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Histopathologic findings on indication renal allograft biopsies after recovery from acute COVID-19

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Abstract

Current knowledge on histopathological changes occurring after COVID-19 in transplanted kidneys is limited. Herein, we present renal allograft pathology findings in patients recovered from COVID-19.

Six patients underwent indication biopsy, and one required allograft nephrectomy after acute COVID-19. Demographic data, clinical characteristics, and laboratory findings were recorded. The histopathological analysis included light microscopy, immunostaining, and electron microscopy.

Five patients were hospitalized for acute COVID-19, and all were diagnosed with imaging-confirmed pneumonia, one requiring mechanical ventilation, and two requiring dialysis. Two patients had mild form. Histopathologic examination of renal allograft specimens revealed collapsing, perihilar, tip-lesion and secondary FSGS in one patient each. One patient had borderline acute cellular rejection, and two had chronic antibody-mediated rejection. Histopathologic changes of glomerular tufts were accompanied by acute tubular injury in four patients. None of our patients had signs of viral inclusions in kidney cells.

One patient died and one remained dialysis-dependent after the good initial response to treatment. Patients with collapsing and perihilar FSGS had further progression of their chronic allograft nephropathy still without need for dialysis.

In conclusion, diverse kidney pathology may be found in SARS-CoV-2-infected renal transplant patients. It seems that viral infection may affect the immune system with triggering of glomerular diseases, while the acute tubular injury is of multifactorial etiology. Direct viral effect is less likely.

KEYWORDS

biopsy, COVID-19, histopathology, renal transplantation, SARS-CoV-2

1 | INTRODUCTION

Kidney transplant recipients (KTR) are a vulnerable group that might be particularly susceptible to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection and subsequent complications. Immunosuppressive state, direct kidney infection, disturbance of the renin-angiotensin-aldosterone homeostasis, and the pro-inflammatory cytokine milieu may contribute to kidney injury. The hypothesis that the kidney might be a target of the SARS-CoV-2 virus is supported by the findings of isolated virus from the urine of infected patients and the fact that ACE 2 is abundantly present in kidney tissue, mostly in podocytes and in the brush border of the proximal tubule.^{1,2} Controversy on the renal tropism of SARS-CoV-2 is going on while some of the authors observed viral elements in kidney tissue and others did not.³⁻⁵ However, direct viral effects were proposed, and collapsing glomerulopathy, coagulopathy, endothelial damage, complement activation, and inflammation were suggested as possible etiopathogenetic pathways.⁶ Goldman et al. in one of the most extensive series of patients with SARS-Cov-2 associated acute kidney injury, observed considerable similarities between this acute kidney injury and sepsis-associated acute kidney injury.³ Additional insult on kidney structure and function induced by nephrotoxic drugs and multiorgan injury should not be neglected in KTR. Understanding of COVID-19 kidney transplant-related injuries is still evolving. Herein, we present renal allograft pathology findings in seven transplant recipients recovered from COVID-19.

2 | PATIENTS AND METHODS

All patients who met the criteria for discontinuation of quarantine after acute COVID-19 (afebrile with two negative real-time reverse transcriptase-polymerase chain reaction tests for SARS-CoV-2 24 h apart) continued with regular follow-up at our outpatient clinic. Patients with acute allograft dysfunction and/or proteinuria at the regular outpatient visit after the acute COVID-19 underwent percutaneous renal allograft biopsy.

Data were obtained from the renal transplant patient database and from the patients' records. The following variables were documented: patient demographics, comorbid conditions/causes, clinical symptomatology and findings on physical examination, radiological and laboratory results, histopathologic findings on allograft biopsies, treatment, and clinical course.

A prospective observational cohort study evaluated the histopathology of seven renal transplant patients who underwent indication biopsy after acute COVID-19.

Patients had laboratory blood tests including complete blood count, renal function tests, urine examination, prothrombin time, activated partial thrombin time, D-dimers, fibrinogen, C3, C4, serum electrophoresis, and transplant kidney ultrasonography with Doppler studies prior to allograft biopsy. Donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs) were determined by Immucor (One Lambda). Reverse-transcriptase polymerase chain reaction was used to

determine proliferation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), John Cunningham virus (JCV), and BK virus.

Transplant biopsies were performed under ultrasound guidance with 16G needles by a nephrologist. All patients were kept under observation for 24 h after the procedure. Before discharge, repeat ultrasound examination was performed to look for hematoma formation.

Samples were processed by light microscopy, immunofluorescence, and electron microscopy by two independent nephropathologists unaware of clinical course. For light microscopy, samples were stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Schiff, and Jones methenamine silver. For immunofluorescence, a 3–4 μ m cryostat sections were processed by using polyclonal FITC-conjugated antibodies to IgA, IgG, IgM, C3, C1q, kappa, lambda, C4d and fibrinogen, (Dako Corporation, Carpinteria, CA, USA). Additional investigations were performed individually. All biopsies were evaluated according to the 2019 Banff classification.

Tissue submitted for electron microscopy was fixed with McDowell's fixative, then processed in 1% osmium tetroxide, dehydrated in an acetone gradient, and embedded in an epoxy embedding medium. One-micrometer-thick sections were cut and stained with toluidine blue stain. Ultrathin sections were stained with UranylLess and lead citrate and examined with a FEI- MORGAGNI 268D electron microscope.

Detection and identification of the viruses was performed as described previously.⁷ Namely, the presence of 80–140 nm uniform particles within intracellular vacuoles with dense membrane coat, spikes facing inside the vacuoles, and internal dense dots was considered as the presence of viruses.⁷

Ethics Committee approved the study, and all patients gave their consent.

3 | RESULTS

3.1 | Patients' characteristics

This retrospective analysis included all patients who underwent percutaneous renal allograft biopsies from December, 2020 to April, 2021, at the University Clinical Hospital Centre Zagreb, Croatia. Over the observed period, allograft specimens were collected after the COVID-19 in seven renal transplant recipients. Six patients underwent indication biopsy, and one required an allograft nephrectomy. The group included four women and three men (Table 1).

All patients had comorbidities including arterial hypertension. Patient 1 was noncompliant, with a history of peripheral upper arm embolization after thrombosis of the arteriovenous fistula. Patient 2 had biopsy-proven BK virus nephropathy diagnosed in July 2015. Patient 3 had chronic active antibody-mediated rejection in July 2016, with repetitive CMV reactivations and frequent genital herpes infections. Patient 4 had prolonged delayed graft function and had developed new-onset diabetes after transplantation. Patient 5 also had delayed graft function and chronic hepatitis B infection. He had two

TABLE 1 Patients' characteristics and COVID-19 details

Case	Sex/Age	Primary kidney disease	AH	Time from TX (months)	IS regimen	COVID-19 symptoms	Hospitalization for acute COVID-19	Treatment of acute COVID-19
1	F/40	Lupus nephropathy	Yes	200	CS, MMF, steroid	Fever, cough, dyspnea, diarrhea	Yes	IS reduction, antibiotics, LMWH
2	M/60	Nephroangiosclerosis	Yes	76	Tac, MMF, steroid	Fever, cough, dyspnea	Yes	IS reduction, antibiotics, LMWH
3	F/38	FSGS (not-specified)	Yes	104	Tac, MMF, steroid	Fever, cough, dyspnea	Yes	IS reduction, antibiotics, LMWH
4	M/53	ADPKD	Yes	25	Tac, MMF, steroid	Asymptomatic	No	None
5	M/54	Nephroangiosclerosis	Yes	117	CS, MMF, steroid	Fever, cough	Yes	IS reduction, antibiotics, LMWH
6	F/56	Unknown	Yes	125	CS, MMF, steroid	Fever, cough, dyspnea, psychomotor agitation	Yes	IS reduction, antibiotics, LMWH, dialysis
7	F/31	Unknown	Yes	156	Tac, steroid	Fever	No	None

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AH, arterial hypertension; CS, cyclosporine; F, female; FSGS, focal segmental glomerulosclerosis; IS, immunosuppression; LMWH, low molecular weight heparin; M, male; MMF, mycophenolate mofetil; Tac, tacrolimus; TX, kidney transplantation.

episodes of SARS-CoV-2 infection, 3 months apart, with three negative RT-PCR tests between them. Biopsy was performed after the second episode. Patient 6 had renal allograft artery stenosis and underwent balloon dilatation with stenting in July 2018. Patient 7 had acute antibody-mediated rejection followed by a disseminated cryptococcal infection 12 months prior to COVID-19. She underwent indication biopsy to tailor the immunosuppression. She had experienced significant increase in DSA after acute COVID-19 and had low overall immunosuppression due to cryptococcal infection.

Five patients were hospitalized to treat a severe form of acute SARS-CoV-2 infection, and all were diagnosed with bilateral imaging-confirmed pneumonia. Besides the respiratory symptoms, Patient 1 had gastrointestinal symptoms and required dialysis during acute infection. Patient 4 was asymptomatic. He was diagnosed with SARS-CoV-2 infection during evaluation of the new-onset proteinuria. Patient 6 had the most severe presentation with oliguria and psychomotor agitation. She required mechanical ventilation and dialysis during acute COVID-19. All hospitalized patients received low-molecular-weight heparin in the prophylactic dose. Immunosuppression was modified during the COVID-19 for all but patient 4. Mycophenolate mofetil was discontinued for 5 days with increase in the dosage of steroids.

At the time of presentation, all patients had peripheral edema, and patient 3 had anasarca.

3.2 | Laboratory findings

Baseline (the last value before COVID-19) and post-COVID-19 kidney allograft function parameters are shown in Table 2.

D-dimers were increased in four patients and three had hypogammaglobulinemia. Patients 3 and 6 had low serum C3 with C4

level within the normal range which suggested complement alternative pathway activation. Viral reactivations were common, with the Epstein-Barr virus being the most frequent (four patients) (Table 2).

3.3 | Histopathology findings

The light microscopic appearance of glomerular lesions included focal segmental glomerulosclerosis (collapsing, perihilar, tip-lesion, and secondary in one patient each), transplant glomerulopathy in two patients and mesangial proliferation in one patient. Acute tubular injury was recorded in four patients. All patients had degenerative lesions, including interstitial fibrosis, tubular atrophy and arteriosclerosis of diverse severity (Figure 1, Table 3).

The main feature by direct IF was a diffuse and bright granular glomerular deposition of C3 absent only in the sample of patient 4. C1q was positive in patients 1, 3 and 5. C4d was positive in patients 4 and 7. No significant staining was observed with anti-kappa and lambda except in patient 1.

By electron microscopy, performed in all patients, the dominant feature was foot process effacement (six patients) of various severity. Four patients had widened mesangial space with proliferation recorded in patient 6. Glomerular basement membrane changes included duplications and deposits in three patients.

Patient 1 had abundant inflammatory infiltration within the tubulointerstitial department. Beside the eosinophil and neutrophil cells, additional immunostaining revealed predominance of CD3 positive lymphocytes with CD138 positive plasma cells. CD20 positive B lymphocytes constitutes less than 5%, with very rare IgG4 positive cells. Small arteries and few arterioles showed endothelial cell swelling, some of which also showed mild intimal arteritis. Patient with the collapsing FSGS also had swelling of the vascular endothelial cells.

TABLE 2 Laboratory findings, allograft function and donor-specific antibodies: Before and after COVID-19

Case	CRP (mg/L)	Leucocytes (Ly), $\times 10^9/L$	Fibrinogen (g/L)	D-dimers (mg/L)	Virology (copies/ml)	Complement	Gamma globulins (g/L)	BC eGFRml/1.73 m ²	BC Proteinuria (g/day)	PC eGFRml/1.73 m ²	PC Proteinuria (g/day)
1	40	13.3 (1.99)	5.4	4.97	EBV 46300	C3 normal C4 normal	12.8	19	.86	9	2.05
2	1.4	8 (1.82)	4.6	4.43	EBV 184500	C3 normal C4 normal	ND	30	.98	26	2.91
3	1	4.2 (1.01)	2.5	ND	CMV 137	C3 low C4 normal	6.0	27	.92	21	1.91
4	1.8	11.7 (3.30)	3.0	.36	/	C3 normal C4 normal	7.5	49	.63	46	1.73
5	1	6.8 (1.59)	3.4	3.33	/	C3 normal C4 normal	10.3	19	.29	19	7.44
6	18.2	9.9 (1.02)	2.7	4.91	CMV 13700 EBV 311000	C3 low C4 normal	12.7	41	1.0	10	11.23
7	1.5	14 (6.16)	3.6	.19	EBV 32200	C3 normal C4 normal	7	55	.8	62	1

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate CKD EPI equation. CRP, C-reactive protein; ND, not done.

Virus particles were not identified in available specimens.

3.4 | Treatment and follow-up

Follow-up information was available in all patients. Six were alive at a median follow-up of 3 months (range 2–6 months). Patient 5 died from *Acinetobacter baumannii* sepsis, 5 months after the initial COVID-19 symptoms.

Treatment included intravenous immunoglobulins (IVIG) with 6-methylprednisolone (total of 500 mg divided in four applications) in five patients. Patient 3 received .5 g/kg body weight IVIG to correct hypogammaglobulinemia. Patient 5 with collapsing FSGS was not specifically treated.

At the last follow-up, the study group had a median eGFR of 35 ml/min/1.73m² (range, 14–64). Patient 1 remained dialysis-dependent after the good initial response to steroid pulses for the treatment of rejection. Patient 4 with a borderline acute cellular rejection received steroid pulses and had reduction of proteinuria with stable allograft function. Patient 5 with collapsing FSGS had further progression of chronic allograft nephropathy still without need for dialysis, as well as patient with perihilar FSGS (patient 2) (Table 4).

3.5 | Differences between native and transplanted kidneys

KTRs are a specific group of patients exposed to immunosuppressive therapy and with preexisting changes within kidneys. Histopathology significantly differ between native and transplanted kidneys (Table 5).

4 | DISCUSSION

SARS-CoV-2-infected KTR developed diverse glomerular and tubular diseases. The predominant presentation in our group was nephrotic syndrome or proteinuria with acute allograft dysfunction. The most common glomerular disorder was FSGS. Kidney transplant biopsy revealed *de novo* collapsing FSGS on the background of chronic allograft nephropathy in one patient, while one had perihilar, one had tip-lesion and one was diagnosed with secondary FSGS. One case of arteriolar and glomerular microthrombosis was recorded. Acute allograft dysfunction was accompanied by acute tubular injury on histopathology examination in four patients. Four patients had histopathologic signs of rejection, three chronic active antibody-mediated, and two borderline T-cell mediated rejection. Concurrent processes were recorded in most of the cases. Importantly, all patients had preexisting chronic allograft nephropathy. The most common finding on EM was podocyte foot process effacement. Number of cases with FSGS is slightly higher than seen in anecdotal clinical practice. However, 2/4 patients had secondary FSGS and 4/7 patients also had advanced renal dysfunction at baseline with at least CKD stage 4 before COVID-19 infection reflecting the significant baseline chronicity.

Data on histopathological findings in KTRs who survived SARS-CoV-2-infected is limited. Daniel et al. evaluated 18 kidney allograft biopsies. Five of eleven (45%) biopsies obtained within 1 month of acute COVID-19 revealed acute rejection. The remaining six biopsies revealed podocytopathy ($n = 2$, collapsing glomerulopathy and lupus podocytopathy), acute tubular injury ($n = 2$), infarction ($n = 1$), and transplant glomerulopathy ($n = 1$). Biopsies performed more than 1 month after acute COVID-19 showed collapsing glomerulopathy ($n = 1$), acute tubular injury ($n = 1$), and non-specific histologic findings ($n = 5$). In the study of May et al. which included 44 KTRs, the

TABLE 3 Histopathologic findings

Case	Biopsy diagnosis	Specimen	Light microscopy				Immunostaining and electron microscopy		
			Glomerulosclerosis	Tubular or glomerular casts		ATI	Infiltration	Immune	EM
1	Tip lesion FSGS, CCR, bACR, TIN	BX	5/12	/	Yes	Neutrophils and eosinophils cells in TI	IgM (2+), C3 and C1q (1+) in glomeruli, IgA, igG, kappa and lambda chains (2+) in tubular cells	Widened mesangium without hypercellularity, foot process effacement	
2	Secondary FSGS	BX	5/13	Tubular casts	Yes	Mononuclear	IgM and C3 in glomeruli (1+), IgA (3+) in tubular casts	Focal foot process effacement	
3	TG and CAMR	BX	5/14	Hyaline material in capillaries	No	Scarce mononuclear	IgM (3+), C1q (2+) and C3 (2+) deposits in mesangium and GBM	Foot process effacement, widened mesangial spaces, lamellated capillary BM	
4	bACR	BX	3/8	Tubular casts	No	Mononuclear	C4d and IgM in glomeruli (1+), IgA in tubular casts	Widened mesangium without hypercellularity, GBM duplications, degenerative changes of endothelial cells	
5	Collapsing FSGS	BX	8/16	/	Yes	Neutrophil cells in TI	C3 deposits (3+) in GBM, C1q (1+)	Extensive foot process effacement, GBM deposits	
6	MPGN, transplant glomerulopathy	AN	9/18	Hyaline material in tubules, vascular thrombi	Yes	Neutrophil cells in tubulointerstitial space	C3 deposits in glomeruli	Subendothelial and mesangial deposits with interposed cells along the GBM, extensive foot process effacement, endocapillary proliferation	
7	CAMR, transplant glomerulopathy, secondary FSGS	BX	6/26	Tubular casts	No	Mononuclear in TI, mild tubulitis, capillaritis	C4d (2+) in glomeruli, C3 (2+) blood vessel wall and tubular BM, IgA 2+ in tubular casts	Widened mesangium, glomerular BM duplications, focal foot process effacement, lamellated tubular and capillary BM	

Abbreviations: AN, allograft nephrectomy; ATI, acute tubular injury; bACR, borderline acute T-cell-mediated rejection; BM, basement membrane.; BX, biopsy; CAMR, chronic antibody-mediated rejection; CCR, chronic cell-mediated rejection; EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; TG, transplant glomerulopathy; TIN, tubulointerstitial nephropathy.

TABLE 4 Treatment modalities and outcomes

Case	Treatment	Last eGFR (ml/min/1.73m ²)/proteinuria (g/day)	Outcome
1	IVIg 2 g/kg	/	Hemodialysis
2	IVIg 2 g/kg	24/79	Progression of allograft dysfunction
3	IVIg .5 g/kg	35/2.1	Stable
4	Steroid pulses	48/7	Recovery
5	None	14/3.6	Progression of allograft dysfunction
6	IVIg 2 g/kg	/	Allograft nephrectomy
7	IVIg 2 g/kg	64/1.28	Stable

Abbreviations: eGFR, estimated glomerular filtration rate CKD EPI equation.; IVIG, intravenous immunoglobulins.

TABLE 5 Major histopathology findings in native and kidney allograft biopsies (data based on Refs. [8–30])

Histopathologic changes in kidneys						
Native kidneys						
Glomerular changes	Tubular and interstitial changes		SARS-CoV-2			
Collapsing glomerulopathy	Acute tubular injury		Viral particles were initially described in renal tissue but this finding was refuted by others			
Nodular mesangial expansion	Loss of brush border cells					
Hyalinosis of arterioles	Dilatation of tubular lumen					
Ischemic glomeruli	Changes of peritubular capillaries (aggregation of erythrocytes and vascular degeneration)					
Different glomerulonephritides	Intratubular reabsorption vacuoles					
Lymphocyte infiltration	Myoglobin cast nephropathy					
Severe podocytopathy	Acute interstitial nephritis					
Endothelial changes (proliferation, swelling, subendothelial lucent expansion)						
Fibrin platelet thrombi						
Amyloidosis						
Thrombotic microangiopathy						
Transplanted kidneys						
Rejection	Tubular and interstitial changes	Glomerular changes			Vascular changes	SARS-CoV-2
Acute T-cell mediated rejection	Acute tubular injury	FSGS	Severe arteriosclerosis	Not found		
Acute and chronic antibody mediated rejection	Interstitial fibrosis and tubular atrophy	Transplant glomerulopathy	Infarction			
Antibody + T-cell mediated rejection		Collapsing glomerulopathy				
		Recurrent or <i>de novo</i> kidney disease				

Abbreviations: eGFR, estimated glomerular filtration rate CKD EPI equation.; IVIG, intravenous immunoglobulins.

most common diagnosis was allograft rejection (61.4%), followed by acute tubular injury (27.3%) and collapsing glomerulopathy (4.5%), while 4.5% were negative for rejection and one had IgA nephropathy. Allograft rejection was most commonly antibody-mediated (38.6%, while 13.6% had T-cell mediated and 9.1% antibody+T-cell mediated acute rejection). The series of three cases reported grade 2A acute T cell-mediated rejection, cortical infarction, and acute tubular injury.⁸

Noble et al. reported a case of collapsing nephropathy with a borderline T-cell-mediated rejection in a KTR. Their patient had nephroangiosclerosis of native kidneys, and a transplant kidney biopsy performed in 2017 showed cellular rejection without evidence of collapsing glomerulopathy.⁹ Another case of collapsing glomerulopathy in transplanted kidney was reported by Lazareth et al.¹⁰ Abuzeineh et al. described a KTR who elevated donor-specific antibodies and

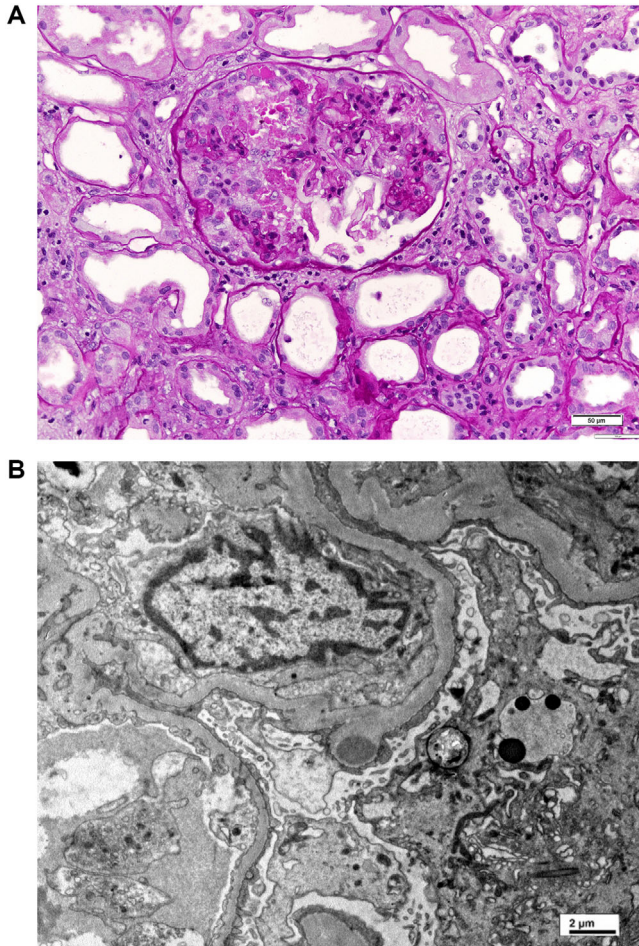


FIGURE 1 Indication kidney allograft biopsy findings after COVID-19. (A). Collapsing FSGS. Global glomerular collapse with podocyte hypertrophy, accumulation of protein resorption droplets and widespread tubular injury with tubular dilatation, flattening of the tubular epithelium and loss of the brush border (PAS original magnification $\times 200$). (B). Intramembranous dense deposit and prominent podocyte foot process effacement (Original magnification $\times 4400$)

plasma donor-derived cell-free DNA during the initial hospitalization for COVID-19. Biopsy was performed 3 months later because of persistent positive COVID-19 tests and stable serum creatinine and revealed chronic active antibody-mediated rejection.¹¹ Mohamed et al. reported a successful management of T-cell mediated rejection in the early posttransplant period in a patient with acute COVID-19.¹² Bajpal et al. have recently reported their experience with renal transplant patients after acute COVID-19. Kidney biopsy was performed in 11 patients and revealed acute tubular injury (nine patients), thrombotic microangiopathy (two), acute cellular rejection (two), and chronic active antibody-mediated rejection (three). Patients with incomplete recovery were likely to have lower eGFR and proteinuria at baseline, same as in our study. They found no cases of FSGS in 11 biopsied patients, but do not specify the criteria for biopsy.¹³ Our results are in line with their findings, while four patients from our cohort had advanced renal dysfunction at baseline proving the sensitivity of

patients with advanced chronic kidney diseases to consequences of COVID-19.

More data is available on biopsy findings from native kidneys. Kidney thrombotic microangiopathy was found in a subset of cases. A few cases of the glomerular disease have been reported, most commonly collapsing glomerulopathy. Other cases included minimal change disease, anti-GBM disease, infection-associated glomerulonephritis, membranous glomerulopathy, ANCA-associated vasculitis and other less frequent findings,⁸⁻²⁹ summarized in Table 5. Various findings from different groups may indicate diverse problems present in specific populations. However, more extensive studies should investigate the role of different approaches to the treatment of acute COVID-19 in the pathogenesis of kidney diseases associated with SARS-CoV-2 infection. The major difference between native and transplanted kidney histopathology findings is the lack of viral inclusion in the latter group. Viral particles in the podocytes, endothelial cells and tubular epithelium initially reported, but this has been later questioned.³⁰ Chronic endothelial injury with multi-lamellation of the peritubular capillaries resembling chronic AMR, was described in one native kidney biopsy after COVID-19,³¹ indicating possible immunological events involved in the pathogenesis of the native kidneys disease.

Heterogenous histopathology suggests multifactorial etiology of kidney allograft changes occurring after COVID-19. Cytokine-mediated podocyte injury is possible in susceptible patients with SARS-CoV-2 infection, especially in those with preexisting kidney pathology. The inflammation present in patients with COVID-19 may promote acute or chronic T cell-mediated or antibody-mediated rejection, especially in KTRs with preformed donor-specific antibodies. Microthrombi in glomerular tufts and arterioles may be a consequence of a hypercoagulability which accompanies COVID-19.³²

Sepsis, hypoperfusion, exposure to nephrotoxic drugs, and injury to other organs may all contribute to the development of acute tubular injury, while immunologic reactions associated with the SARS-CoV-2 infection may trigger glomerular alterations.

Etiology of the vascular infiltration may include TCMR or COVID-19-associated vasculitis. Besides the possible immunomodulatory action of the SARS-CoV-2 virus, reduced immunosuppression during the acute COVID-19 may trigger an immunologic reaction. SARS-CoV-2 has been reported to cause vasculitis and vasculopathy directly through tissue tropism and indirect innate immunity related inflammatory response.³³ Endothelial swelling was recorded in two of our patients, one of them developed collapsing FSGS and the other developed terminal stage of allograft failure. Endotheliopathy and vasculitis have already been connected to COVID-19.^{34,35} Increased D-dimers and fibrinogen may suggest ongoing inflammation but the hypercoagulability.³⁶⁻³⁸

Decreased C3 with normal C4 may indicates activation of the alternative complement pathway which is common in post-infectious glomerulonephritis. High EBV load after acute COVID-19 may indicate immunomodulatory action of the SARS-CoV-2. These findings will require additional evaluations with careful follow-up due to increased risk of malignancy associated with the EBV infection. We will continue

to follow trends in EBV viral load and carefully balance the immunosuppression.

Interestingly, a case of MPGN (patient 6) may present a C3 glomerulonephritis given the lack of immunoglobulin and light chain staining. She had a severe disease course with low systemic C3 and extensive reactivation of both CMV and EBV which may both contribute to development of MPGN.^{39–42}

The absence of viral inclusion bodies in the biopsy findings support the secondary effect of viral infection on kidney allograft cells, and goes against direct SARS-CoV-2 related allograft endothelial cell inflammation and dysfunction. Still, delay between initial SARS-CoV-2 infection and renal allograft biopsy may be associated by viral clearance from the kidney and the absence of viral particles from the biopsy specimens.

Collapsing glomerulopathy is associated with various conditions, including viral infections, autoimmune diseases, hemophagocytic syndrome, glomerular ischemia and drug exposure such as interferon and pamidronate. The presence of the apolipoprotein L1 (APOL1) high-risk genotype is a major risk factor for collapsing glomerulopathy in African Americans.⁴³ It seems possible that SARS-CoV-2 infection may present a "second" hit in people of African ancestry with APOL1 risk alleles inducing an immune dysregulation. Our patient is of Roma origin. We had no possibility to determine the APOL1 genotype, and there is no data regarding the APOL1 in Roma population.

Treatment options in our patients were limited. Recent infection and poor overall status disable aggressive approach. Combination of the immunomodulatory effects of IVIG accompanied with the immunosuppressive and anti-inflammatory actions of steroids may be an adequate treatment strategy.

Descriptive nature is the main limitation of our study. Number of cases is small with short follow-up. However, COVID-19 has been recognized over the last 18 months and our contact with this condition is generally short. Still, it is the most extensive series of post-COVID-19 renal allograft histopathology findings present to date. We could not determine the expression of SARS-CoV-2 in biopsy samples. Additionally, we had no possibility to determine the APOL1 genotype in our patient of Roma origin with collapsing FSGS. All patients underwent indication biopsies, which disable the generalization of our results. Finally, all but one patient had preexisting kidney allograft pathology, which may bias our results, while fortuitous associations with COVID-19 cannot be ruled out.

In conclusion, diverse kidney pathology may be found in SARS-CoV-2-infected renal transplant patients. It seems that viral infection may affect the immune system with triggering of glomerular diseases, while the acute tubular injury is likely multifactorial etiology. None of our patients had signs of viral inclusions in kidney cells. Further studies are needed to elucidate the role of SARS-CoV-2 in development of renal allograft dysfunction after the COVID-19.

AUTHOR CONTRIBUTORS

N.B.J. initiated the study, participated in study planning, designed data collection tools, and questionnaire, monitored data collection, drafted and revised the paper. I.J., V.F.C., L.K., J.K., Z.D., M.F. contributed to study planning, administered and monitored data collec-

tion, and revised the paper. B.J. participated in study planning, analysis, and revising the paper. M.C. and S.B. performed histopathology. Z.K. contributed to study conception, study planning, data collection and monitoring, analysis and revised the paper. All authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

CONFLICT OF INTEREST

None.

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