

Current Views on Collapsing Glomerulopathy

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ABSTRACT

Collapsing glomerulopathy is a proliferative disease defined by segmental or global wrinkling of the glomerular basement membranes associated with podocyte proliferation. These lesions are particularly poor responders to standard therapies. First described as an idiopathic disorder or following HIV infection, it is now associated with a broad group of diseases and different pathogenetic mechanisms, which participate in podocyte injury and mitogenic stimulation. Because of this etiologic heterogeneity, there is clear need for new therapeutic approaches to target each variant of this entity. Historical background, terminology, morphologic and phenotypic features, and suggested mechanisms are reviewed in this manuscript.

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A 20-yr-old black woman was healthy until 4 weeks before admission when she developed gastric discomfort, nausea, and occasional vomiting, followed by progressive edema of lower extremities. On admission she was afebrile and normotensive and physical examination was unremarkable. Urinalysis showed 3+ protein (8 g/24 h), 0 to 2 red blood cells/hpf, 2 to 5 white blood cells/hpf, and occasional granular casts. The serum creatinine was 1.4 mg/dl at presentation and increased to 1.8 mg/dl during hospitalization; blood urea nitrogen was 11 mg/dl, total protein 4.4 g/dl, albumin 2.0 g/dl. The hematocrit was 43% at presentation but decreased to 34% in the following weeks. Hepatic function was normal. Serology for hepatitis B and C, HIV, rapid plasma reagin, and antinuclear antibody was negative. Serum complement was within the normal range.

A renal biopsy contained 35 glomeruli, two obsolescent. Most glomeruli displayed segmental or global glomer-

ular collapse (Figure 1, a and b). Focal neutrophilic tubulitis, granular and Tamm-Horsfall casts, acute tubular injury with scattered mildly dilated tubules, and moderately severe interstitial inflammation were also noted. Immunofluorescence showed nonspecific staining for IgM and C3 in the areas of collapse (Figure 1c). The light microscopy findings were confirmed by ultrastructural analysis (Figure 1d). The morphologic findings were classic for collapsing glomerulopathy (CG; Table 1). Given the patient's history of a recent virus-like syndrome, infection for parvovirus B19 (PVB19) was suspected and confirmed by high IgG and IgM titers. The final diagnosis was CG associated with active PVB19 infection.

The patient was discharged with stable creatinine at 1.8 mg/dl. Immunosuppression was avoided, and she was started on intravenous Ig. A few weeks later, her symptoms improved, the IgM titers decreased, and polymerase chain reaction for PVB19 was negative. Her edema resolved 4

mo after onset, suggesting remission. She was lost to follow-up for a year, after which she presented with renal failure. The patient started hemodialysis and was listed for renal transplantation.

HISTORY OF THE DISEASE AND TERMINOLOGY

CG is now recognized as a common, distinct pattern of "proliferative" parenchymal injury with poor response to empiric therapy. The first description of the disease appeared in 1978 and named "malignant focal segmental glomerulosclerosis" (FSGS) because of rapidly progressive nephrotic syndrome.¹ In the early 1980s, during the HIV pandemic, CG was a relatively frequent diagnosis in large cities of the east and west coasts of the United States and "HIV-associated nephropathy" was the common term to identify the injury. In 1986, Weiss *et al.* described a similar renal lesion in HIV-negative patients with severe proteinuria and rapid progression to renal failure, and the term "collapsing glomerulopathy" was used for the first time to indicate this "new clinical-pathologic entity."² The relationship between idiopathic CG and FSGS was officially introduced in the literature by Detwiler *et al.* who suggested that CG was a variant of FSGS,³ a concept reinforced by a

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Table 1. Morphologic features of collapsing glomerulopathy (CG)

| Light microscopy | |
|---|---|
| Glomeruli | |
| Collapse ^a : | segmental or global wrinkling and folding of the GBM with sub-occlusion or occlusion of the capillaries |
| Pseudo-crescents ^a : | podocyte hyperplasia (proliferation) |
| Hypertrophic podocytes: | with occasional large nuclei |
| Protein reabsorption droplets: | in cytoplasm of podocytes |
| Segmental and/or global sclerosis: | (advance phase) |
| Tubules | |
| Microcysts: | dilated, often serpentine-shaped, tubules with flat epithelium containing eosinophilic proteinaceous casts with peripheral scalloping |
| Acute tubular injury: | flattening of the tubular epithelium, large epithelial cells, large, occasionally atypical, nuclei with prominent nucleoli |
| Tubular atrophy: | |
| Interstitial | |
| Edema: | |
| Inflammation: | |
| Fibrosis: | |
| Vessels | |
| Nonspecific changes: | unless TMA-associated CG |
| Immunofluorescence | |
| Nonspecific entrapment: | of IgM and C3 in areas of collapse |
| Electron microscopy | |
| Extensive foot process effacement: | |
| Loss of detectable actin-based cytoskeleton: | |
| Loss of primary processes: | |
| Large cuboidal podocytes: | with pale cytoplasm |
| Electron dense protein reabsorption droplets: | in podocyte cytoplasm |
| Detachment of podocytes: | from underlying GBM and interposition of newly formed extracellular matrix |
| Tubulo-reticular inclusions: | in endothelial cells in HIV-associated CG, interferon-mediated forms, or lupus-associated forms |

^aRequisite for diagnosis of CG. TMA, thrombotic microangiopathy; GBM, glomerular basement membranes.

second clinical study, where the disease was termed “idiopathic collapsing FSGS.”⁴

Although the term “collapsing FSGS” has been largely used since the mid 1990s, a growing number of authors prefer to use the term “collapsing glomerulopathy.” This preference may have clinical relevance. The term “FSGS” indicates segmental solidification (sclerosis) of the tuft with adhesion to Bowman’s capsule. CG, on the other hand, is defined by collapse and pseudo-crescent formation. The mechanism by which the podocytes are injured is also distinct: proliferation characterizes CG, whereas podocytopenia is implicated in the pathogenesis of FSGS.⁵ Thus, it is not surprising that CG is resistant to standard therapies used for FSGS. Experimental CG can be ameliorated or reversed by inhibiting proliferation or promoting differentiation as shown with inhibitors of cyclin-dependent kinesis or retinoic acid derivatives.¹ In contrast, some forms of experimental FSGS ameliorate after replacement therapy with stem cells.⁶

Another term, “cellular lesion,” was also introduced in the 1980s to identify this entity.⁷ The recently proposed Columbia classification suggests using “cellular lesion” for glomerulopathies characterized by hypercellularity in the intracapillary compartment, in contrast to “collapsing lesions,” where the glomerular tuft appears hypocellular, and increased cellularity is limited to the urinary space.⁸

ETIOLOGY, CLASSIFICATION, AND PATHOGENESIS

The reporting of CG in the literature has increased with the growing awareness among nephrologists and pathologists of its association with disorders other than HIV.¹ A recently proposed taxonomy for the podocytopathies classifies CG apart from FSGS and recognizes three major categories: idiopathic, genetic, and secondary or reactive (Table 2).⁵

Numerous hypotheses for the pathogenesis of CG have been generated, but no specific common trigger for epithelial cell proliferation has emerged. The spectra of clinical associations and etiologic factors is broad and the observation, in some cases, that perturbation of the immune system may occur sug-

gests some role for immune activation in the development of CG.⁹

The prevalence of the disease in blacks suggests a genetic susceptibility,^{1,3,4,10} and the identification of mutations in the chromosome encoding for CoQ2 in a European family¹¹ and for prenyltransferase-like mitochondrial protein in the *kd/kd* mouse,¹² further corroborates this hypothesis. The mechanism by which podocytes react to malfunctioning mitochondria by undergoing proliferation rather than apoptosis is not fully clear. By analogy with a model of myocardial ischemic injury, one could speculate that ion channels in the inner membranes of mitochondria may mediate protection of cells from death. Ion channels have a potential role in redox regulation and mediation of activation of the transcription factor, hypoxia inducible factor-1.¹³ Hypoxia inducible factor-1 has been shown to modulate podocyte phenotype and induce proliferation.¹⁴ Modulation of the redox state of mitochondria is mediated by environmental factors and involved in the onset and progression of the disease.¹⁵ The administration of aminobisphosphonates, a known cause of CG, is also likely to cause mitochondrial degeneration. These observations suggest that disruption of mitochondrial functionality in general may represent a common pathophysiological mechanism in CG.¹⁶

In addition to HIV, other infectious diseases are associated with CG (Table 2). The mechanism of podocyte injury following HIV infection may be direct, with intracellular expression of viral genome or proteins, and/or indirect, mediated by release of cytokines by inflammatory cells in the circulation or in the renal parenchyma (Figure 2).¹ PVB19 infection is associated with podocyte injury in patients with CG, minimal change disease, and FSGS.^{17–19} The detection of PVB19 in renal epithelial cells by immunostaining and *in situ* hybridization suggests, similar to HIV-associated disease, a direct cytopathic effect.¹⁷ The specific relationship between CG and PVB19 infection remains controversial, and the pathogenesis remains unknown. But because the spectrum of manifestation of PVB19 infection range from asymptomatic to fatal in immunocompromised individuals,²⁰ it is prudent to investigate causes of CG

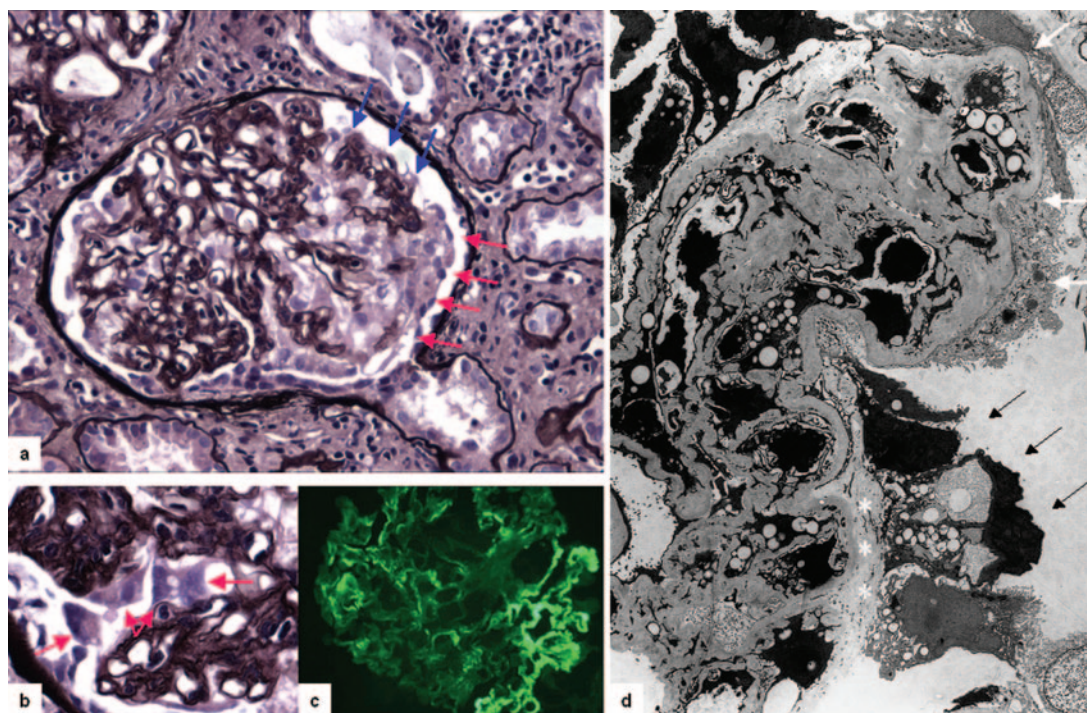


Figure 1. (a) segmental collapse of the glomerular basement membranes (blue arrows) with occlusion of the capillary lumina. Podocytes are hyperplastic and hypertrophic and form pseudo-crescents (red arrows). Pseudo-crescents are generally separated from parietal epithelium by the urinary space (silver stain, original magnification $\times 40$). (b) This enlarged detail of another glomerulus shows that some podocytes adjacent a collapse segmental of the tuft acquire a bizarre shape and contain large smudgy nuclei (red arrows) (silver stain). Despite the presence of these features, immunohistochemistry analysis for PBV was negative (not shown). (c) Nonspecific immunofluorescence staining for C3 in an area of collapse. (d) Electron microscopy shows a collapsed glomerular lobule (white arrow). Podocytes have a cubical appearance, and no primary of foot processes are seen (black arrow). Podocytes are separated from the underlying collapsed glomerular basement membranes by interposition of newly formed extracellular matrix (white asterisk).

in cases otherwise categorized as “idiopathic” before using immunosuppressive therapy. The case here presented is in support of the clinical association between PVB19 infection and CG: the systemic symptoms of viral infection preceded the renal disease; they were followed by decreased hematocrit, and the viral infection was confirmed by positive serology for active/acute phase and detection of the viral DNA by PCR.

Other proposed mechanisms of podocyte injury include dysregulation of vascular endothelial growth factor expression and acute ischemic processes, such as thrombotic microangiopathy after therapy with calcineurin inhibitors.²¹ Alterations of intracellular metabolism after the use of certain medications, or cytopathic effects due to accumulation of light chains, have also been implicated (Figure 2).¹ Some of these forms can be reversed if the

inducing agent is eliminated.²² Lessons from experimental models of CG²³ and the rapid recurrence of CG after transplantation in some patients indicate that a yet to be identified permeability factor should be included in the list of causative agents (Table 2).²⁴

CG is not only a glomerular or podocyte disease, but all renal epithelial cells may be affected. Direct cytopathic damage by viral products also occurs in tubular cells and results in increased proliferation, apoptosis, and translocation of specific proteins from basolateral location to apical location.²⁵ Tubular cell damage may also be secondary to released cytokines by the increased inflammatory cell in the interstitium. These events translate into acute and chronic tubular injury and microcyst formation. The degree of tubulointerstitial damage varies from case to case and appears more pro-

nounced in those forms where intrinsic epithelial cell damage, such as viral infection, is known to be the pathogenic factor (personal observation, L.B.).

PODOCYTE PHENOTYPE AND THE CELLULAR ORIGIN OF THE PSEUDO-CRESCENTS

In CG, podocyte injury results in dedifferentiated phenotype, reflected by the loss of expression of maturity markers and reexpression of proliferative markers; dysregulation of the phenotype, reflected by loss of expression of WT-1; and trans-differentiation toward a macrophage-like phenotype⁵ (Table 3). The degree of dedifferentiation and dysregulation varies between subclasses of CG and appears less prominent in some of the secondary/reactive or genetic forms

Table 2. Classification of collapsing glomerulopathy (CG)

| Idiopathic Forms | Genetic Forms | Reactive Forms |
|------------------|---|---|
| Idiopathic CG | <p><i>Non-syndromic</i></p> <p>CoQ2 nephropathy</p> <p>Familial, unknown gene^a</p> <p><i>Syndromic</i></p> <p>Action myoclonus-renal failure</p> <p>Mandibuloacral dysplasia^b</p> | <p><i>Infection</i></p> <p>Viruses (HIV-1, PVB19, CMV, <i>Campylobacter enteritis</i>^c)</p> <p>Others (Loa Loa, filariasis, visceral leishmaniasis, <i>Mycobacterium tuberculosis</i>)</p> <p><i>Disease associations</i></p> <p>Autoimmune diseases^d</p> <p>Thrombotic microangiopathy</p> <p>Hematologic malignancy^e</p> <p>Guillian-Barré^c</p> <p><i>Medication</i></p> <p>Interferon-alpha</p> <p>Bisphosphonates</p> <p>Valproic acid^f</p> <p><i>Others</i></p> <p>Permeability factor</p> <p>Severe hyaline arteriopathy^g</p> |

^aFive siblings of the same family presented with CG; 4 of these 5 patients and the youngest brother without renal disease shared the same MHC haplotype inherited from the mother and detected in the grandmother and an aunt. Data from this family suggest that environment may play a role in predisposed individual to develop CG.³⁰

^bMandibuloacral dysplasia is a rare autosomal recessive disorder due to mutations in the zinc metalloproteinase (ZMPSTE24) gene. ZMPSTE24 is involved in post-translational proteolytic cleavage of carboxy terminal residues of farnesylated prelamin A.³¹

^cThis patient with Guillan-Barré syndrome following *Campylobacter enteritis* infection developed CG. Both Guillan-Barré syndrome and CG resolved within a month.³²

CMV, cytomegalovirus.

^dAutoimmune diseases include adult Still’s disease, mixed connective tissue disorder, systemic lupus erythematosus, and lupus-like syndrome.¹

^eHematological malignancy includes multiple myeloma, acute monoblastic leukemia, and hemophagocytic syndrme.¹

^fValproic acid.³³

^gSevere hyaline arteriopathy associated with glomerular collapse has been observed in several conditions, including calcineurin inhibitor toxicity in transplant patients²¹ and diabetic nephropathy (personal observation).

compared with idiopathic and HIV-associated forms (Table 4).

Although the epithelial cells forming pseudo-crescents are thought to originate

from podocytes, the theory of the dysregulated podocyte has been recently challenged. Some authors suggest that pseudo-crescents are formed by parietal epithelial cells, based on 2 observations: the presence of bridging cells between Bowman’s capsule and the pseudo-crescents and positive staining for CK and PAX2.²⁶ Against these arguments is that immature or developing podocytes express PAX2 and transiently CKs (Table 3). Bridging of parietal epithelial and parietal podocytes is a normal event occurring in nondiseased kidney.²⁷ Studies on an inducible model of podocyte injury show bridging of parietal cells is a late event, probably representing a mechanism of repair resulting in sclerosis, following an early phase dominated by proliferation.²⁸ It is intriguing to speculate that the resident stem cells lining Bowman’s capsule²⁹ may also participate in repair processes.

CG is a unique pattern of glomerular and tubulointerstitial injury for which the pathologic diagnosis is based on histologic findings, but the final diagnosis and treatment require

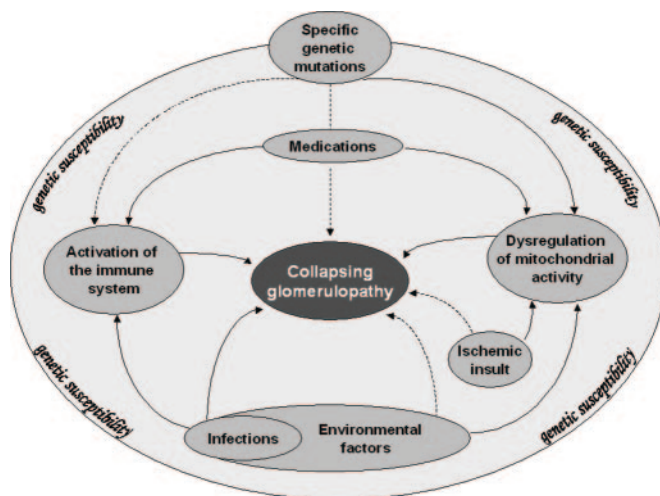


Figure 2. Pathophysiology of podocyte proliferation and collapsing glomerulopathy. Several mechanisms are involved in the pathophysiology of CG. Two major common pathways have been identified: activation of the immune system and dysregulation of mitochondrial activity. In addition, both genetic susceptibility and environmental factors play a major role in modulating the pathogenetic process. Solid arrows indicate mechanisms that have been already investigated, and the dotted arrows indicate potential pathways to be investigated.

Table 3. Podocyte phenotype in human collapsing glomerulopathy (CG)

| | Pattern of Staining by Immunohistochemistry | S-Shape Body Stage | Mature Glomeruli | CG |
|--------------|--|--------------------|------------------|----|
| Synaptopodin | Cytoplasm of foot processes | – | + | – |
| Podocin | "Abluminal" side of podocytes | – | + | – |
| Podocalyxin | "Luminal" side of podocytes | + | + | – |
| GLEPP1 | "Luminal" side of podocytes | + | + | – |
| CALLA | No preferential cellular membrane distribution | – | + | – |
| C3b receptor | No preferential cellular membrane distribution | + | + | – |
| WT1 | Nucleus | + | + | – |
| Nestin | Cytoplasm | + | + | + |
| Dystroglycan | "Abluminal" side of podocytes | + | + | + |
| PAX2 | Nucleus | + | – | + |
| p27 | Nucleus | – | + | – |
| p57 | Nucleus | – | + | – |
| Ki67 | Nucleus | + | – | + |
| CK | Cytoplasm | + | – | + |
| CD68 | Cytoplasm | – | – | + |

Dedifferentiated podocytes do not express maturity markers, such as synaptopodin, podocin, podocalyxin, GLEPP1, and CALLA (CD10), C3b receptors. Dedifferentiated podocytes reexpress cytokeratins (CK), which are transiently expressed during differentiation but not in adult life and include CK8, CK18, CK19, and CAM5.2. CK7 is expressed only in CG but not during fetal life. Dedifferentiated podocytes reenter the cell cycle and proliferated, as indicated by positive staining for Ki-67 and down-regulation of p27 and p57 expression. Dystroglycan is present in podocytes and parietal and tubular epithelial cells during nephrogenesis, and its expression is preserved in CG. WT-1 and nestin are specific podocyte markers present during nephrogenesis from the beginning of podocyte ontogenesis; thus, loss of WT1 expression indicates dysregulation of the phenotype.³⁴ On the contrary, the intermediate protein nestin has been reported preserved in dysregulated podocytes and may serve as a potential and reliable podocyte marker. The preserved expression of nestin and dystroglycan may also indicate incomplete dysregulation. PAX2 expression is under the control of WT1 and is up-regulated in dysregulated podocytes. *De novo* expression of CD68 in CG indicates that podocytes may undergo trans-differentiation. GLEPP1, glomerular epithelial protein; CALLA, common acute lymphoblastic leukemia antigen; WT1, Wilms' tumor protein. The abluminal side of podocyte is the portion of the cell membrane and cytoplasm located against the glomerular basement membranes in contrast with the luminal side, which faces the urinary space.

Table 4. Critical pathologic features to differentiate subcategories of collapsing glomerulopathy (CG)

| | Idiopathic | Genetic | Viral | Drug-Induced | Ischemia-Associated | Others |
|---|--|---|--|---|---|---|
| Microcysts | ++ | +++ | ++ | +/- | +/- | +/- |
| Acute tubular injury | ++ | ++ | +++ | + | ++ | + |
| Podocyte and tubular cell nuclear atypia | + | – | +++ | – | + | – |
| Tubuloreticular inclusions | – | – | + | – | – | – (can be seen in SLE-associated forms) |
| Podocyte dedifferentiation (negative staining for synaptopodin) | Widespread to collapsed and noncollapsed areas | Limited to areas with pseudo-crescent formation | Widespread to collapsed and noncollapsed areas | Limited to areas with pseudo-crescent formation | Limited to areas with pseudo-crescent formation | ? |
| Podocyte dedifferentiation (negative staining for PAX2) | Widespread to collapsed and noncollapsed areas | Limited to areas with pseudo-crescent formation | Widespread to collapsed and noncollapsed areas | ? | ? | ? |
| Podocyte dysregulation (negative staining for WT-1) | Widespread to collapsed and noncollapsed areas | Podocyte phenotype is not dysregulated | Widespread to collapsed and noncollapsed areas | ? | ? | ? |

Morphologically, all categories are characterized by pseudo-crescent formation and collapse and variable tubulointerstitial damage. Most of the above-described features are not absolute criteria to discriminate between the various categories but still may help in the differential diagnosis. SLE, systemic lupus erythematosus; +, mild and/or focal, or not always present; ++, moderate and/or mode widely present, or occasionally present; +++, severe and/or diffuse, or very often present; –, absent.

close collaboration between renal pathologists and nephrologists. In an era dominated by biomarkers, pathologists should participate in the development of new tools to expand standard morphologic descriptions with information about etiology, pathogenesis, and phenotype, to guide nephrologists to identify more rational therapeutic approaches.

DISCLOSURES

None.

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