Collapsing glomerulopathy (CG) is an aggressive and distinct histologic variant of focal segmental glomerulosclerosis characterized by segmental or global glomerular tuft collapse with hypertrophy and hyperplasia of the overlying podocytes. Mouse model data have been variously interpreted to suggest that the extraglomerular cells characteristic of CG may include dedifferentiated podocytes or parietal epithelial cells. Because segmental glomerular scars are not always seen, the term CG is preferred to collapsing focal segmental glomerulosclerosis. Accompanying acute tubular injury, tubular dilation with microcyst formation and interstitial inflammation are common.

CG can be primary or associated with a wide variety of infectious agents, inflammatory conditions (such as systemic lupus erythematosus and hemophagocytic syndrome), malignancies, glomerular ischemic insult (associated with thrombotic microangiopathy, cholesterol embolization, or sickle cell disease), genetic mutations, and drugs (such as pamidronate and interferon) (Figure 1). A causal association between HIV-1 infection and CG is well-established, based in part from work on HIV-transgenic mice. Other viruses, including cytomegalovirus, parvovirus B19, and Epstein-Barr virus, also have been linked to CG.

A major genetic contributor to risk for glomerulosclerosis and particularly to CG, regardless of etiology, among patients of African ancestry, is the presence of APOL1 high-risk genotype (carriage of G1/G1, G1/G2, or G2/G2 genotypes). How these APOL1 risk alleles alter podocyte biology, phenotype, and function is not fully understood. Various mechanisms have been proposed from kidney biopsy.
studies, transgenic mouse studies, and cell culture studies. These include opening of plasma membrane cation channels, impaired mitochondrial function, altered endolysosomal trafficking, inflammasome activation, protein kinase R activation, and most recently, through interference with APOL3 control of actomyosin in podocytes.\(^5\)

In this issue of *Kidney International Reports*, Larsen et al.\(^6\) and Peleg et al.\(^7\) independently report 2 patients with CG associated with COVID-19. Simultaneously, a third case of CG associated with COVID-19 is being reported by Kissling et al.\(^8\) in *Kidney International*. One of the authors (SHN) is also aware of more than a dozen additional cases that have not been reported yet. The 3 reported patients all presented with severe AKI, heavy proteinuria, and hypoalbuminemia. In 2 of them, the AKI coincided with moderate respiratory symptoms (without associated sepsis or acute respiratory distress syndrome).\(^5^6,8\) but interestingly in the third patient, AKI occurred 1 week after recovery from mild respiratory symptoms.\(^7\) Despite improvement of pulmonary symptoms, AKI did not recover in 2 patients, who needed dialysis at discharge. These observations suggest that kidney involvement is independent of lung involvement. Histologically, severe CG, prominent acute tubular injury, diffuse podocyte foot process effacement, and endothelial tubuloreticular inclusions were present.

The pathogenesis of COVID-19–associated CG is likely multifactorial. Coronavirus particles were observed by electron microscopy within the cytoplasm of podocytes in the patient with CG reported by Kissling et al.\(^5^8\) and by postmortem examination of patients with COVID-19 who had AKI and proteinuria,\(^6\) supporting direct viral infection of podocyte. This is not surprising because podocytes (and tubular cells) express membrane-bound angiotensin-converting enzyme 2,\(^5^9\) the receptor for SARS-CoV-2. Thus, direct toxic viral effect on podocyte, as occurs in HIV-associated nephropathy, is possible in some cases. However, in the 2 other reported cases of COVID-19–associated CG, *in situ*...
hybridization studies for SARS-CoV-2 RNA failed to show viral RNA in the kidney and no viral inclusions were seen in renal tissue by electron microscopy, arguing against viral infection. The authors postulated that CG could be a consequence of the cytokine release syndrome characteristic of patients with COVID-19. Indeed, plasma inflammatory markers (C-reactive protein, interleukin-6, and interleukin-2 receptor) were elevated in the patient described by Peleg et al. Importantly, all 3 patients were of sub-Saharan African descent, and the 2 tested had APOL1 high-risk genotype, suggesting that this genotype is an important risk factor, similar to CG associated with HIV and other viruses. It has been previously shown that APOL1 expression is upregulated by viral infections and other inflammatory diseases that activate the Toll-like receptor-3. Viral infections stimulate host interferon production, and interferon is a potent stimulus to APOL1 gene expression. Thus, it appears likely that, in African American individuals, SARS-CoV-2 infection acts as a “second hit” that leads to podocyte dysregulation and injury leading to CG.

In summary, although reports from China indicate that COVID-19 manifestations can include renal tubular injury, there are emerging reports highlighting CG as another renal manifestation of COVID-19. The 2 plausible mechanisms by which SARS-CoV-2 causes CG are direct toxic viral effect on podocytes and/or virus-induced cytokine injury to podocytes. Genetic susceptibility, particularly the presence of high-risk APOL1 genotypes, likely play a crucial role in the pathogenesis of this entity among individuals of African descent. Further work is needed to define the clinico-pathologic characteristics, outcome, and the role of antiviral therapy and corticosteroids for treatment of this lesion, and to understand the molecular mechanisms of podocyte injury by SARS-CoV-2.

DISCLOSURE
All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary References.

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