



Collapsing glomerulopathy following COVID 19 infection; a mini-review to the recent data

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Abstract

Collapsing glomerulopathy has been delineated as the most common morphological feature in COVID-19 individuals presenting with rapidly progressive renal failure and massive proteinuria. This condition, also known as COVID-19-associated nephropathy, has a poor prognosis. In COVID-19-related collapsing glomerulopathy, an immune dysfunction-mediated "second hit" to podocytes of African origin with APOL1 risk alleles was suggested. However, further research is still required to clarify this aspect of glomerulopathy.

Keywords: COVID-19, Focal segmental glomerulosclerosis, SARS-CoV-2, COVID-19 associated nephropathy, Podocytes, Glomerulosclerosis, Acute kidney injury, APOL1 risk alleles, Collapsing glomerulopathy

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Introduction

The first COVID-19 case was reported in December 2019 in Wuhan, China. This virus can cause SARS-CoV-2, and it manifests from no symptoms, mild upper respiratory tract infection, to critical illness. Hospitalized patients with atypical pneumonia developed acute respiratory distress syndrome (ARDS) and were admitted to the intensive care unit (1). Multiple organs are impacted by this disease, including the kidneys (2). Renal involvement is recognized as a poor prognostic factor in COVID-19. Depending on the study participants, the incidence varies. In hospitalized individuals, it is predicted to be 5.1% (3). Renal disease is a main complication of viral diseases, which can lead to acute kidney injury (AKI) or even chronic kidney disease with multiple mechanisms like renal cell damage, provocation of the immune system, and renal systemic effects of antiviral medications (4). Renal involvement is joint in patients with COVID-19, varying from painless hematuria, proteinuria, and, in some conditions, AKI that may require kidney replacement therapy. Studies have shown that AKI occurs in up to 25% of critically-ill patients with SARS-CoV-2 infection, particularly in patients with underlying disease. AKI in these patients has a high death rate and is an independent

Key point

Collapsing glomerulopathy is detected in some cases of COVID-19 patients, particularly in African origin individuals. This disease presented with AKI and significant proteinuria, indicating a poor prognosis.

risk factor for inpatient mortality (5,6). Studies in China have shown recurrent renal involvement in COVID-19 is associated with a high mortality rate (7). The mechanisms and pathophysiology of AKI in COVID-19 patients are unclear and appear multifactorial. One of the factors may be associated with the effect of COVID-19 mechanisms, like direct cell damage by virus entry across the receptor angiotensin-converting enzyme 2. Until now, there is no definitive treatment for AKI associated with COVID-19, and the managements are mostly supportive (5,6). Mechanisms for AKI development includes tubular cytotoxicity by the virus and tubular damage caused by sepsis-related injury (8).

Search strategy

For this review, we searched PubMed/Medline, Directory of Open Access Journals, Web of Science, Google Scholar, EBSCO, Scopus, and Embase, using different keywords such as COVID-19, COVID-19 associated nephropathy, podocytes, acute kidney injury, focal

segmental glomerulosclerosis, collapsing glomerulopathy, glomerulosclerosis, *APOL1* risk alleles and SARS-CoV-2.

Collapsing glomerulopathy following COVID-19

Recently much attention has been directed toward the relationship between COVID-19 and collapsing glomerulopathy. Previous studies have shown that other viruses like parvovirus B19, HIV-1 infection, cytomegalovirus, and Epstein-Barr virus can also cause collapsing glomerulopathy, resulting in renal failure (9). A recent investigation showed that COVID-19-related collapsing glomerulopathy is similar to that seen in HIV disease (10). In the current SARS-CoV-2 pandemic, glomerular disease like collapsing glomerulopathy was one of the common complications in COVID-19 patients (4). This glomerulopathy is associated with segmental or overall tuft collapse followed by hyperplasia and hypertrophy of the podocytes (11). Resemble other collapsing glomerulopathy; we also face the segmental or general failure of the glomerular capillary tufts, accompanied by hyperplasia and hypertrophy of the overlying podocytes and parietal epithelial cells (12). Previous studies have also documented instances of collapsing glomerulopathy resulting from coronavirus. Additionally, they found three points of collapsing glomerulopathy associated with COVID-19. The patients showed symptoms such as severe AKI, hypoalbuminemia, and massive proteinuria. In two cases, AKI was accompanied by moderate respiratory symptoms. In the third case, AKI happened seven days following recovery from lung symptoms. However, renal involvement may be separate from respiratory involvement. Several factors are involved in the pathogenesis of collapsing glomerulopathy related to COVID-19. Electron microscopy revealed the presence of coronavirus particles in the cytoplasm of podocytes in cases of collapsing glomerulopathy following COVID-19. These particles were observed by post-mortem assessment of AKI associated with COVID-19 (13). In general, this disease presents with massive proteinuria and rapid deterioration of renal function. This glomerulopathy is traditionally classified as a focal and segmental glomerulosclerosis (FSGS) variant.

There is a causative role for podocytes following COVID-19 in this disease. Previous studies have detected that podocyte injury or insult to the glomerular endothelium or even disruption of the endothelial-podocyte glomerular cell signaling axis can contribute to this glomerulopathy (14). This glomerulopathy was also named COVAN (COVID-19-associated nephropathy). Further studies showed high-risk *APOL1* genotypes are the main hazard in COVID-19-associated nephropathy (15). The pathophysiology of COVAN may be related to immune dysregulation in cases with Covid-19. Some cytokines like interleukin-1 β , -6, interleukin-10, and IFN- γ are upregulated under these infection conditions (16). Qamar et al evaluated around 38 studies containing

74 males, with a mean age of 54.2 years old, in a systematic review and meta-analysis. They found proteinuria was the most detected laboratory result in 89.5% of the patients. In addition, the most common morphologic abnormality was acute tubular damage, seen in 77.2% of cases. Moreover, a raised risk of collapsing glomerulopathy in dialysis-dependent patients was observed (17).

A recent study assessed 76 studies regarding kidney pathology (from the onset of COVID-19 to February 2023). These studies contained 511 cases of native kidneys and 85 instances of transplantation. Of 76 studies, 36 were from North America, 22 were from Asia, 16 were from Europe, one from South America, and one from Africa. Of the 511 biopsies, 410 cases had glomerular lesions, 99 had tubulointerstitial lesions, and two had no significant pathology. The most common pathology was collapsing glomerulopathy (36.1%), followed by primary podocyte injury (11%), diabetic nephropathy (9%), glomerulonephritis (7.6%), membranous nephropathy (5.6%) and immunoglobulin A nephropathy (5.6%). The remaining 103 individuals have other glomerular diseases (15). In a previous study, May et al found that 91.7% of African Americans whose renal biopsy revealed collapsing glomerulopathy had two risk alleles of *APOL1*. However, only 35.6% of patients without collapsing glomerulopathy had two risk alleles of *APOL1* (18). Collapsing glomerulopathy generally indicates poor prognosis—around 70% of patients need dialysis. However, half of them could come off dialysis (19). This glomerulopathy was also detected following COVID-19 vaccination. In a recent report, Neves et al described two cases of biopsy-proven collapsing glomerulopathy following SARS-CoV-2 adenovirus-vector-based vaccination. They demonstrated one of the cases had only one risk allele for *APOL1*; in the second one, their patient presented a high-risk genotype *APOL1*, a genetic condition that has previously been associated with an increased risk of collapsing glomerulopathy and chronic kidney disease (20). It is well-known that collapsing glomerulopathy secondary to COVID-19 infection mainly involves African American descent due to *APOL1* gene mutations. However, this glomerulopathy is sporadically reported in white individuals (21). This disease is rarely reported in kidney transplant biopsies. Thorburn et al. recently described a patient with collapsing glomerulopathy in a white kidney recipient with SARS-CoV-2 infection (22). Similarly, Gómez Preciado et al presented a patient of renal transplantation who developed massive proteinuria and kidney dysfunction following mRNA vaccination against COVID-19. Collapsing glomerulonephritis was detected by kidney biopsy (23).

Discussion

Collapsing glomerulonephritis is a variation of FSGS found to progress to end-stage renal disease. The histological features of this disease are podocytopathy.

Dysregulation of podocytes decreases glomerular filtration rate (GFR) due to kidney injury and portends a poor prognosis (17). A study regarding the possible etiology of COVID-19-related collapsing glomerulopathy shows an immune dysfunction mediated “second hit” to podocytes in African origins with *APOL1* risk alleles. These cases also had mild pulmonary symptoms with no other accompanying cytokine storm-mediated renal damage, septic shock, or acute respiratory distress syndrome, showing that hemodynamic instability was less probably the mechanism of collapsing glomerulopathy. However, most of the reported patients became dialysis-dependent, implying a poor prognosis for recovery from renal failure (24). Therefore, gene testing for *APOL1* seems necessary for African descent patients with COVID-19 infection and massive proteinuria with rapidly progressive kidney failure (21).

Conclusion

Collapsing glomerulopathy is detected in some cases of COVID-19 patients, particularly in African origin individuals. This disease presents with AKI and significant proteinuria, indicative of a poor prognosis. However, more studies are needed by more significant investigations directed toward detecting prognostic parameters, management modalities, prompt strategies to improve outcomes, and finally, long-term effects of COVID-19 on the kidneys.

Authors' contribution

Conceptualization: HN
 Data curation: HN and LA.
 Funding acquisition: HN.
 Investigation: LA.
 Resources: HN.
 Validation: HN and LA
 Visualization: HN and LA
 Supervision: HN
 Writing—original draft : LA
 Writing—review and editing: LA, AK, MAEP, MF.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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