Collapsing Glomerulopathy

By Joshua A. Schwimmer, Glen S. Markowitz, Anthony Valeri, and Gerald B. Appel

Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis (FSGS) characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease. The cause of this disorder is unknown, but nearly identical pathologic findings are present in idiopathic collapsing glomerulopathy and human immunodeficiency virus (HIV)-associated nephropathy, and collapsing glomerulopathy has been associated with parvovirus B19 infection and treatment with pamidronate. The pathogenesis of collapsing glomerulopathy involves visceral epithelial cell injury leading to cell cycle dysregulation and a proliferative phenotype. Clinically, collapsing glomerulopathy is characterized by black racial predominance, a high incidence of nephrotic syndrome, and rapidly progressive renal failure. Collapsing glomerulopathy also may recur after renal transplantation or present de novo, often leading to loss of the allograft. The optimal treatment for collapsing glomerulopathy is unknown. Treatments may include steroids or cyclosporine in addition to aggressive blood pressure control, angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, and lipid lowering agents. The role of other immunosuppressive agents such as mycophenolate mofetil in the treatment of collapsing FSGS remains to be defined. Prospective clinical trials are needed to define optimal therapy of this aggressive form of FSGS.

FOCAL SEGMENTAL glomerulosclerosis (FSGS) has become one of the most common causes of idiopathic nephrotic syndrome in adults and is the most common cause in blacks.[1,2] Of the distinct morphologic variants of FSGS, collapsing glomerulopathy stands out for its aggressiveness. Recent studies have clarified the epidemiologic features, histopathology, natural history, and response to treatment of this pattern of FSGS.[3-5]

INITIAL RECOGNITION

Collapsing glomerulopathy, also known as collapsing FSGS or malignant FSGS, initially was described as a distinct clinicopathologic entity in 1986, when Weiss et al[3] reported a group of 6 patients with nephrotic syndrome, rapidly progressive renal failure, and glomerular collapse. Renal biopsy examination displayed the characteristic features of collapsing glomerulopathy: segmental and global collapse of the glomerular capillaries, wrinkling and retraction of the glomerular basement membrane (GBM), and marked hypertrophy and hyperplasia of podocytes. Tubulointerstitial changes also were prominent and included tubular dilatation and degeneration, epithelial necrosis, and interstitial fibrosis and edema (Fig 1). In this initial report, all 6 patients were black, and all presented with nephrotic syndrome and varying degrees of renal insufficiency. Five of the 6 patients also had a nonspecific febrile illness before presentation, but no clear etiologic factor was identified.

Soon after, patients infected with human immunodeficiency virus (HIV) were recognized to have a similar presentation and nearly identical pathologic findings on renal biopsy examination. Patients with HIV-associated nephropathy (HIVAN) are predominantly of black race and usually present with nephrotic syndrome and rapidly progressive renal failure. On renal biopsy examination, the most characteristic lesion of HIVAN is a collapsing glomerulopathy that usually is associated with severe tubulointerstitial injury.[6-8] (HIVAN is discussed in greater detail in another article in this issue.)

Idiopathic collapsing glomerulopathy initially was reported in HIV-negative patients by Detwiler et al.[4] Of 16 patients, 12 tested serologically negative for HIV and the remaining patients had no risk factors for HIV or evidence of acquired immune deficiency syndrome at follow-up evaluation. Eight percent to 92% of glomeruli had active collapsing lesions, and the percentage of active collapsing lesions correlated inversely with the percentage of chronic sclerosing lesions. Based on the spectrum of pathologic findings, the morphologic appearance of collapsing glomerulopathy appeared to be an early finding that ultimately led to

From the Division of Nephrology, Department of Medicine, and the Department of Pathology, Columbia College of Physicians and Surgeons, New York, NY.

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Address reprint requests to Gerald B. Appel, MD, Columbia College of Physicians and Surgeons, 622 West 168 St, PH4 Room 124, New York, NY 10032.

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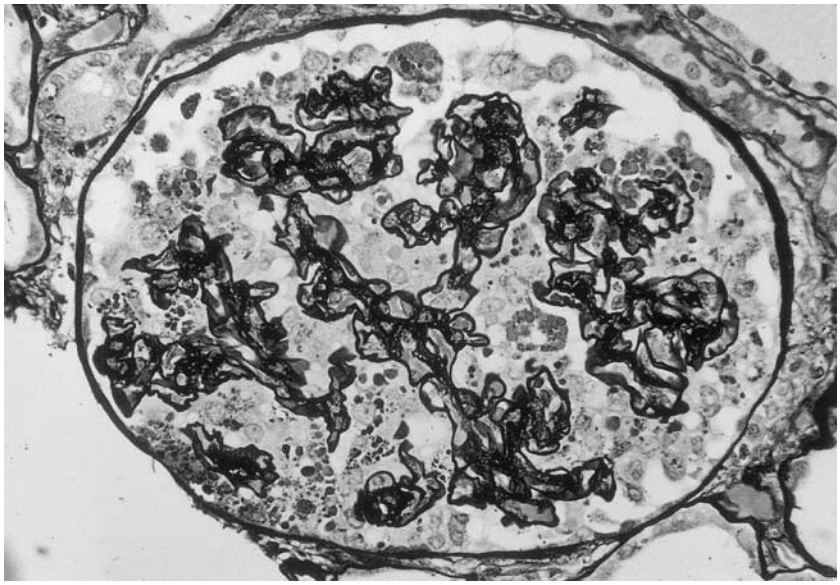

Fig 1. A glomerulus with collapsing focal segmental glomerulosclerosis exhibiting global wrinkling and retraction of the glomerular basement membrane and marked proliferation and swelling of overlying visceral epithelial cells which contain protein resorption droplets (Jones methenamine silver, ×400).

the formation of discrete segmental scars typical of classic FSGS. The 16 biopsy specimens also had varying degrees of tubular atrophy, interstitial fibrosis, and interstitial inflammation composed predominantly of mononuclear leukocytes. In contrast to patients with HIVAN, in whom tubuloreticular inclusions are found commonly in glomerular endothelial cells by electron microscopy, only 1 of the 16 patients with collapsing glomerulopathy had endothelial tubuloreticular inclusions.[4]

ETIOLOGIES

As opposed to the many secondary causes of classic FSGS,[9,10] most cases of collapsing glomerulopathy are either HIV-associated or idiopathic. In addition, a secondary cause of collapsing glomerulopathy is treatment with high-dose pamidronate, a bisphosphonate used to treat osteolytic bone lesions and hypercalcemia of malignancy. In 2001, 7 patients who were white, HIV negative, and developed collapsing glomerulopathy after treatment of multiple myeloma or breast cancer with pamidronate were reported. Patients were treated with pamidronate for 15 to 48 months before renal biopsy examination, and 5 of the 7 had received more than the recommended dosage of 90 mg intravenously per month. All patients developed renal insufficiency and nephrotic syndrome, with a mean creatinine level of 3.6 mg/dL and a mean 24-hour urinary protein excretion of 12.4 g/d. Three of 5 patients in whom pamidronate was withdrawn had stabilization of their renal function.[11] The same group later reported a case of collapsing glomerulopathy in which the patient's proteinuria significantly decreased after withdrawal of pamidronate but then worsened with reintroduction of this agent.[12] Since the original report of 7 patients, 10 additional cases of pamidronate-associated collapsing glomerulopathy have been seen.[12] Other centers also have reported cases of FSGS and collapsing glomerulopathy after treatment with pamidronate.[13,14]

Recent studies and case reports have suggested an association between collapsing glomerulopathy and parvovirus B19 infection.[15] This association is intriguing given the establishment of HIV as a viral cause of collapsing glomerulopathy and the frequent reports of a nonspecific febrile illness before the development of collapsing glomerulopathy.[4,16] One study of 40 patients by Tanawattanacharoen et al[17] reported a significantly greater prevalence of parvovirus B19 DNA by using polymerase chain reaction in patients with idiopathic FSGS and collapsing glomerulopathy compared with patients with membranous nephropathy and minimal change disease. A second study by Moudgil et al[18] analyzed biopsy specimens of 23 patients with collapsing glomerulopathy for parvovirus B19 DNA by using polymerase chain reaction and compared the results with biopsy specimens of classic FSGS, HIVAN, and controls with other renal diseases. Parvovirus B19 DNA was detected in 78.3% of biopsy specimens with collapsing glomerulopathy, significantly more than was detected in biopsy

specimens with HIVAN (15.8%), classic FSGS (22.2%), and controls (25.9%) ($P < .01$). This data suggest that infection of renal epithelial cells by parvovirus B19 may be an etiology of collapsing glomerulopathy in susceptible patients. Infection of visceral and tubular epithelial cells has been documented in cases of HIVAN.[19-21]

PATHOGENESIS

Glomerular visceral epithelial cell injury underlies the pathogenesis of collapsing FSGS. Podocyte injury is characterized by increased cell turnover and reversion to an immature state. In a study of 8 patients with collapsing glomerulopathy, Bariety et al[22] showed that podocytes detach from the GBM, lose their normal podocyte markers (vimentin, podocalyxin, and CR1), and acquire macrophage-associated epitopes (KP1, PG-M1, and M 18). Barisoni et al[23] studied the expression of podocyte maturity markers (WT-1, CALLA, C3b receptor, GLEPP-1, podocalyxin, synaptopodin) and the proliferation marker Ki-67 in 10 cases of idiopathic collapsing glomerulopathy, 8 cases of HIVAN, 5 cases of membranous nephropathy, and 5 cases of minimal change disease. In patients with idiopathic collapsing FSGS and HIVAN (but not in patients with other glomerular diseases), decreased expression of podocyte markers of maturity and increased expression of Ki-67 was observed. This data suggests that both idiopathic collapsing glomerulopathy and HIVAN are associated with a dysregulated, cycling podocyte phenotype.

In collapsing glomerulopathy, expression of cyclin A (a positive cell cycle regulatory protein) is increased while expression of synaptopodin, cyclin D1, and the negative cell cycle regulatory proteins p27 and p57 are decreased.[24] Shankland et al[25] evaluated a series of 9 patients with collapsing glomerulopathy, 16 patients with HIVAN, and 37 patients with other causes of nephrotic syndrome. Expression of p27 and p57 was uniformly decreased in collapsing glomerulopathy, cellular FSGS, and HIVAN. These 2 studies support the concept of an immature, proliferative podocyte phenotype.

POSTTRANSPLANT COLLAPSING GLOMERULOPATHY

Stokes et al[26] reported 6 patients with de novo posttransplant collapsing glomerulopathy and 1 patient with recurrent disease, and Meehan et al[27] reported 5 cases of de novo collapsing glomerulopathy after renal transplantation, which represented 0.6% of renal allograft biopsy specimens. The mean time to diagnosis after transplantation was 17.6 months in the series by Meehan et al[27] and 74 months in the series by Stokes et al,[26] indicating that collapsing glomerulopathy may be a late complication of renal transplantation. Collapsing glomerulopathy after renal transplantation has a poor prognosis. In the studies by Stokes et al[26] and Meehan et al,[27] 71% and 100% of patients reached end-stage renal disease (ESRD) during the period of follow-up, respectively. The time to ESRD after biopsy procedure ranged from 2 to 24 months (average, 9.8 mo) in Meehan et al's[27] series, and from 0 to 4 months (average, 2.6 mo) in Stokes et al's[26] series. Recurrent posttransplant collapsing and classic FSGS may be treated with plasmapheresis, which is more effective if initiated early.[28]

Although the patients in Stokes et al's[26] series of posttransplant collapsing glomerulopathy are similar to previously reported nontransplanted patients with respect to the severity of renal insufficiency on presentation, there are a number of important differences. Only 14% of patients in this series were black, as compared with greater than 50% of patients in previous series from the United States. Patients also presented with markedly less proteinuria (average, 1.8 g/d) and a lower incidence of nephrotic syndrome (14%) than patients with collapsing glomerulopathy in the native kidney. The reasons for these differences in clinical presentation in Stokes et al's[26] series are unclear, but may be related to more aggressive biopsy practices in transplant patients with renal insufficiency or modification of disease by immunosuppressive agents used in transplant patients. In contrast, in Meehan et al's[27] series the percentage of patients who were black (40%) and the percentage of patients with nephrotic range proteinuria (80%) was similar to patients in previous studies of idiopathic collapsing glomerulopathy.

An intriguing possibility suggested by multiple investigators is that the pathogenesis of de novo collapsing glomerulopathy in transplant patients may be related to renal ischemia. In Meehan et al's[27] series, 4 of 5 patients had moderate to severe arteriolosclerosis[27] and in Stokes et al's[26] series, 5 of the 7 cases had moderate to severe vascular injury that was related to thrombotic microangi-

opathy, cyclosporine toxicity, and/or arteriolosclerosis.[26] Recently, Nadasdy et al[29] at the University of Rochester described 3 allograft nephrectomy specimens that showed a zonal distribution of collapsing glomerulopathy related to obliterative vascular changes including chronic transplant arteriolopathy, acute vascular rejection, and thrombotic microangiopathy.

The concept that microvascular injury may contribute to the pathogenesis of collapsing glomerulopathy is supported by a study by Greenberg et al[30] of 24 patients who on renal biopsy examination were found to have cholesterol atheroembolic renal disease. FSGS was observed in 15 patients (63%), and 10 (42%) of these patients had the cellular variant of FSGS with features of collapsing glomerulopathy. An association between renal artery stenosis and FSGS also has been reported.[31] These studies suggest that de novo collapsing glomerulopathy in transplant patients may be related to renovascular disease.

PATHOLOGY

There are 2 pathologic findings that together define the collapsing variant of FSGS.[4,5] First, there is implosive wrinkling and retraction of the GBM (Fig 1). Second, there is marked hypertrophy and hyperplasia of overlying visceral epithelial cells (podocytes). Visceral epithelial cells frequently contain protein resorption droplets and may appear detached from the underlying GBM. Lesions of collapsing FSGS often coexist in the same biopsy specimen with other patterns of FSGS, including cellular lesions and discrete segmental scars typical of the classic form of FSGS.

The changes seen in collapsing FSGS are not confined to glomeruli. There are typically widespread tubular degenerative changes including luminal ectasia, cytoplasmic simplification and vacuolization, loss of brush border, nuclear pleomorphism with prominent nucleoli, and multiple mitotic and apoptotic figures. Proximal tubules also display protein resorption droplets. In almost half of cases, tubular microcysts are seen and typically display a proteinaceous filtrate that stains positively with the periodic acid Schiff stain.[5] Interstitial edema and a mild to moderate chronic inflammatory infiltrate characteristically accompany the tubular degenerative changes. Rare foci of mild tubulitis may be apparent. With progression of disease, tubular atrophy and interstitial fibrosis intervene.

In the setting of collapsing FSGS, immunofluorescence typically reveals positivity for immunoglobulin M (IgM) and C3 in the distribution of the lesions of FSGS. The intensity of staining is typically trace to 1+ but may be up to 2+ (scale: 0, trace, 1-3+). Staining for IgG, IgA, and κ and λ light chains is negative.

Electron microscopy reveals an increase in the number and size of podocytes. On the subcellular level, there may be an increase in organellar content and transport vesicles, microvillous transformation, lipid and protein resorption droplets, and extensive foot process fusion. Although the podocyte changes normally are diffuse, glomeruli containing lesions of collapsing FSGS will display more prominent podocyte changes as well as wrinkling and retraction of the GBM. Within the capillary lumina, focal hyaline insudation and rare endocapillary foam cells may be apparent. Electron dense deposits typically are absent although rare mesangial deposits should not be a deterrent from making the diagnosis of collapsing FSGS.

In the setting of collapsing FSGS, endothelial tubuloreticular inclusions should be sought carefully on ultrastructural evaluation. Tubuloreticular inclusions are seen in the majority of cases of collapsing FSGS associated with HIVAN but only in a minority of cases of idiopathic collapsing FSGS or collapsing FSGS secondary to treatment with pamidronate or parvovirus B19 infection.

The differential diagnosis for collapsing FSGS includes other variants of FSGS as well as alternate forms of glomerular disease. Among the variants of FSGS, the collapsing variant is most commonly misdiagnosed as cellular FSGS. Both the collapsing and cellular variants are characterized by the widespread hypertrophy and hyperplasia of visceral epithelial cells. The defining features that separate the 2 entities are the implosive wrinkling and retraction of the GBM seen in collapsing FSGS as opposed to the presence of endocapillary hypercellularity seen in the cellular variant. In some cases of collapsing FSGS, the visceral epithelial cell proliferation may be so exuberant as to form a pseudocrescent. In such cases, the histologic findings may be mistaken for a crescentic glomerulonephritis. Proper integration of the clinical history and light microscopic, immunofluores-

Table 1. Clinical Characteristics of Collapsing Glomerulopathy

Study	Patients (No.)	Average Age (Range)	M/F Ratio	Black (%)	Average Proteinuria (g/d)	Average Cr (mg/dL)
Weiss (1986)[3]	6	35 (17-75)	2	100%	N/R	2.6
Detwiler (1994)[4]	16	41.4 (19-81)	2.2	81%	13.2*	3.5*
Haas (1995)[32]	21	30.4	1.63	86%*	14.3*	3.8*
Valeri (1996)[5]	43	32.2 (1.5-72)	1.38	61%*	10.2	4.2
Bariety (1998)[22]	8	42 (28-57)	1	63%	15.4	7.3
Laurinavicius (1999)[33]	42	38.5 (13-77)	0.83	57%	13.3	5.4
Grcevska (1999)[7]	16	34 (13-60)	3	0%	5.8	2.1

Abbreviation: N/R, not reported.
*$P < .05$ compared with controls with classic FSGS.

cence, and ultrastructural findings will aid in this differential diagnosis.

Lesions of collapsing FSGS may be present segmentally or globally within glomeruli and typically involve multiple glomeruli in a given biopsy sample. Although this is true in the majority of cases, it raises the issue of how many collapsing lesions are necessary to assign a diagnosis of collapsing FSGS. For instance, what if a biopsy sample includes 20 glomeruli of which 7 display lesions of FSGS, but only a single glomerulus displays a lesion of collapsing FSGS? As yet, no study has satisfactorily answered this question. Given that the collapsing variant of FSGS has a worse prognosis than the other subtypes of FSGS, we feel that even a single lesion of FSGS bears mentioning. Future studies are needed to better address this issue.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Detwiler et al's[4] and Valeri et al's[5] original reports established collapsing glomerulopathy as a distinct subset of idiopathic FSGS with black racial predominance, heavy proteinuria, and unusually rapid progression of renal failure.[3] Other major series of idiopathic collapsing glomerulopathy[7,22,32,33] and collapsing glomerulopathy after renal transplantation[26,27] have further clarified the epidemiology, clinical presentation, and natural history of this disease (Table 1).

In 2 recent series, the percentage of native renal biopsy specimens with idiopathic collapsing glomerulopathy was 1.8% and 1.9%.[4,7] In the largest case series of patients with collapsing glomerulopathy, investigators at Columbia University noted an increasing frequency of cases that appeared to parallel the increase in frequency in cases of HIVAN and idiopathic classic FSGS. The first case was identified in 1979, and the proportion of collapsing glomerulopathy in this biopsy population increased from 11% of all cases of idiopathic FSGS from 1979 to 1985, to 20% of all cases from 1986 to 1989, to 24% from 1990 to 1993. The reason for this increase in frequency of cases is not clear, and suggests a possible shift in exposure to certain infections, pharmacologic agents, or other environmental factors. Haas et al[32] at the University of Chicago reviewed their cases of focal sclerosis from 1974 to 1993. Their first case of collapsing glomerulopathy was identified after 1980, and during the time period of 1980 to 1993 collapsing FSGS represented 5.3% of cases of idiopathic FSGS. A follow-up study from the same center from 1995 to 1997 identified collapsing glomerulopathy in 9% of patients with FSGS.[2] Occasional reports of cellular FSGS before 1980 described lesions that appear to be indistinguishable from collapsing glomerulopathy but were not identified previously as a distinct entity.[34-37]

The median age of patients with idiopathic collapsing glomerulopathy is 30 to 40 years, but a wide range of ages have been reported, with patients as young as 1.5 years and as old as 82 years (Table 1). Most studies have reported a male predominance,[3-5,7] although in one series, a female predominance was noted.[33]

Since Weiss et al's[3] original series, in which all 6 patients with collapsing glomerulopathy were black, a predominance of black patients in the United States has been noted. Two studies in the United States, by Detwiler et al[4] and Valeri et al,[5] noted a statistically significant higher percentage of patients who were black with collapsing glomerulopathy compared with control patients with

Table 2. Treatment and Outcome of Collapsing Glomerulopathy

Study	SR (No.)	Steroids	CSA	Cytotoxics	Average Follow-Up (mo.)	Outcome
Weiss (1986)[3]	0	0% (0.2) R	N/A	N/A	NR	100% ESRD, 9 mo. median renal survival
Detwiler (1994)[4]	0	25% (1/4) R	N/A	0% (0/1) R	15	36% ESRD,* 21% died
Haas (1995)[32]	NR	NR	NR	NR	78	71% ESRD,* 15 mo. mean renal survival*
Valeri (1996)[5]	2 CR, 1 PR	0% (0/26) R	33% (1/3) CR, 33% (1/3) PR	0% (0/6) CR, 17% (1/6) PR	32.2	51% ESRD, 13 mo. median renal survival*
Bariety (1998)[22]	1 PR	N/A	N/A	1 CR	22.9	63% ESRD
Laurinavicius (1999)[33]	0	8.7% (2/23) CR, 30.4% (7/23) PR	0% CR, 33% (1/3) PR	0% (0/6) R	21.4	71.4% ESRD
Grcevska (1999)[7]	0	0% (0/7) R	N/A	0% (0/8) R	60	100% ESRD*

Abbreviations: SR, spontaneous remission; NR, not reported; N/A, not applicable; PR, partial remission; CR, complete remission; R, remission, not further defined.

$P < .05$ compared with controls with classic FSGS.

classic FSGS (81% versus 44% and 61% versus 22%, respectively, $P < .05$ for both studies). A study of 8 patients in France by Bariety et al[22] also noted a predominance of black patients (63% from Antilles or Africa). In a recent study by Grcevska and Polenakovik[7] of patients from the Republic of Macedonia, all 16 patients were white, suggesting that idiopathic collapsing glomerulopathy may be present in significant numbers in predominantly white populations.

The clinical manifestations of collapsing glomerulopathy are similar to those of idiopathic classic FSGS but generally are more severe. More than 80% of patients with collapsing glomerulopathy present with nephrotic range proteinuria, and studies have shown a significantly greater incidence of nephrotic syndrome (91% versus 60%, $P < .025$)[5] and higher levels of proteinuria (average. 13.2 g/d versus 4.6 g/d and 14.3 g/d versus 7.7 g/d, both $P < .05$)[4,32] in patients with collapsing glomerulopathy compared with control patients with FSGS. Other severe manifestations of the nephrotic syndrome are frequent, including hypoalbuminemia (average, 1.6-2.4 g/dL), hypercholesterolemia (average, 316-404 mg/dL), and edema (74%-100%), but none of these manifestations are significantly different than in patients with classic FSGS (Table 1). Studies by Detwiler et al[4] and Haas et al[32] found that patients with collapsing glomerulopathy presented with significantly greater renal insufficiency than control patients with FSGS.

NATURAL HISTORY

Based on retrospective series, only generalizations can be made about the natural history of collapsing glomerulopathy, prognostic factors, and the response to treatment (Table 2). Patients with collapsing glomerulopathy are at high risk of progressing to ESRD. Even with treatment, the incidence of ESRD is 50% to 100% in most series. In 4 studies, the renal survival of patients with collapsing glomerulopathy was significantly worse than patients with classic FSGS.[4,5,7,32] Of 14 patients followed-up by Detwiler et al[4] for 15 months, 5 (36%) were on dialysis and 3 (21%) had died of complications of renal failure. In comparison, during the same time period none of the control patients with classic FSGS were on dialysis or had died ($P = .0004$). The difference in renal survival by life table analysis remained highly significant even when controlling for entry serum creatinine and race. In Haas et al's[32] series, there was a significant difference in both the percentage of collapsing glomerulopathy patients progressing to ESRD (71% versus 20%, $P < .05$) and the rate of progression (mean renal survival, 15 versus 38 mo) compared with control patients with FSGS. Grcevska et al[7] also found that patients with collapsing glomerulopathy had significantly worse renal survival compared with patients with classic FSGS. During 5 years of follow-up evaluation, 100% of patients with collapsing glomerulopathy

reached ESRD and one patient had died. In comparison, 41.4% of patients with classic FSGS reached ESRD ($P = .025$ by life table analysis).

Valeri et al[5] noted an insignificant difference in the overall incidence of ESRD at last follow-up evaluation in patients with collapsing glomerulopathy compared with classic FSGS (51% versus 42%, P = NS). However, there was a 4-year difference in the median renal survival time after biopsy examination (13.0 versus 62.5 mo, $P < .05$). Furthermore, the period from diagnosis of renal disease to biopsy examination was much shorter in patients with collapsing glomerulopathy (7.9 versus 48.6 mo, $P < .025$).

Multiple studies have examined prognostic indicators in collapsing glomerulopathy. Valeri et al[5] found that progression to ESRD was predicted by serum creatinine level at biopsy examination ($P < .05$) and lack of remission of proteinuria ($P < .025$), but did not find a correlation between severity of proteinuria or other features of the nephrotic syndrome with outcome. Using the rate of decline of renal function defined as the inverse of creatinine-versus-time curve, the rate of progression of renal failure in the collapsing FSGS group correlated highly with the severity of tubular degenerative and regenerative changes ($P < .02$) but not with any other parameter of tubulointerstitial or glomerular change. The serum creatinine level at biopsy examination correlated significantly with male sex, degree of global glomerulosclerosis, tubular degenerative changes, and tubular atrophy. The rate of progression of renal failure correlated best with male sex.[5]

Laurinavicius et al[33] used data from 42 patients with collapsing glomerulopathy and 18 patients with HIVAN to investigate predictors of serum creatinine level, proteinuria, and progression of renal disease. The model to predict serum creatinine level at time of biopsy examination included extent of interstitial fibrosis, percentage of glomeruli with collapsing lesions, and male sex ($P = .0001$). Degree of proteinuria was predicted best by using percentage of foot process effacement and patient age ($P = .0002$). In their multivariate model, the risk for ESRD was increased significantly by interstitial fibrosis of greater than 20%, creatinine level greater than 2.0 mg/dL, proteinuria greater than 8 g/d, glomeruli with collapsing lesions greater than 20%, and HIV infection ($P = .0001$). The rate of decline of renal function (defined as the inverse of creatinine-versus-time) correlated with the degree of proteinuria at biopsy examination ($P = .002$), accounting for 27% of the variance.[33]

RESPONSE TO TREATMENT AND RECOMMENDATIONS

There are no prospective treatment trials of collapsing glomerulopathy. Recent studies in patients with idiopathic FSGS using steroids, cyclosporine, and other immunosuppressive agents have shown that remissions were obtainable in over 50% of patients and may produce prolonged renal survival.[38-40] In contrast, data from retrospective studies of collapsing glomerulopathy suggested that progression to ESRD was frequent, spontaneous remissions were rare, and the disease was relatively resistant to most immunosuppressive agents (Table 2). Controlled, prospective treatment trials are needed.

Initial studies suggested that collapsing glomerulopathy was unresponsive to steroids in the majority of patients. In the study by Valeri et al,[5] when treated with prednisone, none of 26 patients had a complete or partial remission. However, although all patients received at least a 2-month trial of steroids, only 5 of 26 (19%) received the recommended 6-month course, limiting the significance of these findings. Moreover, most patients in this study already had severe renal insufficiency (mean serum creatinine level of 4.2 mg/dL). Twenty-three patients in Laurinavicus et al's[33] study were treated with steroids with only slightly better results: 2 (8.7%) had a complete remission and 7 (30.4%) had a partial remission. However, 4 of 7 patients with a partial remission reached ESRD and only 2 (8.7%) had a normal creatinine level at the end of follow-up evaluation.

The published data on cytotoxic agents in the treatment of collapsing glomerulopathy is sparse and unfavorable. In a study by Grcevska et al,[7] none of 8 patients responded to a combination of cyclophosphamide and steroids. Similarly, none of 6 patients who were treated with cytotoxic agents in the study by Laurinavicius et al[33] achieved a remission of nephrotic syndrome. Bariety et al[22] reported one patient treated with steroids and azathioprine who continued to have a complete remission after 8 years of follow-up evaluation. In the series by Valeri et al,[5] only 1 patient of 6 (17%)

who was treated with cyclophosphamide achieved a partial remission.

Data on treatment of collapsing glomerulopathy with cyclosporine also is limited, although the results are more encouraging. In the study by Valeri et al,[5] 3 patients were treated with cyclosporine, with 1 complete remission and 1 partial remission. Three patients were treated with cyclosporine in the study by Laurinavicius et al[33]; 2 did not respond and 1 patient (33%) developed cyclosporine-dependent nephrotic syndrome and chronic renal failure.

Although the ability to draw conclusions from this data is limited, the poor prognosis of collapsing glomerulopathy is an incentive to attempt treatment. Given the limited efficacy of cytotoxic agents and their significant toxicity, their use does not appear justified. We have had a number of patients achieve complete remissions with corticosteroids or cyclosporine alone. Other patients with steroid-resistant disease have achieved partial remissions with cyclosporine alone or in combination with mycophenolate mofetil (MMF) (CellCept; Roche Pharmaceuticals, Nutley, NJ). The chance of achieving a remission appears to be greatest when treatment is initiated early in the course of the disease.

Oral corticosteroids are an appropriate first-line therapy for collapsing FSGS. Our practice is to administer oral steroids using an every other day regimen for a full 6 months (eg, 120 mg prednisone every other day for the first several months, then tapered), although daily steroid therapy also may be used. Steroids should be used cautiously, if at all, in patients with diabetes or patients who are at high risk for infections or other complications.

Given its proven efficacy in the treatment of steroid-resistant classic FSGS, cyclosporine is a reasonable first- or second-line agent in patients with collapsing glomerulopathy.[39] Treatment may be started at 3.5 mg/kg/d in 2 divided doses (or 100 mg twice daily), for a target whole blood trough level between 125 and 200 μg/L. Cyclosporine may be tapered if there is no response within 4 months. Given the severity of the clinical manifestations of collapsing glomerulopathy and its resistance to most immunosuppressive agents, combining cyclosporine with MMF may be considered. There is limited data on the use of MMF in idiopathic FSGS,[41-43] although this agent has been used in a number of trials including lupus nephritis,[44] IgA nephropathy,[45-47] and membranous nephropathy.[43,48] As yet, the role of MMF in the treatment of collapsing FSGS has yet to be defined.

In addition to immunosuppressive therapy, all patients should be treated with an angiotensin converting enzyme inhibitor and/or an angiotensin receptor blocker in an attempt to aggressively control blood pressure, reduce proteinuria, and reduce progression of renal insufficiency.[49] Although some patients will not tolerate these agents owing to hyperkalemia or a reduction in the glomerular filtration rate, the majority will benefit from reduced proteinuria and possibly by decreased progression of their renal disease. Patients with hyperlipidemia will benefit from therapy with lipid-lowering agents with a reduced risk for cardiovascular disease and perhaps slower progression of renal failure.[50-52]

CONCLUSION

Collapsing glomerulopathy is a morphologic variant of FSGS characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease. The cause of this disorder is unknown, but nearly identical pathologic findings are present in HIVAN, idiopathic collapsing FSGS, and collapsing FSGS associated with parvovirus B19 infection and treatment with pamidronate. The pathogenesis of collapsing glomerulopathy involves visceral epithelial cell injury leading to cell cycle dysregulation and a proliferative phenotype. Clinically, collapsing glomerulopathy is characterized by black racial predominance, a high percentage of patients with heavy proteinuria and nephrotic syndrome, and rapidly progressive renal failure. Collapsing glomerulopathy may also recur after renal transplantation or present de novo and often leads to loss of the allograft. Renovascular ischemia may be a contributing factor in collapsing glomerulopathy in transplant patients. The optimal treatment for collapsing glomerulopathy is unknown; spontaneous remissions are rare, progression to ESRD is frequent, and the disease appears to be relatively resistant to steroids and most immunosuppressive agents. Treatments may include steroids or cyclosporine in addition to aggressive blood pressure control, treatment with angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, and treatment of hyperlipidemia. The

role of MMF and other immunosuppressive agents in the treatment of collapsing glomerulopathy remains to be defined. Prospective clinical trials are needed to define optimal therapy of this aggressive form of FSGS.

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