COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19

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Reports of collapsing glomerulopathy in patients of African ancestry and high-risk *APOL1* genotype infected with SARS-CoV-2 have emerged during the COVID-19 pandemic. This new entity, which we term COVID-19-associated nephropathy (COVAN), may particularly impact individuals in some regions of the world. Awareness of this potentially ominous complication of COVID-19 must be raised.

> “collapsing glomerulopathy has emerged as a distinct global nephropathy associated with SARS-CoV-2 infection”

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Individuals of African ancestry are at increased risk of chronic kidney disease (CKD) and kidney failure owing to the presence of polymorphisms in the apolipiprotein L1 (*APOL1*) gene[1]. Approximately 14% of the African American population are homozygous for the G1 or G2 *APOL1* risk alleles. Although these genetic variants explain a substantial proportion of the increased burden of CKD and kidney failure in African Americans, most individuals who carry two *APOL1* risk alleles do not develop kidney disease[2]. When disease does develop, it has a wide clinical spectrum ranging from arteriolonephrosclerosis with slowly progressive kidney disease to the most fulminant form, collapsing glomerulopathy, which is associated with a high risk of irreversible and rapid progression to kidney failure[1]. Notably, the highest risk conveyed by two *APOL1* risk alleles is seen when certain diseases act as ‘second hits’ and trigger collapsing glomerulopathy (Supplementary Table 1).

Collapsing glomerulopathy was first characterized in the setting of HIV infection and subsequently became recognized as the classic histomorphological form of HIV-associated nephropathy (HIVAN). During the pandemic of HIV and AIDS in the 1980s, affected patients presented with nephrotic syndrome and accelerated loss of kidney function. Studies subsequently showed that *APOL1* risk variants conferred a ~30–90-fold increased risk of developing collapsing glomerulopathy in the setting of HIV, explaining the preponderance of HIVAN in individuals of African ancestry. Beyond HIV, several other viral infections are now understood to be associated with collapsing glomerulopathy, including parvovirus B19, cytomegalovirus and Epstein–Barr virus. In addition, collapsing glomerulopathy can develop in susceptible patients with systemic lupus erythematosus (Supplementary Table 1). A common denominator for many aetiologies of collapsing glomerulopathy is the activation of interferon. In fact, endothelial tubuloreticular inclusions, which have been described as ‘interferon footprints’, are commonly identified ultrastructurally within glomeruli of individuals with collapsing glomerulopathy.

Further supporting a connection between interferon and *APOL1*, interferon therapy used for the treatment of hepatitis C viral infection has been reported to cause collapsing glomerulopathy in patients who are homozygous for *APOL1* risk alleles (Supplementary Table 1). Moreover, cases of collapsing glomerulopathy have been reported in individuals of African descent with systemic conditions characterized by interferon activation, including haemophagocytic lymphohistiocytosis (HLH) and stimulator of interferon genes-associated vasculopathy with onset in infancy (STING-SAVI) (Supplementary Table 1). The precise mechanism by which *APOL1*-associated glomerulopathy interacts with interferon signalling pathways is unclear. Experimental work has shown that interferon markedly upregulates levels of *APOL1*, although whether this upregulation occurs directly or via chemokines is unclear[3,4]. In support of a role for chemokines in this process, data from the NEPTUNE cohort demonstrated upregulation of the chemokine gene *CXCL9* in glomeruli of high-risk *APOL1* allele carriers[5]. Once activated by the interferon–chemokine pathway, the *APOL1* risk variant seems to cause disruption of autophagy and mitochondrial homeostasis and ultimately induces glomerular epithelial cell death[4] (FIG. 1).

The current COVID-19 pandemic has unveiled a rebirth of reports of collapsing glomerulopathy akin to those seen during the HIV epidemic. To date, five case reports have been published — three from the USA, one from Switzerland and one from France — describing cases of collapsing glomerulopathy in association with SARS-CoV-2 infection (Supplementary Table 1). Of note, all of these cases were in patients of

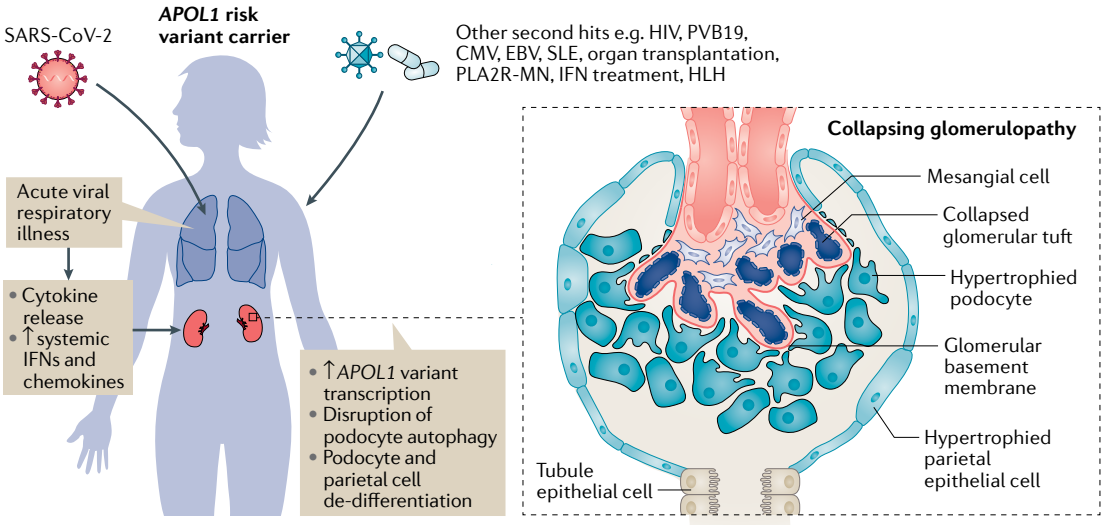

Fig. 1 | **Proposed pathogenesis of COVAN.** We propose that collapsing glomerulopathy associated with COVID-19 (an entity we term COVID-19-associated nephropathy; COVAN) is an entity that specifically affects individuals who carry two *APOL1* risk variants. In these individuals, infection with SARS-CoV-2 through the respiratory tract triggers an inflammatory cascade that involves activation of the interferon–chemokine pathway, which in turn interacts with the *APOL1* variant gene, leading to impairment in glomerular epithelial cell autophagy, mitochondrial function and cell injury. A similar collapsing glomerulopathy phenotype is observed in the context of other viral infections and conditions that increase levels of interferon. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HLH, haemophagocytic lymphohistiocytosis; IFN, interferon; PLA2R-MN, PLA2R-associated membranous nephropathy; PVB19, parvovirus B19; SLE, systemic lupus erythematosus.

African ethnicity. Our own report described six patients with SARS-CoV-2 infection and collapsing glomerulopathy within the South Gulf region during a COVID-19 upsurge in New Orleans, USA[6]. All of these patients were of African descent and had two high-risk *APOL1* alleles. Clinically, these patients presented with acute kidney injury (AKI) and nephrotic-range proteinuria. The observed histopathological lesions resembled those seen in other forms of collapsing glomerulopathy, with segmental to global collapse of the glomerular capillary tuft, hypertrophy and hyperplasia of the overlying podocytes and parietal epithelial cells, and protein resorption droplets within hyperplastic glomerular epithelial cells. Tubulointerstitial lesions typically associated with *APOL1*-related disease, including microcystic tubular dilatation and tubular injury, were also present. No viral particles were identified ultrastructurally and SARS-CoV-2 was not detected within the kidney biopsy tissue by immunohistochemistry or in situ hybridization. Although it has been proposed that expression of angiotensin-converting enzyme 2 (ACE2) in podocytes could be a port of entry for SARS-CoV-2 into the glomeruli[7,8], available evidence does not support that contention. Therefore, the development of collapsing glomerulopathy in patients with COVID-19 may follow a host immune response involving the activation of interferon and chemokines rather than direct infection of glomerular cells (FIG. 1).

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It is now apparent that hyperinflammation is a key driver of disease severity in patients with SARS-CoV-2 infection. Distinct stages of the immune response have been delineated, starting with an early stage with induction of a potent interferon response, followed by a delayed response that may lead to progressive tissue damage and a third stage characterized by excessive macrophage activation[9]. Although much about the response to SARS-CoV-2 infection remains unknown, it is clear that immune dysregulation is important for the pathogenesis in patients with severe COVID-19 and that the inflammatory milieu is likely similar to those seen in other diseases associated with collapsing glomerulopathy.

Given the emerging reports of collapsing glomerulopathy associated with COVID-19, further studies are needed to assess the relative risk of kidney disease conferred by homozygosity for *APOL1* risk alleles in patients with SARS-CoV-2 infection. If confirmed, this association could have important public health implications in certain geographical regions. Beyond the initial episode of AKI, the long-term consequences are uncertain. *APOL1* genotyping could easily be deployed for prognostication and/or to identify patient populations that might benefit from early initiation of antiviral or anti-cytokine therarapeutics, although clinical trials are urgently needed to identify agents with proven efficacy and acceptable safety profile. Conversely, the identification of patients who are homozygous for *APOL1* risk alleles could guide against some proposed treatments. For example, a phase II clinical trial in Hong Kong found a triple antiviral therapy consisting of a combination of interferon-β1b, lopinavir–ritonavir and ribavirin to be safe and superior to lopinavir–ritonavir alone in patients with COVID-19 (REF.[10]). However, one would hypothesize that interferon-based therapy may not be suitable for use in patients with *APOL1* risk alleles, as it could act as a second hit to induce kidney injury.

In summary, collapsing glomerulopathy has emerged as a distinct global nephropathy associated with SARS-CoV-2 infection, which seems to specifically affect individuals of African ancestry who are carriers

of *APOL1* risk variants. Given the clinico-pathological resemblance of the collapsing glomerulopathy phenotype with HIVAN and the remarkable parallel between viral infection and susceptibility conferred by genetic background, we propose the term COVID-19-associated nephropathy (COVAN) be used to describe this specific entity. This type of nephropathy is to be distinguished from most cases of AKI in COVID-19, which are characterized by acute tubular injury. In light of the current pandemic and an anticipated second wave of COVID-19 in the near future, we expect that we will encounter a growing number of cases of COVAN. This condition should be particularly suspected in patients of African descent who present with COVID-19, AKI and nephrotic-range proteinuria. Given the race to develop new anti-inflammatory and anti-cytokine therapies for COVID-19, we recommend that carriers of *APOL1* risk variants are considered to be at 'particular risk of COVAN' and suggest that enrolment of these individuals into clinical trials should be prioritized.

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Competing interests
J.C.Q.V. has participated in Advisory Board meetings for Mallinckrodt Pharmaceuticals and Retrophin and is a member of the Speaker Bureau for Otsuka Pharmaceuticals. None of the products related to those engagements are discussed in this manuscript. T.C. and C.P.L are employees of Arkana Laboratories, which is a vendor of *APOL1* genotype clinical testing.

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