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Collapsing glomerulopathy: A clinically and pathologically distinct variant of focal segmental glomerulosclerosis

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Collapsing glomerulopathy: A clinically and pathologically distinct variant of focal segmental glomerulosclerosis. Sixteen patients with renal biopsy findings of extensive focal glomerular capillary collapse, visceral epithelial cell hypertrophy and hyperplasia, and variable degrees of tubulointerstitial injury in the absence of evidence for human immunodeficiency virus (HIV) infection or intravenous drug abuse were prospectively identified by renal biopsy. The pathologic process was designated collapsing glomerulopathy to distinguish it from other patterns of focal glomerular sclerosis. The clinical and pathologic characteristics of these 16 patients were analyzed and compared to a group of 25 patients with noncollapsing focal segmental glomerulosclerosis (FSGS). Thirteen of 16 patients with collapsing glomerulopathy were black as compared with 11 of 25 with FSGS ($P = 0.018$). The most common findings at presentation were hypertension and manifestations of the nephrotic syndrome. Although the duration of symptoms prior to presentation was no longer in the collapsing glomerulopathy group, the presenting mean serum creatinine was higher in patients with collapsing glomerulopathy than in those with noncollapsing FSGS (3.5 ± 3.4 mg/dl vs. 1.3 0.6 mg/dl, $P = 0.001$). Twenty-four-hour urine protein excretion was also higher in the collapsing glomerulopathy group (13.2 ± 7.7 g/day vs. 4.6 ± 4.5 g/day FSGS, $P = 0.005$). The collapsing glomerulopathy patients had a mean age of 41.4 ± 19.1 (range 19 to 81), a male-to-female ratio of 11:5 and a black-to-white ratio of 13:3. Renal survival, evaluated by life-table analysis, was markedly worse in collapsing glomerulopathy patients than in FSGS patients ($P = 0.0004$). It is proposed that collapsing glomerulopathy is a distinct entity characterized by black racial predominance, massive proteinuria, relatively rapidly progressive renal insufficiency, and distinctive pathologic findings. The data suggest that collapsing glomerulopathy is clinically, pathologically, and epidemiologically different from noncollapsing FSGS. Although collapsing glomerulopathy resembles HIV-nephropathy both pathologically and clinically, it differs clinically by having no evidence for associated HIV infection and differs pathologically by lacking endothelial tubuloreticular inclusions.

In 1986 Weiss et al reported six patients with nephrotic syndrome, progressive irreversible renal failure, and predominant pathologic features of glomerular capillary collapse and visceral epithelial cell swelling and hyperplasia [1]. They suggested that this may be a distinct clinicopathologic entity. Similar glomerular findings have been reported in patients with human immunodeficiency virus (HIV) infection, where the lesion is often referred to as HIV-nephropathy [2]. With the exception of one patient reported to have developed AIDS, HIV status was not addressed in the patients described by Weiss et al [1]. This omission has led to speculation that the patients described by Weiss et al may actually have had unrecognized HIV-nephropathy [3].

We have prospectively identified 16 patients, without evidence of HIV infection or known HIV risk factors, who exhibited pathologic features similar to those described by Weiss et al [1]. We have designated this lesion collapsing glomerulopathy. The epidemiologic, clinical, pathologic, and prognostic characteristics of these 16 patients are described and compared to a group of patients with classic primary focal segmental glomerulosclerosis.

Methods

Patient selection

Out of 849 consecutive nontransplant renal biopsies evaluated at the University of North Carolina between November 1988 and October 1990, 16 specimens with pathologic features of collapsing glomerulopathy and no evidence for HIV infection or intravenous drug abuse were prospectively identified. Biopsy diagnosis of collapsing glomerulopathy was based on light microscopic findings of focal segmental or global glomerular capillary collapse, wrinkling and folding of the basement membranes within the collapsed segments, and visceral epithelial cell hypertrophy and hyperplasia, sometimes accompanied by conspicuous cytoplasmic hyaline droplets. Other associated pathologic features, such as mesangial matrix expansion, sclerosis, and tubulointerstitial injury were noted but were not utilized as primary criteria for diagnosis. Exclusion criteria included HIV seropositivity, history of intravenous drug abuse, and any evidence of other HIV risk factors. Through the Glomerular Disease Collaborative Network (GDCN), which is a collaborating group of over 120 nephrologists, clinical data on all 16 patients were obtained. Follow-up data were obtained until the completion of the study in May 1992. Study end-points were defined as end-stage renal disease or death caused by complications of renal failure.

Without knowledge of their clinical status, 25 patients with a renal biopsy diagnosis of noncollapsing FSGS were randomly selected as a comparison group. Patients with glomerular tip lesion were classified separately and were not included in the comparison group [4]. Presenting clinical data and follow-up

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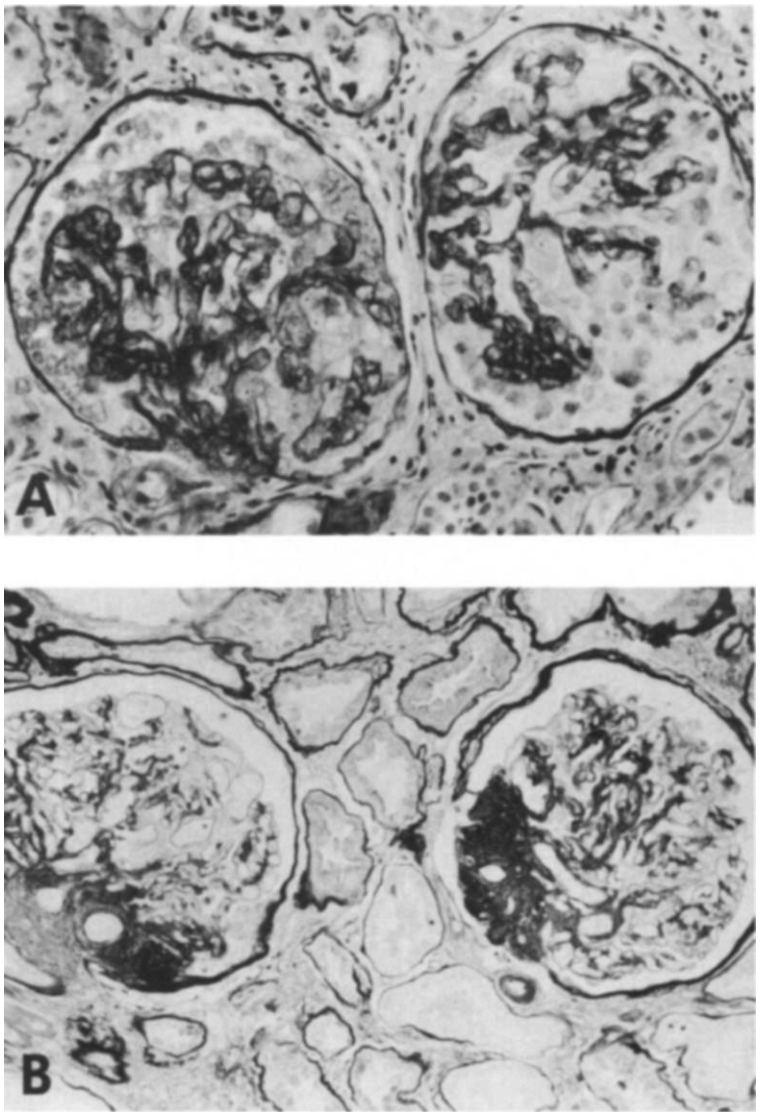

Fig. 1. *Collapsing glomerulopathy (A) and noncollapsing FSGS (B).* Note the epithelial hypertrophy and hyperplasia in A and the perihilar location of the segmental sclerosis in B. Periodic acid Schiff stain (magnification A, 225× and B, 150×).

data were obtained through the GDCN in a fashion similar to the study group.

Pathology analysis

All collapsing glomerulopathy and FSGS biopsy specimens were evaluated by light microscopy using standard paraffin section techniques. Eleven to 13 levels of section were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), Masson trichrome, or combined hematoxylin and eosin and methenamine silver technique. There were an average of 17 glomeruli per level of section in the collapsing glomerulopathy specimens, and 20 per level of section in the FSGS specimens. At the time of initial renal biopsy evaluation, a diagnosis of collapsing glomerulopathy was made if a majority of injured glomeruli (excluding those with global end-stage sclerosis, that is, total obsolescence) had segmental or global capillary collapse associated with epithelial hypertrophy. Epithelial hyaline droplets and hyperplasia were typically present, but were not required for diagnosis. If there was clinical evidence for HIV infection or intravenous drug abuse at the time of biopsy, the patients were excluded from the cohort of collapsing glomerulopathy patients evaluated in this study. A diagnosis of glomerular tip lesion was made if there was focal glomerular consolidation, cellular swelling, foam cell formation and sclerosis confined exclusively to the glomerular tip opposite the hilum. A diagnosis of FSGS was made if: (1) the criteria for neither of these diagnoses were present; (2) there was focal segmental glomerular sclerosis; and (3) there was no pathologic evidence for primary disease that could have produced secondary sclerosis, such as ultrastructural evidence for basement membrane nephropathy or immunohistologic evidence for immune complex mediated glomerulonephritis. All collapsing glomerulopathy specimens [16] were selected for evaluation. A comparison group of 25 noncollapsing FSGS specimens were randomly selected from patients with a pathologic diagnosis of FSGS.

Fifteen collapsing glomerulopathy specimens were evaluated by direct immunofluorescence microscopy after staining with antibodies specific for IgG, IgA, IgM, lambda light chains, kappa light chains, C3, C1q and fibrin. All 16 collapsing

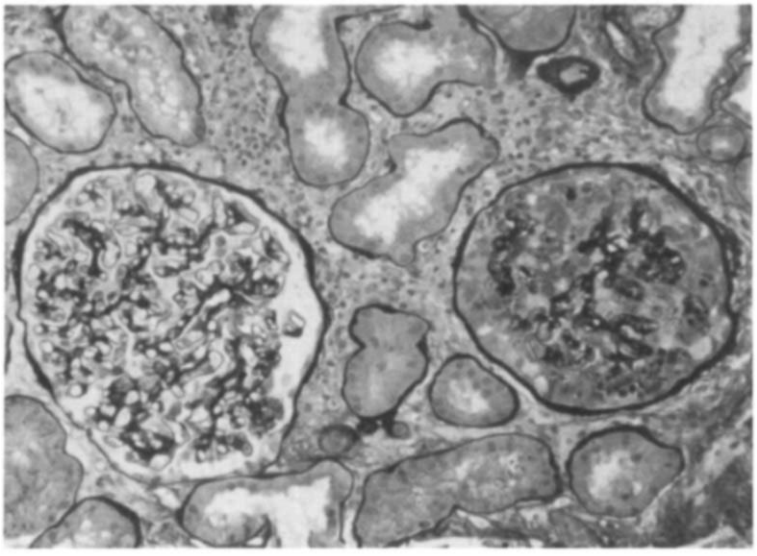

Fig. 2. *Focal global glomerular collapse with marked visceral epithelial hypertrophy.* Note also the interstitial infiltration of mononuclear leukocytes. Methenamine silver stain (magnification 170×).

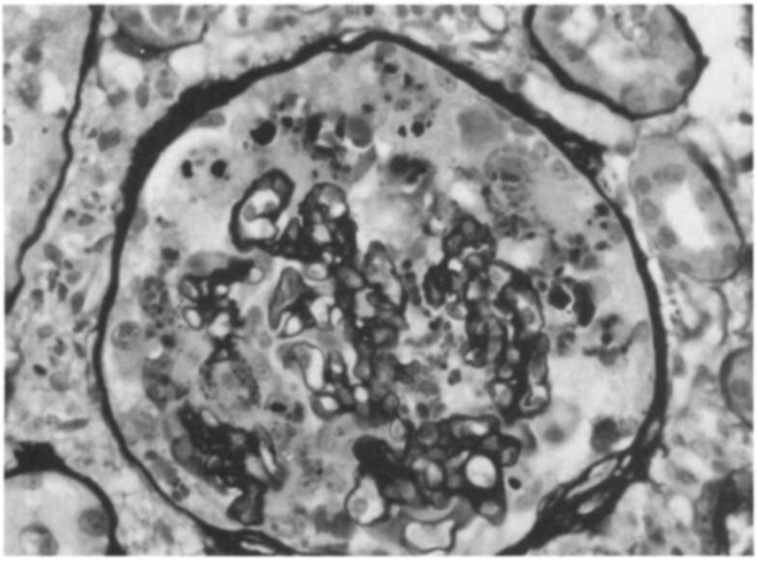

Fig. 3. *Light microscopy of one glomerulus with capillary collapse and hypertrophy of visceral epithelial cells, many of which contain droplets.* Methenamine silver stain (magnification 400×).

glomerulopathy specimens were evaluated by standard transmission electron microscopy. The 25 FSGS specimens that were compared to the collapsing glomerulopathy specimens were similarly evaluated by immunofluorescence and electron microscopy.

Statistical analysis

Differences in laboratory values between the collapsing glomerulopathy and FSGS groups were tested using Wilcoxon's rank sum test. Comparisons of race and gender between groups were made using a continuity adjusted Chi-square test. Bonferroni inequality was used for adjusting the *P*-values to account for multiple testing. Wilcoxon and likelihood ratio tests for survival curves were used to compute non-parametric estimates to test for equality of survival curves between the two groups. The log rank test was used to test for association of survival time with covariates. A parametric model for time failure data was fit in order to test the significance of diagnosis (collapsing glomerulopathy versus FSGS) while adjusting for the presence of other effects. Reciprocal creatinine was used to provide a Gaussian distribution of this variable for the model [5].

Results

Renal biopsy findings

The pathologic *sine qua non* for a diagnosis of collapsing glomerulopathy was the presence of focal, segmental or global glomerular capillary collapse (Figs. 1 through 4). This lesion was characterized by collapse and wrinkling of glomerular basement membranes, obliteration of capillary lumens, disappearance of endothelial and mesangial cells, and hypertrophy and hyperplasia of adjacent visceral epithelial cells. Table 1 demonstrates the percentage of glomeruli in each specimen involved by collapsing lesions, as well as the percentage of glomeruli with end-stage sclerosis and the severity of glomerular epithelial alterations and tubulointerstitial injury. When the

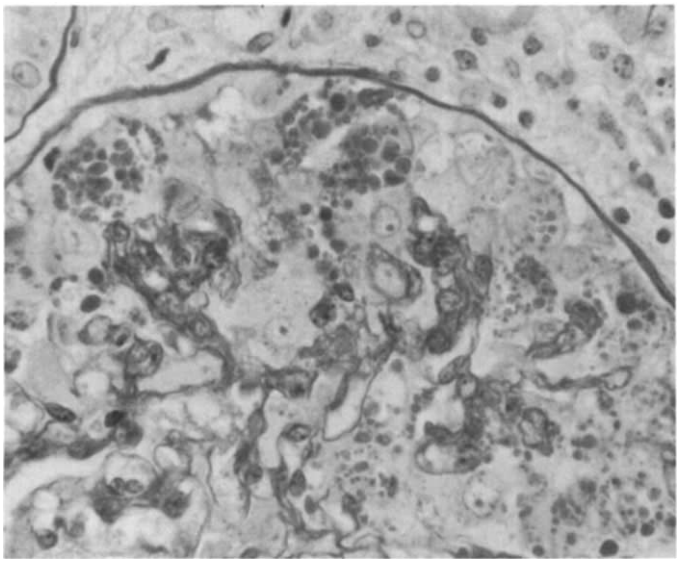

Fig. 4. *PAS-positive hyaline droplets in hypertrophied visceral epithelial cells.* Periodic acid-Schiff stain (magnification 500×).

Table 1. Severity of injury in renal biopsies from patients with collapsing glomerulopathy

Patient	Active collapsing lesions[a]	Chronic sclerosing lesions[b]	Glomerular epithelial hypertrophy[c]	Glomerular epithelial droplets[c]	Tubulointerstial injury[c]
1	92	0	3	3	3
2	69	0	2	3	3
3	63	0	4	3	3
4	63	0	3	3	2
5	56	0	2	1	3
6	55	0	3	2	2
7	50	0	2	0	1
8	38	31	4	2	4
9	35	20	1	1	1
10	33	8	1	0	2
11	20	0	2	1	2
12	17	0	2	3	2
13	17	17	2	3	4
14	13	13	1	1	2
15	11	56	1	1	3
16	8	38	1	1	3

Patients are arranged in order of decreasing frequency of active collapsing lesions.

[a] Percent of glomeruli with segmental or global collapse and epithelial changes, but without end-stage global sclerosis

[b] Percent of glomeruli with global end-stage sclerosis

[c] Severity on a scale of 0 to 4+ with 0 = none and 4+ = severe

injury was segmental, there was no predilection for the perihilar or tip segments. This differed from the lesions in noncollapsing FSGS, which had a predilection for perihilar segments (Fig. 1B). The noncollapsing FSGS lesions also had more hyalinosis.

Extrapolating from the least severe to the most severe lesions, it appeared that the earliest change was hypertrophy of epithelial cells and capillary collapse, followed by loss of endothelial and mesangial cells, and finally increase in amorphous matrix material. The end-stage glomerular lesion of collapsing glomerulopathy appeared to be dense global sclerosis that was indistinguishable from end stage sclerosis caused by other types of glomerular injury. Table 1 demonstrates that the specimens with the greatest amount of active glomerular collapse (that is, collapse with adjacent epithelial changes) had the least end-stage global sclerosis.

Silver and periodic acid-Schiff stains were most effective in demonstrating the basement membrane and matrix lesions. Compared to noncollapsing FSGS and the sclerosing phase of inflammatory glomerulonephritides, the injured segments in collapsing glomerulopathy had much less tendency to form adhesions to Bowman's capsule, although a few adhesions did occur. Hypertrophied epithelial cells sometimes contained large hyaline droplets that were intensely periodic acid-Schiff positive and fuchsinophilic, and variably silver-positive (Figs. 3 and 4). Hypertrophied epithelial cells often had large nuclei, sometimes with large nucleoli. In a few glomeruli, the epithelial hypertrophy and hyperplasia was so marked that it resembled crescent formation; however, close inspection revealed increase in epithelial mass predominantly as a result of cell enlargement rather than cell proliferation and involvement of primarily the visceral rather than the parietal epithelial cells.

All 16 specimens had some degree of focal interstitial fibrosis, tubular atrophy and interstitial influx of predominantly mononuclear leukocytes. Foci of dilated tubules containing amorphous cast material often were present. In most specimens, proximal tubular epithelial cells had conspicuous resorption droplets. In occasional specimens, some proximal tubular epithelial cells contained massive numbers of large resorption droplets while others had no droplets. Fourteen specimens had sclerotic changes in arteries and arterioles, which ranged from mild to marked.

By immunofluorescence microscopy, the injured glomerular segments usually had irregular staining for IgM, C3 and C1q (Fig. 5). Of the 15 specimens evaluated, five had segmental to global mesangial staining for C3, 3 mesangial staining for C3, and 3 mesangial staining for C1q. Hypertrophied visceral epithelial cells sometimes contained resorption droplets that stained with antibodies against immunoglobulins and complement (Fig. 5). Otherwise, there was no significant staining of glomeruli with antibodies specific for IgG, IgA or fibrin.

By electron microscopy, there was variable effacement of visceral epithelial cell foot processes and microvillous transformation of epithelial cytoplasm. Some visceral epithelial cells had markedly increased cytoplasm that contained clear or electron dense vacuoles. Some epithelial cells had reticulogranular changes in nuclear chromatin and a few intranuclear inclusions. There were no capillary wall or mesangial immune complex-type electron dense deposits. Only one of the 16 specimens had endothelial tubuloreticular inclusions, and in this specimen they were sparse.

Clinical characteristics

Mean age at diagnosis was 41.4 ± 19.1 years (range 19 to 81) for the collapsing glomerulopathy patients and 35.4 ± 11.7 years (range 15 to 54) in the FSGS patients (P = NS). Male sex was predominant in both groups (male:female ratio 11:5 for collapsing glomerulopathy vs. 14:11 for FSGS, P = NS). Black race was disproportionately represented in the collapsing glomerulopathy group compared with the FSGS group (13 of 16 vs. 11 of 25 black, P = 0.018). This black:white ratio of 13:3 was

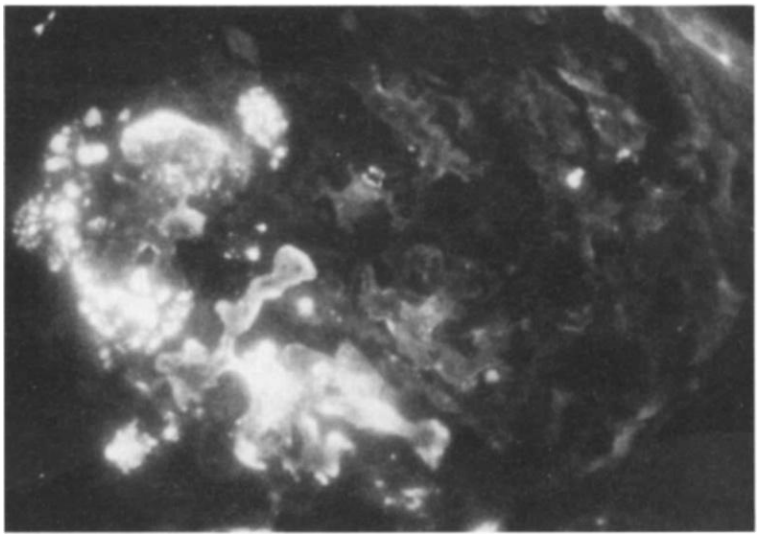

Fig. 5. *Direct immunofluorescence microscopy demonstrating irregular segmental glomerular immunostaining corresponding to a collapsed segment, as well as staining of droplets within visceral epithelial cells.* Anti-C3 (magnification 400×).

dramatically higher than the overall ratio of 1:2 in our renal biopsy population.

Duration of symptoms prior to presentation was less than six months in all collapsing glomerulopathy patients, with the exception of one patient with proteinuria and a biopsy diagnosis of minimal change glomerulopathy made three years prior to diagnosis of collapsing glomerulopathy. The most common presenting clinical findings in collapsing glomerulopathy patients were hypertension and manifestations of the nephrotic syndrome. Many patients also experienced fevers, anorexia, weight loss, and diarrhea (Tables 2 and 3). The presence of hypertension was not significantly different between the collapsing glomerulopathy and FSGS groups. Prior documented illnesses included five patients with a history of "essential" hypertension, two patients with coronary artery disease, and one patient each with morbid obesity, rheumatoid arthritis, asthma, chronic urticaria, psoriasis, minimal change glomerulopathy, and childhood "Bright's disease." Two patients developed a debilitating illness characterized by diffuse muscle weakness and dementia of unknown cause. Seven patients had a recent history of non-steroidal anti-inflammatory drug ingestion. No patients had known toxin exposure. All 12 patients tested serologically for HIV infection and all nine tested for hepatitis B infection were negative. The patients untested for HIV and/or hepatitis B had no evidence for acquired immunodeficiency syndrome (AIDS) or hepatitis at the time of biopsy or after follow-up, and denied all risk factors for obtaining these viruses. One patient had a family history of renal disease in multiple family members, although pathologic confirmation of the renal disease in the relatives was not available.

Presenting serum creatinine was significantly higher in the collapsing glomerulopathy patients than the FSGS patients (3.5 ± 3.4 mg/dl vs. 1.3 ± 0.6 mg/dl, $P = 0.001$). Ten of 16 collapsing glomerulopathy patients had entry serum creatinine >2.0 mg/dl whereas only two of 25 FSGS patients had serum creatinine >2.0 mg/dl (Fig. 6). Twenty-four-hour urinary protein excretion was significantly higher in the collapsing glomerulopathy patients than those with FSGS (13.2 ± 7.7 g/day vs. 4.6 4.5 g/day, $P = 0.005$). Eleven of 15 patients with collapsing glomerulopathy had >10 g/day urine protein excretion, whereas only one of 25 FSGS patients had >10 g/day (Fig. 7). Serum albumin was lower in the collapsing glomerulopathy group, although this was not statistically significant (2.4 ± 0.9 vs. 3.4 ± 1.0 mg/dl, P = NS). Total cholesterol was not statistically significantly different between the two groups (368 174 collapsing glomerulopathy vs. 262 109 FSGS, P = NS).

Two collapsing glomerulopathy patients had anti-nuclear antibody positivity at a titer of 1:80. No patients were noted to have gross hematuria, dysuria, thrombocytopenia, thrombocytosis, leukopenia, transaminase elevation, hypocomplementemia, coagulopathy, hyperkalemia, hyperglycemia, or hypernatremia. There was no significant difference between the two groups with regard to hematocrit.

Table 2. Presenting clinical features of patients with collapsing glomerulopathy ($N = 16$)

Hypertension	56%
Peripheral edema	56%
Anorexia/weight loss	44%
Fever (subjective)	25%
Dyspnea	25%
Diarrhea	19%
Ascites	19%
Pleural effusion	19%
Dementia	13%
Arthralgias/myalgias	13%
Rash	13%
Polyuria	6%

Table 3. Laboratory findings at presentation in patients with collapsing glomerulopathy ($N = 16$)

Hypercholesterolemia	100%
Hypoalbuminemia	88%
Nephrotic range proteinuria (>3.5 g/day)	81%
Pyuria	58%
Anemia	29%
Microscopic hematuria	27%
Leukocytosis	21%
Hyponatremia	7%
Hypokalemia	7%
Eosinophilia	7%

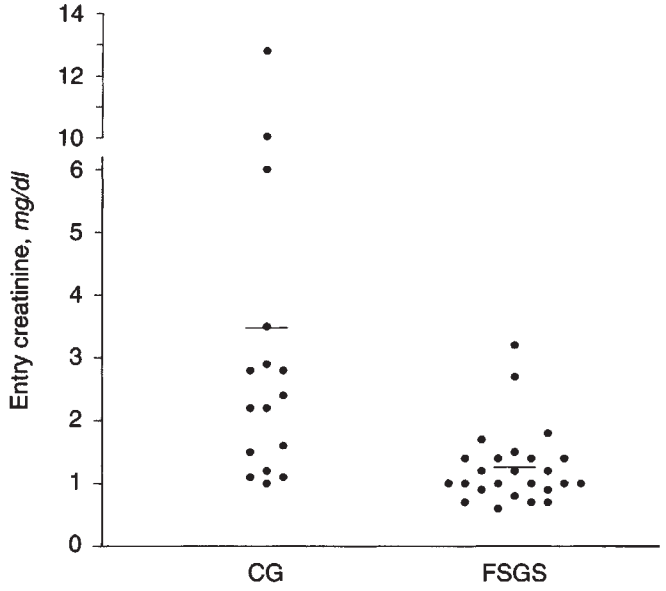

Fig. 6. *Serum creatinine at presentation.* Individual entry serum creatinine in mg/dl for collapsing glomerulopathy (CG) and FSGS patients. Note that 10 of 16 CG patients had entry creatinine >2.0 mg/dl while only 2 of 25 FSGS patients were >2.0 mg/dl. Mean values ± SD for CG and FSGS were 3.5 ± 3.4 and 1.3 ± 0.6 mg/dl, respectively ($P = 0.001$).

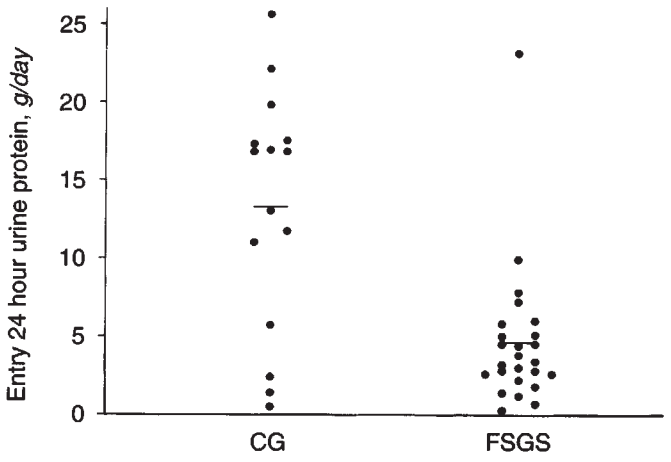

Fig. 7. *Urinary protein excretion at presentation.* Individual 24-hour urinary protein excretion in g/24 hr for collapsing glomerulopathy (CG) and FSGS patients. Note that 11 of 15 CG patients had >10 g/24 hours while only 2 of 25 with FSGS exceeded 10 g/24 hours. Mean values ± SD were 13.2 ± 7.7 and 4.6 ± 4.5 for CG and FSGS patients, respectively ($P = 0.005$).

Renal survival and treatment

Adequate follow-up data were available on 14 of 16 patients with collapsing glomerulopathy and 22 of 25 with FSGS. Renal survival, as determined by life-table analysis, was significantly worse in the collapsing glomerulopathy patients (Fig. 8, $P = 0.0004$). This poor outcome correlated with the type of injury irrespective of entry serum creatinine or race. In other words, the difference in survival between FSGS and collapsing glomerulopathy remained statistically significant when controlling for entry serum creatinine and race ($P = 0.0028$).

Of the 14 collapsing glomerulopathy patients with follow-up data, within 15 months, five were on dialysis and three had died of complications of renal failure. By comparison, during the first 15-months of follow-up, none of the FSGS patients was on dialysis and none had died. Of the six patients with collapsing glomerulopathy not reaching a study end-point, one had an apparent clinical remission, four had persistent nephrotic syndrome, and one patient presenting with asymptomatic nonnephrotic proteinuria remained asymptomatic. The three patients who died with collapsing glomerulopathy had unwitnessed cardiopulmonary arrests with anasarca and renal insufficiency (Cr > 2.0 mg/dl) documented just prior to death. One of these patients had fever and oliguria prior to death, one was awaiting permanent access placement for dialysis, and one died at home with severe malnutrition and fluid overload after multiple hospitalizations for treatment of infections and fluid management.

Five of 14 patients with collapsing glomerulopathy and available follow-up data were treated with immunosuppressive therapy. Of four patients treated with corticosteroids alone, one died, two had persistent nephrotic syndrome, and one experienced clinical remission. One patient was treated with cyclophosphamide and corticosteroids with no reduction in proteinuria and progression of renal insufficiency.

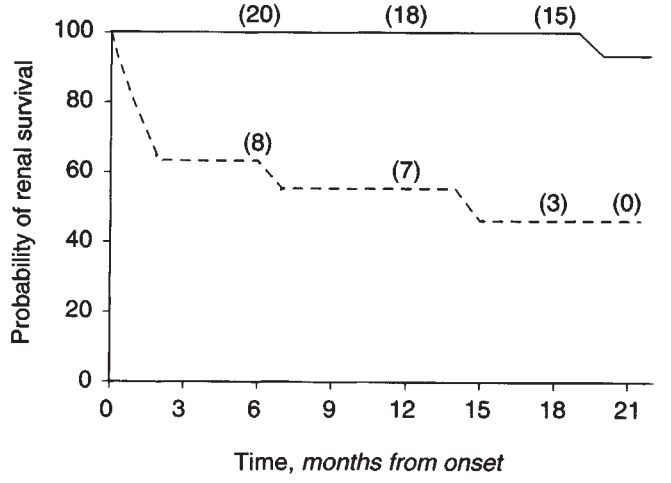

Fig. 8. *Renal survival.* Life-table analysis of patients with collapsing glomerulopathy (- - -; $N = 16$; $P = 0.0004$) vs. FSGS (—; $N = 25$). End-points for renal survival were defined as end-stage renal disease or death due to renal failure. The number of patients at 6, 12, 18, and 21 months with available follow-up who had not reached a study end-point is shown in parentheses.

Discussion

Weiss et al originally described a disease with the unusual renal histopathologic findings of prominent glomerular capillary collapse, visceral epithelial cell swelling with hyaline droplets, and extensive tubulointerstitial inflammation combined with an aggressive clinical course of progressive renal insufficiency and nephrotic syndrome [1]. There have been no further confirmatory studies supporting the claim that this disease might be a distinct clinicopathologic entity. In fact, the possibility has been raised that the patients reported by Weiss et al may have had

HIV infection, and therefore that the observed disease might have been unrecognized HIV-nephropathy [3]. We have, however, identified 16 patients with pathologic findings identical to those described by Weiss et al who have no evidence for AIDS or HIV infection.

Clinical characteristics of these patients with collapsing glomerulopathy included strong black racial predilection, a wide age distribution, slight male predominance, massive proteinuria with nephrotic syndrome, high likelihood of baseline renal insufficiency, and poor renal survival. The somewhat overlapping histologic features of the focal lesions of collapsing glomerulopathy with those of noncollapsing FSGS raises the possibility that this lesion has been classified as FSGS by other pathologists. However, in the current study, comparison of collapsing glomerulopathy patients to patients with noncollapsing FSGS revealed striking epidemiologic, clinical and pathologic differences. Patients with collapsing glomerulopathy are more likely to be black, are more prone to have >10 g/day proteinuria, have a higher likelihood of baseline renal insufficiency, and progress to end-stage renal disease or death caused by renal failure much more rapidly than those with FSGS. Pathologically, collapsing glomerulopathy differs from noncollapsing FSGS in that there are: (1) extensive and often global collapse of the glomerular tufts without as much matrix expansion or adhesion formation as is usual for FSGS; (2) striking visceral epithelial cell hypertrophy, usually accompanied by conspicuous cytoplasmic hyaline droplets; (3) no predilection for perihilar segment; and (4) more extensive tubulointerstitial inflammation, tubular atrophy and fibrosis than in FSGS with a comparable degree of glomerular injury.

Other investigators have suggested that advanced tubulointerstitial injury [6], presence of visceral epithelial cell changes [7], and large amounts of proteinuria [8, 9] are poor prognostic indicators in FSGS. It is possible that some of these reports included patients we have classified in this study as collapsing glomerulopathy.

Collapsing glomerulopathy does not appear merely to represent an advanced form of FSGS. This is supported by the relatively short duration of symptoms in collapsing glomerulopathy patients prior to presentation, the known natural pathologic progression of FSGS [10], which does not pass through a late phase that resembles collapsing glomerulopathy, and the observation that patients in the comparison FSGS group did not develop a similar clinical course even after an extended follow-up period.

Additional support for collapsing glomerulopathy being distinct from FSGS is provided by a preliminary report from Szabolcs and associates [11]. Using immunohistochemical markers for cell proliferation, they observed that, compared to noncollapsing FSGS, collapsing glomerulopathy had an increased expression of proliferation markers in glomerular and tubular epithelial cells.

We have been intrigued by the pathologic and clinical similarities between collapsing glomerulopathy and HIV-nephropathy. Early reports of renal disease in AIDS described FSGS in addition to other lesions [12–14]. The focal glomerular sclerosis of HIV-nephropathy was initially felt to be indistinguishable from other forms of FSGS [12]. However, careful analysis has revealed histopathologic and ultrastructural features that differentiate HIV-nephropathy from FSGS [2, 15, 16]. D'Agati et al recently described the characteristic glomerular lesion of HIV nephropathy as "global, prominent 'collapse' of the glomerular tuft . . . defined as a severe retraction of the glomerular capillary walls with resulting loss of patency of glomerular capillary lumens, but without increase in mesangial matrix or intracapillary matrix" [2]. They also emphasized, as have other authors, the prominent tubulointerstitial changes and visceral epithelial cell hypertrophy of HIV-nephropathy [2,15,16]. This pathologic description closely approximates what we have observed in collapsing glomerulopathy. Clinically, the course of collapsing glomerulopathy and HIV-nephropathy are similar in that both are characterized by rapidly progressive renal failure and severe proteinuria [17, 18].

In view of these striking clinical and pathologic similarities, we have carefully attempted to eliminate the possibility that collapsing glomerulopathy actually is unrecognized HIV-nephropathy. HIV seronegativity was demonstrated in all 12 patients who could be tested. We also carefully reviewed the social history of the study patients with particular attention to any history of HIV risk factors, including a history of intravenous drug abuse. Furthermore, although HIV-nephropathy and collapsing glomerulopathy are similar pathologically, there was an important difference, namely the absence of endothelial tubuloreticular inclusions in 15 of 16 collapsing glomerulopathy biopsies (the one patient with tubuloreticular inclusions also had a positive antinuclear antibody assay but no glomerular immune complex deposits). In our experience, and in published reports [15, 16], endothelial tubuloreticular inclusions are present in 80% to 90% of specimens with HIV-nephropathy compared to approximately 10% of all renal biopsy specimens. Finally, no patient developed clinical evidence of AIDS during the follow-up period.

Although the collapsing glomerulopathy patients do not have evidence to suggest HIV as a cofactor for their renal disease, the possibility that HIV-nephropathy and collapsing glomerulopathy are pathophysiologically related cannot be excluded. An infection, other than HIV, common to patients with HIV-nephropathy and collapsing glomerulopathy could be causing both diseases, and might explain the systemic symptoms experienced by some of the collapsing glomerulopathy patients. However, because there is evidence from animal and human studies that HIV may be directly responsible for the injury in HIV-nephropathy [19, 20], any theory attempting to link HIV nephropathy and collapsing glomerulopathy would imply a common response to different, although possibly related, etiologic stimuli. In support of a possible viral etiology are data indicating that viruses other than HIV can cause focal sclerosing glomerular injury. Mice transgenic for recombinant retrovirus MPSVneo [21] and the early portion of Simian virus 40 [22] have both been demonstrated to develop focal glomerular sclerosis. In humans, focal glomerular sclerosis was reported in a patient with HIV II infection, although it is unclear from the pathologic description if this was a lesion similar to collapsing glomerulopathy [23]. Therefore, a retroviral infection other than HIV is an attractive but highly speculative hypothesis for the etiology of collapsing glomerulopathy.

Intravenous drug abuse may be a cofactor in the development of HIV nephropathy [24]. It is also associated with FSGS in the

absence of HIV infection [25, 26]. Intravenous drug abuse-induced FSGS is reported to be pathologically similar to idiopathic FSGS, although like collapsing glomerulopathy and HIV-nephropathy it carries a worse prognosis [25, 26]. We have observed several patients with a history of intravenous drug abuse and no evidence for HIV infection who have had pathologic findings similar to those of collapsing glomerulopathy. Because of the link between intravenous drug abuse and HIV infection, as well as the link with focal glomerular sclerosis, all patients with a history of intravenous drug abuse were excluded from the current study. We also excluded patients with renal transplants from this study, although we have seen *de novo* or recurrent collapsing glomerulopathy in four renal allografts. The failure to detect hepatitis B seropositivity in our patients with collapsing glomerulopathy lends further support to the contention that we were able to exclude intravenous drug abuse as a potential contributor to the observed glomerular injury. It seems unlikely that intravenous drug abuse is linked to the pathogenesis of the collapsing glomerulopathy in the 16 patients reported here. However, our unpublished observation that a collapsing glomerulopathy pattern of injury does occur in patients with intravenous drug abuse suggests that collapsing glomerulopathy may occur in this population.

The history of proteinuria in relatives of two patients with collapsing glomerulopathy and the striking black racial predilection suggest a possible genetic component to this disorder. Black race also has been considered a risk factor in HIV-nephropathy [17, 24, 27] and intravenous drug abuse nephropathy [28]. It is conceivable that there is a genetic predisposition to development of the pattern of glomerular collapse and injury observed in collapsing glomerulopathy, HIV infection, and intravenous drug abuse [27]. Alternatively, these three groups could share some other etiologic factor; for example, exposure and susceptibility to an infectious pathogen capable of causing this pattern of glomerular injury.

The prevalence and geographic distribution of collapsing glomerulopathy remain to be determined. During the interval in which patients were being entered into this study, November 1988 and October 1990, 1.9% of renal biopsy specimens evaluated by the University of North Carolina Nephropathology Laboratory had collapsing glomerulopathy. It is our impression that this pattern of disease was rare in our region until recently, and is now increasing in frequency. Recently, Valeri and associates have reported an increasing frequency of collapsing glomerulopathy in New York [29]. As is true in our patients, the disease in their patients, compared to FSGS, was characterized by greater black racial predominance, more severe nephrosis, more marked visceral epithelial and tubulointerstitial lesions, and more rapid progression to end-stage renal disease. Also of interest is a report from Zaire noting a striking increase in FSGS in the recent past [30]. The photomicrographs in this publication raise the possibility that the disease that is increasing in frequency in Zaire is collapsing glomerulopathy. In fact, in the legend to their Figure 4 they note that "epithelial hyperplasia coexists with collapsed sclerotic areas" in the glomeruli [30]. A problem with drawing conclusions from these data, however, is the lack of systematic data on testing for HIV infection.

In conclusion, collapsing glomerulopathy is characterized by black racial predominance, massive proteinuria, and, in a high proportion of patients, relatively rapid progression to end-stage renal disease. Its predominant histopathologic findings are focal glomerular capillary collapse, visceral epithelial cell hypertrophy, hyperplasia and hyaline droplet formation, and associated tubulointerstitial injury. Focal glomerular injury with the pathologic features of collapsing glomerulopathy causes more severe nephrosis and renal insufficiency at presentation, and more rapid progression of renal failure than glomerular sclerosis without collapsing features. Although collapsing glomerulopathy is clinically and pathologically similar to HIV nephropathy, it occurs in patients without evidence of HIV infection and pathologically lacks endothelial tubuloreticular inclusions. Collapsing glomerulopathy is clinically, pathologically, and epidemiologically distinct from noncollapsing FSGS, but the presence of variable degrees of focal glomerular sclerosis raises the possibility that it may ultimately be classified as an aggressive or malignant subcategory of FSGS.

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