newly recognized glomerulopathy at their respective centers.

The current study is the largest clinicopathologic analysis of this recently identified subgroup of FSGS. In reviewing all 240 biopsies with a diagnosis of idiopathic FSGS accessioned at Columbia-Presbyterian Medical Center from the years 1974 to 1993, no biopsy with histologic features similar to collapsing FSGS was found prior to 1979 [3]. Since then, both the absolute number and relative incidence of collapsing FSGS has progressively increased through the 1980s and into the 1990s [3]. In the 1990s, collapsing FSGS comprised 24% of all idiopathic FSGS in our series [3].

Table 8. Correlations of rate of progression in idiopathic collapsing FSGS (from time of biopsy)—clinical features

	Collapsing FSGS	Control FSGS
Rate of progression (= slope of inverse creatinine-time curve)		
vs. $UV_{protein}$	$r = 0.23$, P = NS	$r = 0.32$, P = NS
vs. $U_{protein}/U_{creatinine}$	$r = 0.25$, P = NS	$r = 0.72$, $P < 0.02$
vs. serum albumin	$r = 0.32$, P = NS	$r = 0.53$, $P < 0.02$

$UV_{protein}$ is 24-hour urinary protein excretion; $U_{protein}/U_{creatinine}$ is the spot urinary protein-to-creatinine ratio. By linear regression analysis.

Table 9. Multivariate analysis of predictors of serum creatinine at time of biopsy

	Parameter estimate	Standard error	P value
Collapsing FSGS ($r^2 = 0.75$)	F = 10.79		0.001
Male gender	−2.15	0.87	0.0203
% Global glomerulosclerosis	+0.08	0.03	0.0144
Tubular regeneration	+1.30	0.56	0.0295
Tubular atrophy	+1.44	0.51	0.0095
Control FSGS ($r^2 = 0.64$)	F = 40.59		0.0001
% Global glomerulosclerosis	+0.06	0.01	0.0001
Tubular regeneration	+3.28	0.71	0.0001

Table 10. Multivariate analysis of predictors of progression (dependent variable − slope of the inverse creatinine-time curve)

	Parameter estimate	Standard error	P value
Collapsing FSGS ($r^2 = 0.09$)	F = 3.43		0.076
Male gender	+23.46	12.66	0.076
Control FSGS ($r^2 = 0.46$)	F = 12.69		0.0001
Serum albumin	+8.55	2.14	0.0003
% Segmental collapse in glomeruli	−2.14	0.55	0.0004
% Total glomerulosclerosis (global + segmental)	−0.26	0.09	0.0042

Although we were unable to document collapsing FSGS in our FSGS biopsies prior to 1979, the number of FSGS biopsies received from 1974 to 1979 was relatively small and may have been subject to sampling bias. Several early reports of FSGS describe visceral cell hyperplasia and retraction of the glomerular basement membrane [20–22] and thus is it likely that examples of collapsing FSGS existed prior to 1980, although the significance of these morphologic features was not widely recognized. It is also possible that under-recognition of collapsing FSGS as a manifestation of idiopathic FSGS prior to 1980 accounts in part for its low prevalence in that era. However, it is likely that the continued increase in the observed frequency of this lesion from 1979 to the present reflects a true change in disease incidence since this rising trend has been sustained over two decades in a large biopsy population with standardized, consistent renal biopsy interpretation.

Idiopathic collapsing FSGS is defined by its histopathologic features. Both Weiss and Detwiler's series describe the biopsies of their patients as manifesting prominent "collapse" of the glomerular capillaries [9, 10]. In Weiss' series collapse was focal,

involving from 25 to 50% of all glomeruli, and varied from segmental to global in distribution. Repeat biopsies in two patients showed global collapse of all glomeruli. Detwiler's patients displayed segmental or global collapse in 8 to 92% of the glomeruli of each biopsy. Our patients also manifested prominent segmental and global glomerular tuft collapse involving on average more than 50% of glomeruli. This is in contrast to age-matched controls with idiopathic FSGS who manifested glomerular scars consisting of increased inframembranous matrix with frequent hyalinosis and capsular adhesions. All histologic markers of tubulointerstitial damage were greater in collapsing FSGS group. The previously reported series also described significant tubulointerstitial damage with interstitial fibrosis, tubular atrophy, tubular dilation with cast formation, and mononuclear infiltration of the interstitium [9, 10].

There is considerable confusion surrounding the definition of collapsing FSGS and its relationship to "cellular FSGS" as defined in 1985 by Schwartz and Lewis [5]. While collapsing FSGS can be considered a particular subtype of cellular lesion, not all cellular lesions are necessarily collapsing. According to the definition proposed by Schwartz [5], cellular lesions of FSGS are characterized by visceral cell "reactive and proliferative changes" whether overlying capillaries with minimal histologic abnormalities, hypercellular glomerular capillary segments, segmental scars or collapsed capillaries with wrinkled basement membrane. We reserve the term collapsing FSGS for the latter situation, in which there is acute retraction (that is, "collapse") of the glomerular basement membrane without endocapillary hypercellularity and accompanied by visceral cell hypertrophy and hyperplasia. This is to be distinguished from examples of cellular FSGS in which there is endocapillary hypercellularity (including proliferation of endothelial cells, foam cells, infiltrating leukocytes and karyorrhectic debris) as well as extracapillary (that is, visceral cell) proliferation, mimicking a proliferative glomerulonephritis. Extracapillary hypercellularity characterizes both these forms, but only the collapsing lesion has glomerular basement membrane wrinkling and retraction. In short, we prefer to distinguish two subtypes of cellular FSGS as defined by Schwartz, one a collapsing form without endocapillary hypercellularity and the other a non-collapsing form with endocapillary hypercellularity, both of which share the features of visceral cell proliferation and reactivity.

Clearly, there is significant overlap in the histologic features of FSGS in the cellular, collapsing and classic subgroups. Within our control group with typical perihilar expansile scars, rare glomeruli with segmental collapsing features were observed in 5 of 50 cases, affecting less than 20% of glomeruli. Similarly, in the collapsing group, glomeruli with classic segmental scars were often observed side by side with collapsed glomeruli. These observations reinforce our opinion that collapsing glomerulopathy represents one possible morphologic expression of severe glomerular injury within the increasingly broad pathologic spectrum of FSGS. Thus, we favor that collapsing glomerulopathy constitutes a histologic variant of FSGS rather than a separate or distinct disease entity. An analogy can be drawn to HIV-associated nephropathy where collapsing lesions and perihilar scars often co-exist in a given biopsy, but the prevalence of collapsing lesions exceeds that observed in series of idiopathic FSGS and correlates with the more accelerated course to renal failure.

Our series of idiopathic collapsing FSGS exhibited a strong black racial predominance of 61% versus 22% in controls. This racial predilection has been noted in both previous smaller series of collapsing FSGS patients. Indeed, all the patients in Weiss's report and over 80% of those reported by Detwiler et al were black [9, 10]. The disease is not, however, limited to blacks and appears akin to other sclerosing glomerulopathies such as heroin-associated nephropathy and HIVAN, both of which have a strong black racial predominance [23, 24]. Whether the racial predilection is related to HLA differences, altered production and modulation of sclerosing cytokines such as TGF-β or other growth factors, a tendency towards more severe or poorly controlled hypertension or other genetic, or environmental factors cannot be determined from our study [25–28]. Of interest, among our patients with idiopathic collapsing FSGS, blacks did not have a worse course than non-blacks (data not shown), implying that these predisposing factors may play a greater role in initiating the collapsing pattern of FSGS than in determining its ultimate progression and outcome.

Heavy proteinuria and the nephrotic syndrome are a prominent clinical feature of idiopathic collapsing FSGS. The patients in Weiss's series all had between 10 and 30 grams of proteinuria daily, while 69% of the patients reported by Detwiler had over 10 grams proteinuria per day [9, 10]. In our series, as well, the mean level of proteinuria was higher (10.2 vs. 6.9 g/day) and the percentage of patients with severe proteinuria, defined as 10 g or more daily or a spot urinary protein-to-creatinine ratio of 10 or more, was greater in collapsing FSGS (16 of 43 cases or 37%) than in controls (12 of 50 cases or 24%). Several other prominent clinical features of collapsing FSGS, including greater hypoalbuminemia, hypercholesterolemia and prevalence of edema, are probably related to the greater severity of the protein loss. It is not known whether the increased proteinuria in collapsing FSGS is not only a manifestation of more severe glomerular injury but also directly contributes to the progressive glomerular and tubulointerstitial damage [29–32]. In a number of large series of patients with FSGS, those with nephrotic range proteinuria have had a more progressive course than patients with subnephrotic proteinuria [1, 32, 33]. Even among FSGS patients with the nephrotic syndrome, those with the highest proteinuria have had the most rapid progression to renal failure [34]. Similarly, in other forms of primary glomerular disease such as membranous nephropathy and membranoproliferative glomerulonephritis, heavy proteinuria constitutes a risk factor for progressive renal damage [35, 36].

At presentation, patients with idiopathic collapsing FSGS are more likely to have impaired renal function, manifested by an elevated serum creatinine, when compared to patients with classic idiopathic FSGS. An elevated serum creatinine was present in all the patients reported by Weiss, and 62% of 16 patients described by Detwiler et al had a serum creatinine at presentation of greater than 2 mg/dl [9, 10]. While this may, in part, be a consequence of glomerular collapse and sclerosis, there is also far greater tubulointerstitial damage in these patients. In many glomerular diseases, including a number of studies dealing with FSGS, it is the severity of the tubulointerstitial damage that correlates best with the degree of reduction in glomerular filtration rate (GFR) and the rate of progression to ESRD [36–39]. We found the serum creatinine at biopsy to correlate significantly and independently with both the amount of glomerulosclerosis and the degree of tubular damage in both the collapsing and control FSGS groups (Table 9). This tubulointerstitial damage may be a consequence of the glomerular injury through disruption of the post-glomerular

circulation, tubular protein trafficking with promotion of local cytokine and growth factor production recruiting inflammatory infiltrates and promoting fibrogenesis, the formation of large obstructing casts or other mechanisms. The large echogenic kidneys found by ultrasound in some patients with collapsing FSGS likely relate to the tubulointerstitial infiltrates, edema, fibrosis and dilated tubules as has been documented in HIVAN. In both idiopathic collapsing FSGS and HIVAN, the decline in renal function may be too rapid to allow ample time for fibrosis and contraction of the parenchyma to produce the small shrunken kidneys typical of other forms of chronic glomerulonephritis.

Idiopathic collapsing FSGS and HIVAN have some striking similarities. The prevalence of both diseases has increased dramatically in the 1980s and review of our prior biopsy material from 1974 to 1979 does not document cases of either entity significantly before this decade [3]. Both diseases are associated with a strong black racial predominance, heavy proteinuria and a very rapid progression to ESRD over months rather than years [18, 19, 40]. This contrasts with classic idiopathic FSGS in which even nephrotic patients exhibit a mean time to renal failure of at least 5 to 10 years [33, 34, 37]. Both idiopathic collapsing FSGS and HIVAN share many histopathologic features, including global collapse of the glomerular tuft, marked visceral cell swelling and hyperplasia and prominent tubulointerstitial nephritis with microcyst formation [18, 41]. One of the patients reported by Weiss developed AIDS and the HIV-1 status of the remaining five patients was not clearly defined [9]. However, it does not appear that the patients with collapsing FSGS described by Detwiler et al were HIV-1 infected and 12 of the 16 patients were seronegative for HIV-1 infection. Clinically, none of our collapsing FSGS patients had symptoms suggestive of HIV-1 infection and all 33 who were tested were seronegative for HIV-1, some repeatedly over several years of follow-up. No patients subsequently developed signs or symptoms of HIV-1 infection over a mean follow-up of 32 months. Moreover, no patient was in a high risk group for HIV-1 infection (such as intravenous drug use, homosexual, etc.). The tubulo-reticular inclusions (TRIs) commonly found in the endothelial cells in HIVAN were distinctly absent in 41 cases and extremely sparse in the remaining two cases, and no biopsy displayed granular degeneration of nuclear chromatin [18, 41]. Therefore, despite many similarities, idiopathic collapsing FSGS and HIVAN are distinct entities which can be readily distinguished on clinico-pathologic grounds.

The etiology of idiopathic collapsing FSGS remains obscure. The striking similarities to HIVAN suggest a possible infectious/viral origin. Although less than ten percent of our patients had any manifestations of constitutional signs or symptoms of an infectious process, all of the patients described by Weiss et al and some of those described by Detwiler et al had systemic symptoms such as malaise and fever which could be manifestations of an occult viral illness [9, 10]. Transgenic mice produced from an HIV-1 genome deleted of gag and pol develop heavy proteinuria, collapsing glomerulosclerosis, tubulointerstitial damage and rapidly progressive renal failure [42, 43]. These studies suggest that viral genes may be capable of producing a sclerosing glomerulopathy similar to collapsing FSGS in the absence of transmissible HIV-1 infection, possibly through the transactivation of fibrogenic host genes by viral gene products. Mice made transgenic for other viral genes also have been shown to develop focal glomerulosclerosis [44]. The possibility exists of a yet unidentified virus as an etiologic factor in idiopathic collapsing FSGS. Nevertheless, despite ongoing efforts, no evidence for an infectious etiology of this disease has yet been identified (Jeffery Kopp, NIH, personal communication). Other non-infectious potential etiologies may relate to immunologic or hemodynamic damage to the glomeruli. The striking collapse of the glomerular capillary loops suggest possible alterations in intra-capillary hemodynamics with acute vasoconstriction leading to global glomerular contraction. It is also possible that acute injury to the visceral epithelial cell alters the compliance of the glomerular capillary walls, perhaps through defective podocyte adhesion and foot process interdigitation. Recently, high levels of a circulating permeability factor have been identified in the serum of some patients with idiopathic collapsing FSGS [45].

Prior studies of idiopathic collapsing FSGS have suggested a rapid course to ESRD. In the study by Weiss et al there was a mean time of 19 months to ESRD and two patients required hemodialysis within ten weeks of clinical onset of renal disease [9]. In the study by Detwiler et al, among 14 patients followed for 15 months, five patients (36%) reached dialysis and three had died from complications of renal failure [10]. Schwartz et al, by contrast, was unable to document a worse prognosis in a group of cellular FSGS patients, some of whom had collapsing features [46, 47]. By life table analysis, our control group of classic idiopathic FSGS patients exhibited a mean time to ESRD of 62.5 months, analogous to that described for similar populations of FSGS patients [33–35]. By contrast, our collapsing FSGS patients demonstrated a much more accelerated course to renal failure with a median time from biopsy to ESRD of only 13 months. Two patients in the series by Weiss et al were treated with prednisone which was felt to be "ineffective" [9]. In Detwiler's series, 5 of the 14 patients with follow-up were treated with immunosuppression [10]. Of four treated with corticosteroids, one experienced a clinical remission, while the single patient treated with cyclophosphamide and corticosteroids did not respond [10]. Analysis of the treatment response in our population is also limited by the retrospective uncontrolled nature of the treatment regimens. Nevertheless, in our series, of the 26 patients treated with corticosteroids for at least two months, there were no complete or partial remissions. This contrasts with a significantly higher response rate for our classic idiopathic FSGS patients, despite the fact that even these patients' treatment course may not have been as prolonged or intensive as some current regimens propose to achieve a high remission rate in idiopathic FSGS [48–50]. Given the rapid progression to ESRD of idiopathic collapsing FSGS, it is unlikely a more prolonged course of steroids will be successful. Clearly, any new treatment regimen for idiopathic collapsing FSGS must use intensive and rapidly acting agents to prevent renal failure. While only limited numbers of our patients were treated with other immunosuppressives, it is of interest that of the three cyclosporine-treated collapsing FSGS patients, one had a partial and one had a complete remission of proteinuria. These results must be viewed cautiously, since there were also 3 spontaneous remissions making it impossible to reach any firm conclusions about the role of cyclosporine without a controlled trial. Cyclosporine, though, has been used to treat many steroid resistant patients with classic idiopathic FSGS [51–53]. These studies document a significant remission rate although relapses are common after discontinuation of the drug [51]. In addition, several pediatric patients with typical HIVAN and a collapsing

pattern of FSGS have achieved complete remissions on cyclosporine therapy [54]. The actions of cyclosporine in these patients may be, in part, immunosuppressive and, in part, hemodynamic. Of interest, four of the original six patients reported by Weiss et al received transplants without recurrence of proteinuria in any patient in up to three years of follow-up [9]. Of our patients, seven received allografts without documented recurrence to date. This may relate to the intensive immunosuppression, including cyclosporine, given at the initiation of transplantation.

In our study, certain factors within the group with collapsing FSGS predicted the progression to renal failure. These included an elevated serum creatinine at biopsy and lack of a remission of proteinuria. Whereas, in the control group, we were able to demonstrate significant correlations of the degree of proteinuria and glomerulosclerosis to the rate of decline in renal function (Tables 8 and 10), no equivalent significant correlates could be found in collapsing FSGS. Though a rare feature, the presence of segmental collapse in the control FSGS group was a strong independent predictor of the rate of decline in renal function. This suggests that our collapsing FSGS group was a more homogenous group in terms of the degree of proteinuria and the severity of various histologic features such that we could not separate out any factors as predictive of the rate of decline in renal function. In other words, it is the presence of glomerular collapse and its associated tubulointerstitial changes rather than their severity which appear to predict poor outcome.

Idiopathic collapsing FSGS is an important subgroup of FSGS with an increasing frequency over the last two decades. Its dramatic clinical presentation, rapid progression to renal failure and poor response to conventional treatment distinguish it clinically from classic idiopathic FSGS. Similarities to HIVAN may shed light on its pathogenesis and potential therapy. Studies dealing with the course and therapy of FSGS should control for patients with the collapsing variant since it clearly has a less favorable course and greater steroid resistance than classic FSGS. The optimal therapy for this disease is unknown. In light of our findings, future studies should consider trials of more intensive intravenous corticosteroids and other immunosuppressive regimens in an attempt to prevent or impede irreversible renal damage.

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