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COVID-19 Associated Collapsing FSGS in an APOL1 Homozygous Transplant Recipient After Successful COVID Vaccination: A Case Report

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ABSTRACT

Organ transplant recipients exhibit lower rates of immune response to coronavirus disease 2019 (COVID-19) vaccination. Even when they do mount a demonstrable antibody response, it is unclear what degree of protection is conferred against the myriad potential complications of COVID-19 infection. We present here a case of a kidney transplant recipient who was homozygous for APOL1 risk alleles on low-dose immunosuppression who developed an antibody response to COVID-19 vaccination and subsequently acquired COVID-19 infection. Although she experienced relatively minor effects in other organ systems, she developed severe collapsing focal segmental glomerulosclerosis that left her dependent on hemodialysis on hospital discharge. This suggests that COVID-19 vaccination may not provide protection from infection-associated focal segmental glomerulosclerosis in patients with APOL1 risk alleles.

VACCINATION against coronavirus disease 2019 (COVID-19) has played a primary role in reducing the spread of the novel coronavirus infection and in reducing the associated morbidity and mortality [1]. However, it is clear that COVID-19 vaccination does not confer equal protection to all populations. Organ transplant recipients have exhibited lower rates of immune response to COVID-19 vaccination in comparison to the general population [2,3]. This is particularly the case for patients who have recently had a transplant and those transplant recipients on higher doses of immunosuppression at the time of COVID-19 vaccination [4]. However, even in patients with an antibody response to vaccination, it is not known whether vaccination confers protection against all complications of COVID-19 infection, such as focal segmental glomerulosclerosis (FSGS) associated with APOL1 risk alleles.

Collapsing FSGS has been reported in association with COVID-19 infection in patients with the APOL1 risk alleles. There have been multiple case reports of patients with 2 APOL1 G1 risk alleles and a patient who had the G1 and G2 risk alleles who developed native kidney collapsing FSGS associated with COVID-19 infection [5−7]. Collapsing FSGS has also been described in association with COVID-19 infection in a patient who was heterozygous for wild-type and G1 alleles of APOL1 [8]. Among renal transplant recipients, a patient with primary FSGS who received a kidney transplant was reported to develop proteinuria and biopsy-proven FSGS in association with COVID-19 infection and positive staining of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein RNA in renal tubular epithelial cells [9]. COVID-19 infection may act as a "second hit" for the development of FSGS in patients with APOL1 risk alleles. Other viral syndromes have been associated with the second hit in transplant recipients of kidneys from donors with 2 APOL1 risk alleles [10,11].

We previously reported a patient who was identified as homozygous for the APOL1 G1 and G2 risk alleles and developed FSGS 18 years after renal transplantation from an identical twin sibling [12]. Here we report a case of rapid-onset collapsing FSGS associated with COVID-19 infection in the same patient after successful COVID-19 vaccination.

The data that support the findings of this study are available from the corresponding author on reasonable request.

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2021.11.001

CASE PRESENTATION

A 57-year-old female with a history of renal transplantation from her identical twin, 2 risk alleles for APOL1, and FSGS in the transplant kidney was admitted with shortness of breath, cough, nausea, and vomiting and was diagnosed with COVID-19 infection based on nucleic acid amplification test.

The patient had a history of end-stage renal disease due to biopsy-proven FSGS prior to receiving a preemptive kidney transplant from her identical twin sister 23 years before this presentation. She received reduced immunosuppression with no induction therapy of anti-lymphocyte antibodies or IL-2 receptor antagonists. Maintenance immunosuppression consisted of mycophenolate 750 mg twice a day and prednisone 5 mg daily. She had received cyclosporine only during the first year posttransplant. She had excellent renal function posttransplant with serum creatinine ranging between 0.8 and 1.1 mg/dL and urine protein-creatinine ratio ranging between 0.3 and 0.8.

However, 18 years after transplantation, the patient was noted on routine follow-up laboratory testing to have a UPCR of 1.8 gm/d. Serum creatine also increased to 1.5 mg/dL. She underwent allograft biopsy at this time, which was negative for rejection but showed focal global (30%) and segmental glomerulosclerosis (NOS [not otherwise specified] type; Fig 1), patchy interstitial fibrosis and tubular atrophy (30%) with associated nonspecific inflammation, mild arteriosclerosis, and hyaline arteriolosclerosis. Immunofluorescence was negative. Electron microscopy showed 30% to 40% foot process effacement. Genetic testing revealed that she and her twin donor carried both a G1 and a G2 risk allele for APOL1. The patient was treated with losartan and spironolactone and UPCR improved to 0.26 by 1 year post biopsy. Serum creatinine remained at 1.5 mg/dL on regular follow-up testing, the last of which was 3 months earlier, and the last UPCR 6 months earlier was 0.74 gm/d prior to presentation. The patient had received the second dose of the Moderna SARS-CoV-2 vaccine approximately 6 weeks prior to presentation.

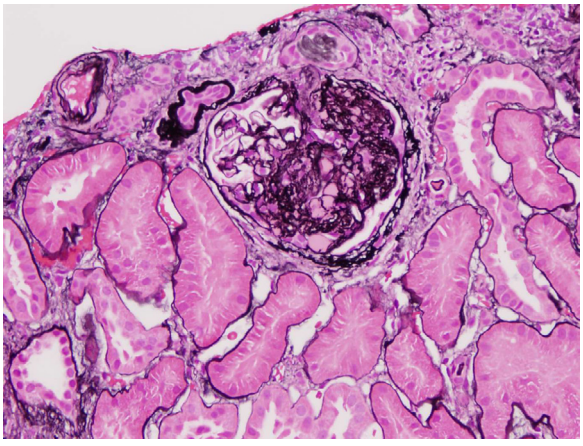

Fig 1. Representative glomerulus from the first biopsy showing segmental glomerulosclerosis, not otherwise specified type, Jones methenamine silver stain; original magnification 200×.

On presentation, the patient's oxygen saturation was 98% on room air, and throughout her hospitalization for COVID-19, her oxygen saturation fluctuated between 92% to 98%, and she required at maximum 2 L/min supplemental oxygen via nasal cannula. Her blood pressure was 122/60 on admission, and she did not experience hypotension, with. Respiratory rate was 20 breaths per minute and heart rate 91 on presentation. Chest x-ray on hospital day 1 showed small bilateral pleural effusions and possible faint parenchymal opacities at the lung bases, which did not significantly change on repeat x-ray on hospital days 3 and 4. On presentation she had a serum creatinine of 12.6 mg/dL. UPCR was 32 gm/d. Other pertinent laboratory findings are presented in Table 1.

The patient was initially treated with methylprednisolone 1 g daily for 3 days for possible acute rejection. Mycophenolate was discontinued because of COVID-19 infection. The patient underwent a second allograft biopsy, which showed acute tubular injury, collapsing glomerulopathy (involving 55% of glomeruli; Fig 2), focal global (35%) and segmental glomerulosclerosis (NOS type), patchy interstitial fibrosis and tubular atrophy (35%), mild arteriosclerosis, and hyaline arteriolosclerosis. There was no evidence of active rejection. Electron microscopy showed extensive efface of podocyte foot processes. Compared to the previous biopsy, there was a similar degree of chronic glomerular, tubulointerstitial, and vascular injury, with new findings of collapsing glomerulopathy and acute tubular injury. She had no improvement in renal function and required initiation of hemodialysis on hospital day 3 and remained dependent on dialysis.

Seven days after her positive SARS-CoV-2 polymerase chain reaction test, the patient had positive immunoassay for SARS-CoV-2 spike protein (7.50 U/mL, via semiquantitative Roche Elecsys anti-SARS-CoV-2 S test). At the same time, she did not have detectable antibodies to the SARS-CoV-2 nucleocapsid antigen (via Roche Elecsys anti-SARS-CoV-2 test). This suggests that she had mounted an immune response to the COVID-19 vaccine but had not yet developed antibodies in response to the COVID-19 infection itself. Although she only experienced mild respiratory and gastrointestinal COVID-19 virus symptoms, she developed severe kidney injury that resulted in graft failure.

Table 1. Laboratory Findings on Presentation

Laboratory Test	Result	Reference Range
Sodium	132 mmol/L	133-145 mmol/L
Potassium	7.3 mmol/L	3.5-5.5 mmol/L
CO_2	13 mmol/L	20-32 mmol/L
BUN	92 mg/dL	6-22 mg/dL
Ferritin	4156 ng/mL	10-291 ng/mL
C-reactive protein	2.7 mg/dL	0.0-0.5 mg/dL
SARS-CoV-2 PCR (Retro-Pharynx)	Detected	Not detected
Donor-specific antibody	Not detected	Not detected

BUN, blood urea nitrogen; SARS-CoV-2, sudden acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

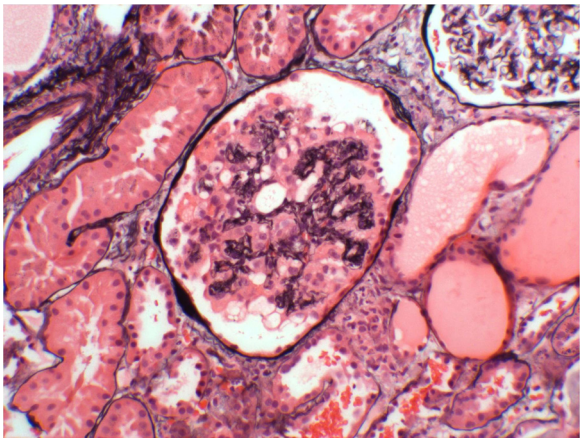

Fig 2. Many glomeruli in the second biopsy showed global collapse of the tufts with hyperplasia of the overlying podocytes (collapsing glomerulopathy), Jones methenamine silver stain, original magnification 200×.

DISCUSSION

Solid organ transplant recipients who develop COVID-19 infection have greater risk of complications. Transplant recipients are more likely to require renal replacement therapy or mechanical ventilation when compared to propensity score−matched populations [13]. Nearly half of solid organ transplant recipients also fail to develop an antibody response to 2 doses of SARS-CoV-2 vaccination, and among those who do develop a response, antibody titers are significantly less than those in immunocompetent vaccine recipients [14].

COVID-19 infection has been associated with kidney injury of different etiologies. In a case series of 42 patients who died of COVID-19, acute tubular injury was the primary finding in patients with acute kidney injury, and 1 patient had FSGS [15]. Both direct viral and cytokine-induced, immune-mediated damage are thought to contribute to kidney injury in COVID-19 infection [16]. Though acute tubular injury might be associated with overall systemic illness and the severity of the sepsis response, our patient in this case presented with renal failure far out of proportion to the severity of her illness in other organ systems, and this was reflected in her kidney biopsy, which demonstrated injury more consistent with FSGS rather than acute tubular injury.

The mechanism of FSGS associated with COVID-19 infection and APOL1 risk status is unclear. COVID-19, like other viral infections, may act as a "second hit" in patients with APOL1 risk alleles, and our experience with this patient suggests that the mechanism of this second hit is not dependent on the overall severity of the infection. Proposed mechanisms of the increased susceptibility to kidney damage in APOL1 risk allele homozygous patients include reduced mitochondrial function and cellular respiratory reserve, altered lysosomal function leading to dysregulated autophagy, and activation of various pro-inflammatory pathways [17]. Potential second hits that may induce the development of FSGS include pharmaceutical and recreational drugs; infections such as human immunodeficiency virus, cytomegalovirus, and Epstein-Barr virus; and reduced nephron mass [18]. Our patient's infection may have acted as an immunologic trigger in an already vulnerable kidney to an inflammatory cascade that led to cell death, and reduced metabolic reserve in her kidney may have led to further damage in the setting of increased metabolic demands of the proinflammatory state.

CONCLUSIONS

This case demonstrates that a transplant recipient on low-dose immunosuppression after transplantation can develop COVID-19 infection despite a positive immune response to COVID-19 vaccination. This patient was at risk for the development of collapsing FSGS related to her donor-associated APOL1 genotype. Successful COVID-19 vaccination may have protected this patient from having severe symptoms of a COVID-19 infection, but it did not protect her from developing collapsing FSGS as a consequence of the cytokine storm. Further research is needed to understand what should be considered an adequate COVID-19 vaccination protocol in the population of transplant recipients with poor antibody response. COVID-19 vaccination in the general population may not provide protection from cytokine storm−associated FSGS in breakthrough infections in patients with homozygous APOL1. Thus, it remains important for individuals at risk for COVID-19-associated nephropathy in the general population and, in particular, poorly responding transplant recipients to take precautions to reduce exposure to the virus even with demonstrated antibody response.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT-OF-INTEREST

None.

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