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COVID-19–Related Collapsing Glomerulopathy in a Kidney Transplant Recipient

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Abstract

We report a case of a kidney transplant recipient who presented with acute kidney injury and nephrotic-range proteinuria in a context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Kidney biopsy revealed collapsing glomerulopathy. Droplet-based digital PCR did not detect the presence of SARS-CoV-2 RNA in the biopsy fragment, and the virus was barely detectable in the plasma at the time of the biopsy. SARS-CoV-2 RNAemia peaked several days later, followed by a seroconversion despite the absence of circulating CD19-positive lymphocytes at admission due to rituximab-based treatment of antibody-mediated rejection 3 months earlier. Genotyping for the two risk alleles of the apolipoprotein L1 (*APOL1*) gene revealed that the donor carried the low-risk *G0/G2* genotype. This case illustrates that COVID-19 may promote a collapsing glomerulopathy in kidney allografts with a low-risk *APOL1* genotype, in the absence of detectable SARS-CoV2 RNA in the kidney, and that podocyte injury may precede SARS-CoV2 RNAemia.

Introduction

Kidney injury is frequent in patients with novel coronavirus disease 2019 (COVID-19)¹. It is proposed that kidney cells are targeted by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thereby causing kidney lesions, viral RNA has been detected in various kidney compartments of patients who died from COVID-19, including glomeruli^{2,3}. Critically, podocytes express membrane proteins such as angiotensin-converting enzyme 2 (ACE2) that are considered to facilitate SARS-CoV-2 entry within the cell⁴. Consequently, SARS-CoV-2 could have a preferential tropism for glomerular cells, and podocyte injury occurring upon SARS-CoV-2 infection may result in collapsing glomerulopathy in native kidneys. However, the presence of the virus in glomerular cells has never been formally demonstrated in living patients⁵⁻⁷. Thus, the mechanism by which SARS-CoV-2 infection promotes glomerular injury is an unresolved issue.

According to the “second-hit hypothesis”⁸, these forms of acute glomerulopathy may be predisposed to occur with a genetic background of high-risk apolipoprotein L1 (*APOL1*) allelic variants. Indeed, two cases of COVID-19-associated collapsing glomerulonephritis were tested and found to carry two high-risk *APOL1* genetic variants (G1 or G2)^{6,7}, suggesting that SARS-CoV-2 infection may act as a trigger promoting collapsing glomerulopathy lesions in at-risk patients with COVID-19.⁹ We herein describe a kidney transplant recipient (KTR) who, 3 months after an episode of acute antibody-mediated rejection (ABMR), was diagnosed with COVID-19 at which time he was found to have collapsing glomerulopathy in the absence of detectable SARS-CoV2 RNA in the kidney. In addition, the donor *APOL1* genotype was “low risk” (*G0/G2*). The onset of glomerular injury was dissociated from SARS-CoV-2 viremia as it preceded it. Viremia occurred secondarily, and resolved with seroconversion, despite the absence of circulating CD19-positive lymphocytes at admission.

Case report

A 29-year-old-man of sub-Saharan origin who had kidney failure due to urinary schistosomiasis received a kidney transplant from a deceased donor in 2015 (the ethnicity of the donor is unknown). The immunosuppression regimen was prednisone, tacrolimus, and mycophenolate mofetil. His baseline serum creatinine was 135 $\mu\text{mol/L}$. A biopsy-proven ABMR episode was diagnosed in January 2020 (**Figure 1A, B and C**). At the time of ABMR diagnosis, serum creatinine was 289 $\mu\text{mol/L}$ (estimated glomerular filtration rate was 28 ml/min/1.73 m² and urinary albumin-creatinine ratio [UACR] was 3.7 mg/mmol). The patient had the following donor-specific antibodies : anti-DQ5 (MFI : 23412), anti-DQ8 (MFI : 8299), and anti DP*03 (MFI : 4975). Treatment consisted of high-dose of corticosteroids (methylprednisolone 500 mg /day for 3 days), rituximab, (375 mg/m²), 5

plasma exchanges, and a high dose of IV immunoglobulins (2 g/kg). Maintenance immunosuppression consisted of prednisone 10 mg/day, tacrolimus 6 mg/day, and mycophenolate mofetil 500mg twice a day. Kidney function did not fully recover (**Figure 2**).

In the second week of May 2020, he was admitted to the hospital because of fever, cough, and vomiting, which had started five days earlier. A reverse transcriptase–polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on a naso-pharyngeal swab sample was positive at admission. CRP level was increased at 92 mg/L (normal < 5 mg/L), as well as fibrinogen 5.7 g/L (normal range 1.5-3.5 g/L), D-dimers 1050 ng/mL (normal < 500 ng/mL), ferritin 2672 µg/L (normal range 24-336 µg/L), and LDH 477 UI/L (normal < 240 UI/L), reflecting systemic inflammation (**Figure S1**).

Acute kidney injury was present at admission with a serum creatinine of 534 µmol/L and a nephrotic range proteinuria (urinary protein-creatinine ratio, 0.8 g/mmol; UACR, 490 mg/mmol; serum albumin, 2.8 g/dL) (**Figure 2 and Figure S2**). Urinary concentrations of the low molecular weight proteins retinol binding protein and β₂-microglobulin were 100 to 1000 times the normal value, indicating that the tubular compartment was injured.

A kidney biopsy performed 2 days after admission revealed a collapsing glomerulopathy with pronounced podocyte hyperplasia and hypertrophy in absence of evidence of ABMR (**Figure 1 D and E**). Acute proximal tubular injury was severe with tubular dilatations, flattening of the tubular epithelium, loss of the brush border and detached tubular epithelial cells in the lumen (**Figure 1 F**). C4D staining of peritubular capillaries was negative (**Figure 1 G**). There was no evidence of thrombotic microangiopathy. Immunofluorescence assays on glomeruli were negative for IgG, IgM, IgA, C3, C1q, κ and λ light chains. Electron microscopy of the biopsy specimen was not performed. Serological tests for human immunodeficiency virus, hepatitis B and C viruses were negative. PCR testing of blood samples for cytomegalovirus, Epstein Barr virus, parvovirus B19 and BK polyomavirus all gave negative results. Recurrent schistosomiasis was ruled out by the absence of schistosome eggs in urine.

Droplet-based digital PCR (ddPCR)-based was used to detect the presence of SARS-CoV-2 nucleic acids in fluids and tissue (**Item S1**). ddPCR is an ultrasensitive technology with a higher efficiency compared to classical qPCR for the detection of rare events^{10,11}. SARS-CoV-2 RNA detected by this method was barely detectable in the plasma at the time of the biopsy (17 copies/ml), peaked thereafter at high concentrations (up to 1000 copies/ml), and rapidly decreased (**Figure 2**). The clearance of the virus was concomitant with seroconversion. Indeed, IgG antibodies against SARS-CoV-2 nucleocapsid (assayed with the ARCHITECT i2000 immunoassay analyzer [Abbott]) were absent at admission and were detected 14 days after (Titration: 2.7 IU/l; cutoff: 1.4 UI/l) despite the absence of circulating CD19-positive cells at admission, and 3 per microliter 15 days later (**Figure 2**). Critically,

SARS-CoV-2 RNA was not found in the kidney biopsy fragment or in urine (which was also collected before the peak of viremia).

The donor was found to have a *APOL1* *Go/G2* genotype, which is considered low risk⁸; the genotype of the recipient was *Go/Go*. The donor was a carrier of the high risk HLA DR4 genotype, and the recipient carried the high risk HLA B44 genotype¹². Systematic screen for other genes that are associated with collapsing glomerulopathy was not performed.

Mycophenolate mofetil was discontinued temporarily. The patient did not require intensive care support but fever and inflammation resolved at the same time viremia cleared (**Figure 2 and Figure S1**). Four weeks after the diagnosis of collapsing glomerulopathy, kidney function only partially recovered with a serum creatinine of 325 μ mol/L, severely increased UACR (171 mg/mmol), and a normalized serum albumin (3.7 g/dl) (**Figure 2**). SARS-CoV-2 was no longer detected on a naso-pharyngeal swab sample. The immunosuppression regimen at the end of the follow-up was prednisone 10 mg/day, tacrolimus 6 mg/day (To 5.8 ng/mL) and mycophenolate mofetil was resumed at 500 mg twice a day.

Discussion

We describe biopsy-proven collapsing glomerulopathy occurring in a KRT with COVID-19 with a low-risk *APOL1* genotype in the absence of detectable SARS-CoV-2 RNA in the kidney. Histological findings in the kidney allograft are similar to those observed in the native kidneys of patients with COVID-19^{3, 5, 7, 13}. However, there are many lessons to be learned from this singular case.

The mechanisms by which glomeruli are injured in the context of SARS-CoV-2 infection are unknown, and whether the virus directly promotes podocytes injury, or indirectly via the activation of antiviral immunity, or both, remains to be established. Nevertheless, the SARS-CoV-2 receptor ACE2 is expressed by podocytes, and SARS-CoV-2 nucleic acids and proteins are present in glomerular epithelial cells², indicating the virus can enter the cell and potentially promote damage. Conversely, patients with COVID-19 may have a collapsing glomerulopathy in the absence of SARS-CoV-2 RNA detected in the kidney^{6, 7}, supporting a role for indirect mechanisms in the pathogenesis of COVID-19-related kidney injury, for example systemic response to SARS-Cov-2 with enhanced type 1 interferon expression¹⁴. However, the detection of virus in kidney tissue may be challenging in terms of sensitivity and specificity¹⁵⁻¹⁷. Thus, highly sensitive and specific methods are required to detect the presence of the virus in the setting of COVID-19-related kidney diseases. Despite the use of ddPCR—an ultrasensitive method to detect nucleic acids—we did not find SARS-CoV-2 RNA in the kidney biopsy fragment. A false-negative finding is unlikely because the endogenous control (RNase P) was correctly amplified. Thus, the temporal sequence of occurrence of a collapsing glomerulopathy negative for SARS-CoV-2 RNA followed by SARS-

CoV-2 RNAemia is a strong, but not definitive, argument for the role of a circulating factor produced upon SARS-CoV-2 infection, rather than a direct cytopathic effect of the virus¹⁸.

This collapsing glomerulopathy in the setting of SARS-CoV-2 infection occurred in a low-risk *APOL1* (*G0/G2*) donor background⁸. *APOL1* risk alleles are associated with a higher rate of occurrence for *de novo* collapsing glomerulopathy¹² and there is growing experimental evidence to suggest that kidney-specific expression of the *APOL1* *G1* and *G2* risk variants may interfere with normal podocyte homeostasis⁸. *APOL1* expression is enhanced in inflammatory settings, including interferons, lipopolysaccharids, Toll-like receptor agonists, tumor necrosis factor, and other cytokines with robust upregulation⁸, and type I interferons stimulate *APOL1* expression *in vitro*, causing severe podocyte injury¹⁸. Inheritance of risk of kidney disease conferred by the *G1* and *G2* *APOL1* variants follows a largely recessive pattern, even if a much smaller effect is often observed in *G1* heterozygotes that has not been seen in *G2* heterozygotes⁸. However, one cannot exclude that, in the specific context of infection due SARS-CoV-2, and in a highly systemic inflammatory burden with activation of type I interferon-mediated signaling pathways, inheriting one copy of the *G2* allele may sensitize podocytes to injury.

Finally, we made the observation that SARS-CoV-2 seroconversion can occur even when circulating CD19-positive lymphocytes are virtually nonexistent. Even if correlative, the association of the clearance of the virus and the appearance of IgGs targeting the SARS-CoV-2 nucleocapsid is highly suggestive of a role of antibodies in the elimination of the virus from the circulation. The origin of the reactive B clone and the mechanism of anti-SARS-CoV-2 IgG production in the context of circulating B cells depletion remain to be established.

In conclusion, this case illustrates that a high-risk *APOL1* donor background is not a prerequisite for severe podocyte injury to occur in kidney allografts in a context of COVID-19. Our findings suggest that a direct cytopathogenic effect of SARS-CoV2 may not be instrumental for the development of collapsing glomerulopathy.

Article Information

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Patient Protections : The authors declare that the patients reported here provided consent for use of their medical records for research and that this work was performed under approval of the hospital ethics committee. Further information is available in Item S2.

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Figures legends

Figure 1 : Kidney allograft pathology findings

A, B, C. Kidney histology of the first kidney allograft biopsy with **A.** Masson Trichrome staining showing patterns of acute antibody-mediated rejection with glomerulitis (arrow) and peritubular capillaritis (*). **B.** Periodic-Acid-Schiff staining showing glomerulitis (arrow). **C.** Immunohistochemistry displaying positive staining for C4d on peritubular capillaries (*) (brown). **D.** Kidney histology of the second graft biopsy with Masson Trichrome staining showing collapsing glomerulopathy with podocytes hypertrophy and hyperplasia, and collapse of the glomerular tuft (arrow). **E.** Kidney histology of the second graft biopsy with Jones methenamine silver staining showing collapsing glomerulopathy with podocytes hypertrophy and hyperplasia, and collapse of the glomerular tuft. **F.** Jones methenamine silver staining showing tubular necrosis. **G.** Immunohistochemistry displaying negative staining for C4d on peritubular capillaries (*).

Figure 2 : Evolution of biological parameters during follow-up

Serum creatinine (SCr), urinary albumin-creatinine ratio (ACR), and SARS-CoV-2 RNA in the plasma were sequentially measured. Kidney biopsies are indicated, as well as serologic test and B cells counts. Conversion factor for SCr in $\mu\text{mol/l}$ to mg/dl , is /88.4. N IgG are IgG antibodies against SARS-CoV2 nucleocapsid.

Figure 1

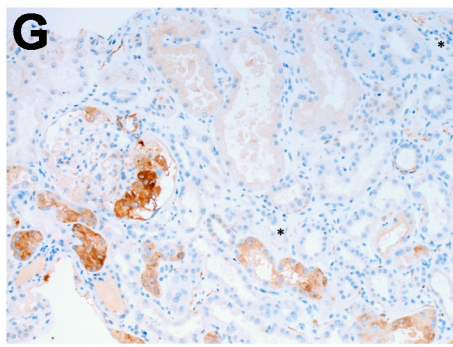
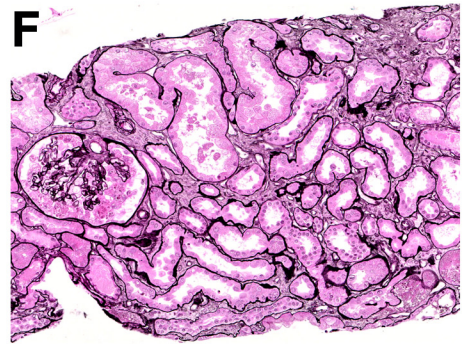
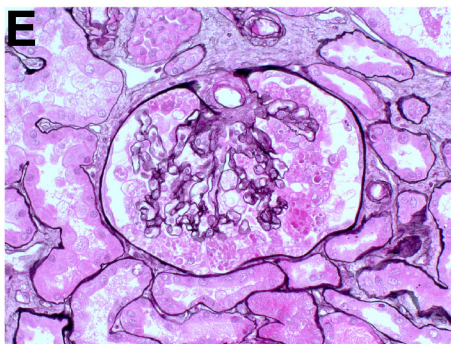
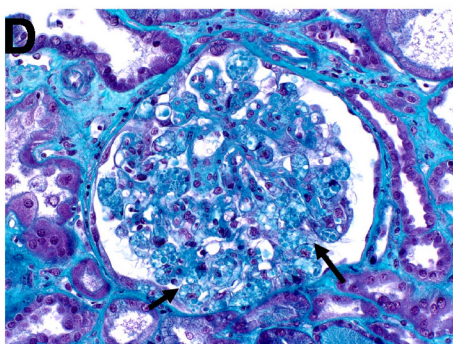
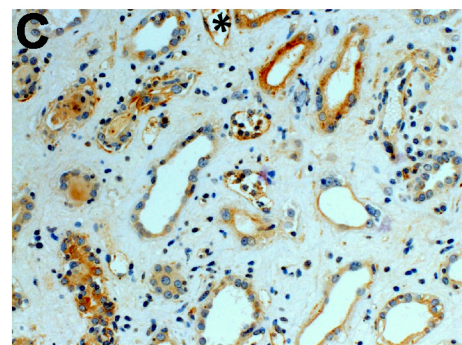
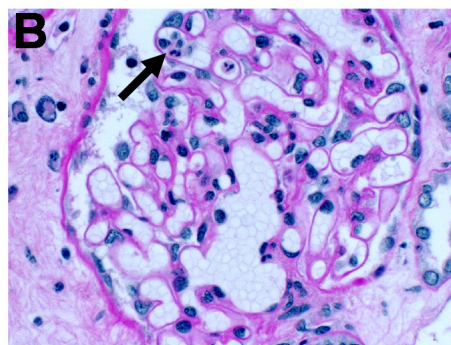
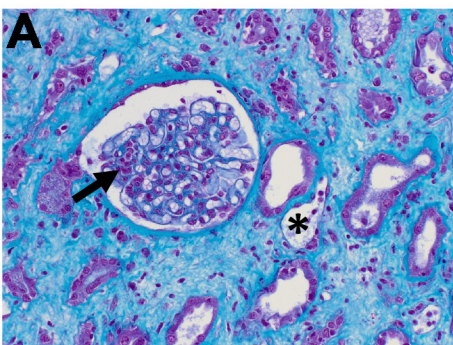


Figure 2

