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Julie Oniszczuk, Anissa Moktefi, Aude Mausoleo, Nicolas Pallet, Stephanie Malard-Castagnet, et al.. De Novo Focal and Segmental Glomerulosclerosis After COVID-19 in a Patient With a Transplanted Kidney From a Donor With a High-risk APOL1 Variant. *Transplantation*, 2021, 105 (1), pp.206-211. 10.1097/TP.0000000000003432 . hal-03160386

HAL Id: hal-03160386

<https://hal.u-pec.fr/hal-03160386v1>

Submitted on 5 Mar 2021

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De novo focal and segmental glomerulosclerosis after COVID-19 in a patient with a transplanted kidney from a donor with a high-risk *APOL1* variant

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JO collected, analyzed the data and contributed to the manuscript editing.

AM performed histopathological evaluation and contributed to the manuscript editing.

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SF performed virological analysis for SARs-Cov 2 identification.

K EK, TS, DS, AB analyzed the data and critically reviewed the manuscript.

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Each author contributed important intellectual content during manuscript drafting. All the authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT : The authors have non conflict of interest with regard to publication of this manuscript

FINANCIAL DISCLOSURE : Dr Audard has received consulting fees from Addmedica outside the scope of this work. The other authors have no financial conflicts of interest to disclose

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LIST OF ABBREVIATIONS

ACE2: Angiotensin-converting enzyme 2

AKI: acute kidney injury

APOL1: apolipoprotein L1

CMV: Cytomegalovirus

COVID-19: coronavirus disease 2019

Ct: Cycle threshold

CT: computerized tomography

DNA: DeoxyriboNucleic Acid

EBV: Epstein Barr Virus

eGFR: estimated glomerular filtration rate

FSGS: focal segmental glomerulosclerosis

HIV: Human Immunodeficiency Virus

NP: nucleocapsid protein

PCR: Polymerase Chain Reaction

RNA: RiboNucleic Acid

SARS-CoV2: severe acute respiratory syndrome coronavirus 2

UPCR: urine protein/creatinine ratio

ABSTRACT

Background. There is compelling evidence that renal complications in a native kidney are a major concern in patients infected with SARS-CoV-2, the causal agent of COVID-19. The spectrum of renal lesions observed on renal grafts in this context remains to be determined.

Methods. We report the case of a renal transplant recipient with non-severe COVID-19, who subsequently developed nephrotic syndrome associated with acute renal injury.

Results. Renal biopsy demonstrated focal and segmental glomerulosclerosis lesions classified as not otherwise specified histological variant. Genotyping for two risk alleles of the apolipoprotein L1 (APOL1) gene demonstrated that the donor was homozygous for the G2/G2 genotype.

Conclusions. In renal transplant patients receiving kidneys from donors with high-risk APOL1 variants, COVID-19 may promote acute glomerular injury in the form of focal and segmental glomerulosclerosis.

KEY WORDS

COVID 19, renal transplantation, Focal and segmental glomerulosclerosis, APOL1

INTRODUCTION

In the current pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a broad spectrum of renal manifestations of the disease have been observed on native kidneys.¹ In a prospective study of 701 patients with a median age of 63 years, Cheng et al. found that 43.9% had substantial proteinuria, 26.7% had hematuria and acute kidney injury (AKI) occurred in 5.1% of patients during disease progression. Interestingly, kidney damage and patient survival were found to be closely related.² These data were confirmed by Pei et al. in a study of 333 patients, 75.4% of whom displayed renal disorders, including AKI, proteinuria and hematuria.³ The pathophysiological processes underlying COVID-19-related kidney impairment seem to be multifactorial and promoted by hemodynamic instability, the direct infection of tubular cells in the parenchyma, interstitial infiltration, micro-thrombus formation and acute glomerular injury.¹ The pathological kidney lesions associated with AKI and proteinuria in patients infected with SARS-CoV-2 were initially described in a post-mortem study.⁴ In this study, the principal pathological lesions observed were acute tubular necrosis with prominent diffuse proximal tubular injury.⁴ Renal biopsies performed in patients with confirmed SARS-CoV-2 infection and nephrotic-range proteinuria subsequently suggested that collapsing glomerulopathy, a histological variant of focal segmental glomerulosclerosis (FSGS), may be a common finding in patients of African ancestry.⁵⁻¹⁰ Interestingly, in four cases tested for high-risk APOL1 genetic variants,^{5,7,9} an association was found between these glomerular lesions and genetic susceptibility, suggesting that, as in other infectious diseases, such as Human Immunodeficiency Virus (HIV) infection or malaria, SARS-CoV-2 infection may act as a trigger promoting FSGS/collapsing glomerulopathy lesions in patients of African ancestry.¹⁰ These data were confirmed in a biopsy series of 14 patients showing, in the setting of COVID-19, a strong association between FSGS collapsing glomerulopathy variant and APOL1 high risk-gene variant.¹¹ It has recently been

suggested that kidney transplant recipients have a higher risk of severe COVID-19.¹²⁻¹⁴ However, to date, in the setting of renal transplantation, biopsy-proven glomerular lesions potentially related to SARS-CoV-2 have been exceptionally described.¹⁵ We provide here a case report in this context, concerning a patient who developed laboratory-confirmed SARS-CoV-2 infection 2.5 months after a first renal transplantation, leading, 10 days later, to nephrotic syndrome with biopsy-proven FSGS lesions on the graft, which was obtained from a donor with a high-risk APOL1 variant

CASE PRESENTATION

A 49-year-old man of African origin was referred to our nephrology department on April 29, 2020, for the assessment of nephrotic syndrome. His medical history included end-stage renal disease of presumed vascular origin that had required chronic intermittent hemodialysis since 2014. No renal biopsy was performed at the time of initial nephrologic evaluation, due to severely impaired renal function in a context of bilateral renal atrophy. At this time, urine protein/creatinine ratio (UPCR) and albumin levels level were at 1100 mg/g and 43gr/L, respectively. The patient had no family history of renal disease or oedema, but had severe hypertension associated with hypertrophic cardiomyopathy. On January, 2020, he underwent a first renal transplantation in which he received a kidney from a 45-year-old man who died in a road accident. There were seven HLA mismatches (2A, 1B, 2C, 2DP) between donor and recipient. The patient's pretransplantation panel reactive antibody level was 0%. Initial immunosuppressive treatment consisted of induction with antithymocyte globulin (thymoglobulin, Mérieux) for five days, combined with methylprednisolone pulses. The maintenance immunosuppressive regimen included tacrolimus (initiated on day 4, with trough concentrations maintained at 8 to 10 ng/mL) associated with mycophenolate mofetil (2 g/day, subsequently adjusted according to clinical safety criteria) and oral steroids. The post-transplantation period was unremarkable and the patient was discharged seven days after surgery, with a creatinine concentration of 1.84 mg/dL (estimated glomerular filtration rate (eGFR): 42 ml/min/1.73m²). Two weeks after transplantation, the patient developed non-compressive lymphocele with no signs of infection that did not require surgery. Two months after transplantation, renal function was defined by a creatinine level of 1.47 mg/dL, (eGFR of 52 ml/min/1.73m²) and UPCR was considered to be in the normal range (201 mg/g). Five weeks after transplantation, the patient displayed a light cough and aguesia without dyspnea, fever or diarrhea (**Figure 1**). These clinical manifestations were highly suggestive of the initial

manifestations of COVID-19. Renal function initially remained stable, but we observed a substantial increase in UPCR (1380 mg/g) (**Figure 1**). Two weeks later, we detected a significant worsening of renal function (creatinine level of 2.17 mg/dL, eGFR of 33 ml/min/1.73m²), with an increase of proteinuria level. The patient was admitted to our department for renal graft biopsy (**Figure 1**). At this time, the patient presented a nephrotic syndrome with an albumin concentration of 27 g/L and a UPCR of 3270 mg/g, with a moderate inflammatory syndrome (C-reactive protein concentration of 19.2 mg/L) and lymphopenia (absolute lymphocyte count of 400 x 10⁹/L and a CD4 T-cell count of 151/μL). Because of nephrotic syndrome occurring in a context of suspected COVID-19, a renal graft biopsy was performed.

MATERIALS AND METHODS

Detection of the SARS-CoV2 genome

Nasopharyngeal swabs were collected and samples were processed for RiboNucleic Acid (RNA) extraction with the QIA symphony platform. Real time- Polymerase Chain Reaction(RT-PCR) was performed with a newly released commercial test kit— RealStar SARS-CoV2 RT-PCR kit 1.0 (Altona, Hamburg,Germany) on a LightCycler® 480 plate-based real-time PCR platform. This kit uses probes conjugated with distinguishable dyes, making it possible to detect B-βCoV-specific and SARS-CoV2-specific RNA simultaneously, together with an internal control to assess possible RT-PCR inhibition and to confirm the integrity of the RT-PCR. The Cycle threshold (Ct) cutoff value is 40. A Ct value < 40 indicates that the RT-PCR test is positive.

Analyses of Kidney Biopsy Specimen

The renal biopsy specimen was processed for light and immunofluorescence microscopy according to standard techniques. It was fixed in formol acetic alcohol, embedded in paraffin and sectioned. The sections were treated with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome and silver stains. Immunofluorescence was assessed on cryosections (3 μm), using fluorescein isothiocyanate–conjugated polyclonal antibodies directed against IgG, IgM, IgA, C3, C1q, and κ and λ light chains (Dako, Glostrup, Denmark). For electron microscopy, samples were fixed in 2.5% glutaraldehyde in 0.1 mmol/L cacodylate buffer (pH 7.4) at 4°C. Fragments were then postfixed in 1% osmium tetroxide, dehydrated using alcohol series, and embedded in epoxy resin. Semithin sections (0.5 μm) were stained using toluidine blue. Ultrastructure sections (80 nm) were contrast-enhanced using uranyl acetate and lead citrate,

and they were examined using a JEOL 1010 electron microscope (JEOL, Ltd., Tokyo, Japan) with a MegaView III camera (Olympus Soft Imaging Systems GmbH, Munster, Germany).

APOL1 genotyping

High-risk APOL1 genotypes were defined as two risk alleles in any combination (homozygous G1/G1, homozygous G2/G2, or compound heterozygous G1/G2). As previously described, G1 variant allele consisting of two non-synonymous coding mutations (S342G and I384M) and the G2 variant allele, a 6 base pair deletion that removes two amino acids (N388 and Y389) of gene encoding APOL1. DeoxyriboNucleic Acid (DNA) was extracted from peripheral blood leucocytes using the Maxwell[®] 16 LEV Blood DNA Kit (Promega, Charbonnières-les-Bains, France) according to the recommendations of the manufacturer. *APOL1* G1 haplotype (rs73885319, and rs60910145) and *APOL1* G2 haplotype (rs71785313) were identified by allelic discrimination assays using TaqMan probes, on an ABI Prism Genetic Analyser System 9700 (Applied Biosystems, Thermo Fisher Scientific, Courtaboeuf, France). All investigations were performed in accordance with the Helsinki Declaration, and was approved by our local institutional review board (IRB 412 Mondor No. 00003835) and by the *Comité de Protection des Personnes d'Ile de France IV* (No. 2016/25NICB).

RESULTS

Testing of specimens for SARS-CoV2 infection

Nasopharyngeal swabs collected from the patient on day 2 after the onset of symptoms were tested positive for SARS-CoV-2 (low viral load, Ct values, 36). The patient's clinical condition at this time did not require the administration of antibiotic or antiviral agents, or hospitalization. Immunosuppressive treatment was left unmodified in the face of this not particularly worrying clinical presentation. A whole-body computerized tomography (CT)-scan revealed moderate bilateral pulmonary parenchymal ground-glass and other rare opacities. At the time of renal biopsy, SARS-CoV-2 PCR test results for nasal swabs remained positive, although the patient no longer had COVID-19 symptoms.

Renal graft pathological findings

The renal biopsy specimen consisted of renal cortex tissues with eight glomeruli, none of which was globally sclerotic. One glomerulus displayed FSGS not otherwise specified with segmental lesion of the glomerular tuft and hypertrophy of the overlying epithelial cells (**Figure 2A**). Acute proximal tubular injury was severe, with a diffuse flattened tubular epithelium and frank focal necrosis (**Figure 2B**). No microcystic tubular dilation, interstitial edema or inflammation were observed. Interstitial fibrosis was mild (ci1) (according to Banff classification) and vessels were normal. There was no evidence of thrombotic microangiopathy or rejection. Immunofluorescence assays on glomeruli were negative for IgG, IgM, IgA, C3, C1q, Kappa, and Lambda. Tests for C4d on peritubular capillaries were also negative. Electron microscopy analysis revealed severe podocyte injury characterized by foot process effacement (**Figure 3A**). We also observed glomerular endothelial changes, consisting on endothelial swelling and numerous tubuloreticular inclusions in glomerular capillaries (**Figure 3B**).

Screening for underlying cause of de novo focal and segmental glomerulosclerosis and outcome

Serological tests for HIV and for other viruses (tests performed for hepatitis B and C viruses) were negative. Search for Cytomegalovirus (CMV), Epstein Barr virus (EBV), parvovirus B19 and BK virus blood replication was negative. No donor-specific antibodies were detected. Immunological tests for antineutrophil cytoplasm, antinuclear and anti- DNA antibodies were negative. Serum complement levels were within the normal range. Serum protein electrophoresis showed total protein concentration to be decreased (55 g/L) without monoclonal immunoglobulin spike on immunoelectrophoresis. Given this case of biopsy-proven FSGS in a renal graft 2.5 months after renal transplantation in a context of COVID-19, we investigated whether the donor had an APOL1 risk allele (using a blood sample collected at the time of kidney donation). The donor was found to have a homozygous G2/G2 genotype. After renal biopsy, the patient developed macroscopic hematuria, associated with a worsening of renal function (due to hypovolemia and post-renal AKI), necessitating blood transfusion and bladder catheterization. Strikingly, without specific treatment (steroid, introduction of new immunosuppressive agent) apart from introduction of a low dose of angiotensin–converting enzyme inhibitor, renal function progressively improved and proteinuria level decreased. At the patient’s most recent follow-up visit (10 weeks after renal biopsy), creatinine level had returned to baseline values (1.64 mg/dL, eGFR of 48 ml/min/1.73m²) and proteinuria level was at 1610 mg/g (**Figure 1**).

DISCUSSION

Patients who have undergone kidney transplantation may be particularly susceptible to COVID-19, because many morbid conditions, including hypertension, diabetes and cardiovascular disease, are common in this population.¹²⁻¹⁴ The initial clinical presentation of COVID-19 in kidney transplant recipients seems to be quite similar that that in the general population.^{9,10} In a study performed in the framework of the Columbia University Kidney Transplant Program, the authors found that six transplant recipients displayed AKI, but the level of proteinuria was not specified and none of the patients underwent graft biopsies to determine the nature of the underlying histological lesions of the kidney.¹³ However, Kadosh et al recently described the case of a patient receiving immunosuppressive agents for heart transplantation who developed collapsing glomerulopathy after COVID-19.¹⁶ We provide here one of the first descriptions of biopsy-proven FSGS occurring in a context of AKI and nephrotic syndrome in a kidney transplant recipient with laboratory-confirmed SARS-CoV-2 infection. Even if, we cannot definitely rule out that initial renal disease may be due to primary FSGS, medical history, clinical and biological data were not consistent with this diagnosis at the time of the first nephrologic assessment. In addition, electron microscopy findings showing endothelial tubuloreticular inclusions are highly suggestive of FSGS related to COVID-19.⁶ As observed in our patient, severe kidney injury may occur in patients with only moderate lung symptoms and may persist even after the pulmonary symptoms have resolved.¹⁰ Two weeks after renal biopsy, with the exception of renal graft parameters (no improvement of the nephrotic syndrome), the patient's clinical condition remains unchanged, with no reduction of immunosuppression. Strikingly, 10 weeks after post COVID-19 FSGS diagnosis, without specific therapeutic intervention and exclusively with usual renal-protective measures, renal function progressively improved and proteinuria decreased. Since no second renal biopsy was performed at this time, and due to lacking data in the literature, regarding the long-term follow-

up of COVID-19 related glomerulopathy, this finding suggesting a possible spontaneous partial recovery remains intriguing and should to be cautiously interpreted. The principal renal histopathological lesions observed in the native kidneys of patients with COVID-19 are tubular injuries, glomerular fibrin thrombi and collapsing glomerulopathy lesions.^{1,5-11} The precise mechanisms by which SARS-CoV2 induces kidney damage remain poorly understood. Angiotensin-converting enzyme 2 (ACE2), which may play a determinant role in intracellular invasion, is expressed on the brush border of the proximal tubule and in podocytes.¹ Retrospective postmortem study analyzing kidneys from patients who died from severe COVID-19 previously reported the *in situ* expression of viral nucleocapsid protein (NP) antigen in the tubular compartment.⁴ Puelles et al. detected SARS-CoV-2 protein and RNA in glomerular epithelial, and tubular cells from autopsy samples, with elegant high-spatial resolution techniques.¹⁷ Of particular interest, Puelles et al. reported that some patients had normal kidney function despite evidence of direct kidney infection.¹⁷ As SARS-CoV-2 displays renal tropism, these data suggest that the kidney may act as a reservoir of the virus during COVID-19. Conversely, several reports have shown that patients with COVID-19 may present AKI and heavy proteinuria due to collapsing glomerulopathy with no evidence of kidney infection, in the absence of SARS-CoV-2 RNA detection by *in situ* hybridization.^{5,7} In the present case, immunohistochemistry against SARS-CoV-2 nucleocapsid protein and SARS-CoV-2 *in situ* hybridization were not available to assess for the absence or presence of SARS-CoV-2 in renal cells. These data suggest a role for indirect mechanisms in the pathogenesis of COVID-19-related kidney injury. Our case, as previously reported for native kidneys from patients of African ancestry^{5,7,9,11} highlights the importance of checking a DNA sample from the donor for high-risk APOL1 variants in the specific context of COVID-19 and renal transplantation. In native kidneys, Afro-Caribbean individuals carrying APOL1 risk alleles have a higher risk of developing FSGS lesions, and collapsing glomerulopathy in particular, as

observed in HIV-associated nephropathy or systemic lupus erythematosus-associated collapsing glomerulopathy.¹⁸ Kidney allografts from donors with high-risk APOL1 variants also have a shorter survival.^{19,20} After renal transplantation, APOL1 risk alleles are independent predictors of a poor outcome, with a higher rate of occurrence for *de novo* collapsing glomerulopathy.²¹ Our patient was not infected with BK, CMV, or parvovirus B19, all of which can act as second hits favoring the occurrence of FSGS and collapsing glomerulopathy in kidney transplant recipients with grafts from donors carrying two high-risk APOL1 alleles.²² Interestingly, in the case published by Lazareth et al, collapsing glomerulopathy occurred later (5 years after kidney transplantation) and the donor APOL1 genotype was considered as “low risk” (G0/G2).¹⁵ The APOL1 protein has been detected in human glomeruli, and there is growing experimental evidence to suggest that kidney-specific expression of the APOL1-G1 and APOL1-G2 risk variants may interfere with normal podocyte homeostasis.^{23,24} Tubuloreticular inclusions, frequently identified in patients with autoimmune and viral infections are considered as a marker of systemic stimulation by endogenous or exogenous interferons. The presence of tubuloreticular inclusions in endothelial cells during COVID-19-associated collapsing glomerulopathy suggests a possible enhancement of the type I interferon response.⁶ Interferon stimulates APOL1 expression *in vitro*, causing severe podocyte injury, and collapsing glomerulopathy has been described in patients receiving interferon treatment.²⁴ However, an inappropriate inflammatory response, with low levels of type I and type III interferon and high levels of IL-6 expression, has been reported in patients with COVID-19.²⁵ In conclusion, our case supports the hypothesis that SARS-CoV-2 infection can be considered a second hit for FSGS after renal transplantation in patients with grafts originating from donors with genetic susceptibility factors. Further reports and analyses of the specific signaling pathways involved in COVID-19-induced glomerular damage are required to confirm this hypothesis.

ACKNOWLEDGMENTS

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FIGURE LEGENDS

Figure 1

Outcome of renal laboratory parameters (proteinuria and serum creatinine levels) after renal transplantation (in purple), at the time of COVID-19 and after kidney graft biopsy (in green)

D= Day, W =Week, KB= Kidney biopsy

Figure 2

Figure 2A: Focal segmental glomerulosclerosis not otherwise specified in the allograft biopsy with segmental lesion of the glomerular tuft and overlying epithelial cell hypertrophy with cytoplasmic vacuolization (periodic-acid Schiff, original magnification x400)

Figure 2B: Acute tubular necrosis with thinning of the tubular epithelium and bare tubular basement membranes (hematoxylin eosin saffron, original magnification x200)

Figure 3

Figure 3A: Ultrastructural examination revealed diffuse foot-process effacement, original magnification x 10000

Figure 3B: Electron microscopy demonstrated endothelial tubuloreticular inclusions (B, black arrow) original magnification x 40000. Stars indicate glomerular basement membrane (white) and capillary lumen (black)





