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Osmotic Tubulopathy and Acute Thrombotic Microangiopathy in a Kidney Transplant Recipient With a Breakthrough SARS-CoV-2 Infection

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Acute kidney injury is a known complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for which many different pathophysiological processes have been reported. Here, we present a case of a 45-year–old kidney transplant recipient with a breakthrough SARS-CoV-2 infection complicated by an episode of acute kidney injury 26 months after transplant. She had minimal respiratory symptoms, pancytopenia, mild hematuria, and proteinuria. A kidney biopsy revealed acute thrombotic microangiopathy (TMA) as well as an osmotic tubulopathy. The TMA was favored to be secondary to the SARS-CoV-2 infection because other etiologies for TMA, such as acute calcineurin inhibitor toxicity and acute antibody-mediated rejection, were excluded. The osmotic tubulopathy was favored to be secondary to remdesivir therapy, specifically related to the sulfobutylether-β-cyclodextrin solubilizing carrier agent used in its formulation. The patient's kidney function improved after resolution of the SARS-CoV-2 infection. This case illustrates a unique occurrence of kidney injury secondary to SARS-CoV-2 infection and anti–COVID-19 therapy.

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INTRODUCTION

Kidney injury is a prominent component of the clinical spectrum of coronavirus disease 2019 (COVID-19). Widely disparate rates of acute kidney injury (AKI) are reported among hospitalized patients with COVID-19, ranging from 0.5%-37%.[1] AKI appears to involve a complex process driven by virus-mediated injury, cytokine storm, angiotensin II pathway activation, dysregulation of complement, hypercoagulation, and microangiopathy interacting with common and known risk factors for AKI. Patients with COVID-19 can also develop glomerular pathologies.[2,3] Moreover, novel antiviral pharmaceuticals are in use, and their potential for kidney toxicity is yet to be fully explored. We report a case of osmotic injury associated with antiviral therapy, another reported pattern of tubular pathology related to COVID-19.

CASE REPORT

A 45-year–old woman with kidney failure secondary to collapsing glomerulopathy received a living unrelated kidney transplant, which was complicated by acute cellular rejection 1 month after transplant treated with intravenous methylprednisolone. Immunosuppression medications were tacrolimus 3 mg twice daily, mycophenolate mofetil 750 mg twice daily, and prednisone 5 mg daily. Her medical history was also significant for normocytic anemia (attributed to chronic kidney disease and immunosuppression), hypertension, obesity (weight, 225 lb; body mass index, 37.4 kg/m^2), sleeve gastrectomy 25 months after transplant, obstructive sleep apnea, gestational diabetes, gestational hypertension, and preeclampsia 4 years before transplant. She had received 2 doses of Moderna COVID-19 vaccine 4 months before presentation. Tacrolimus trough 3 days before presentation was 7.1 ng/mL.

Twenty-six months after transplant, she presented with nausea, vomiting, cramping abdominal pain, and an inability to tolerate oral intake for 4 days. She was afebrile, tachycardic, and hypertensive (137/96 mm Hg) but not hypoxic. She was in no acute distress and had moist mucous membranes, clear respiratory sounds, no edema, and abdominal tenderness. The result of nasopharyngeal swab polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 was positive. She had nonoliguric AKI with a serum creatinine level of 5.86 mg/dL (baseline 2.2 mg/dL; attributed to donor size mismatch), pancytopenia, and elevated lipase (Table 1). She had 1+ protein, 3+ blood, and positive leukocyte esterase (Table 2). Urine culture grew pansensitive *Escherichia coli*, which was treated with ceftriaxone. Computed tomography with oral contrast showed no contrast extravasation or free intraperitoneal air and multifocal ground-glass opacities in the lung bases. An ultrasound duplex of the allograft was unremarkable.

After fluid resuscitation, mycophenolate mofetil was discontinued because of COVID-19. The patient received 1 dose of the monoclonal antibody (casirivimab/imdevimab 1,200 mg in sodium chloride 0.9% 65 mL infusion) for COVID-19, and remdesivir 200 mg was given intravenously for 1 dose on the same day of presentation, followed by 100 mg daily intravenously for 4 additional doses. Because of the absence of hypoxemia, dexamethasone was not administered. Her nausea and vomiting resolved. However, her creatinine level continued to increase to 7.06 mg/dL on hospital day 7. Findings for donor-specific antibodies were negative. A kidney biopsy was performed.

Table 1. Laboratory Values

			Hospital Days				
Laboratory	**Reference Range**	**Unit**	**0**	**1**	**5**	**7**	**11**
Sodium	135-146	mmol/L	141	139	142	144	142
Potassium	3.6-5.3	mmol/L	4.4	3.5	3.4	3.7	3.7
Chloride	96-106	mmol/L	108	106	106	107	104
Total CO_2	20-30	mmol/L	18	19	22	21	23
Urea	7-22	mg/dL	50	51	54	57	58
Creatinine	0.6-1.3	mg/dL	5.86	5.97	6.72	7.06	5.91
Glucose	65-99	mg/dL	108	103	97	96	102
eGFR		mL/min/1.73 m^2	9	8	8	6	9
Calcium	8.6-10.4	mg/dL	8.8	8.5	8.4	9	8.9
Magnesium	1.4-1.9	mg/dL	1.4	1.7	1.5	1.7	1.6
Phosphorus	2.3-4.4	mg/dL	3.7	4	3.9	3.9	3.7
Albumin	3.5-4.9	g/dL	3.5	3.5	3.5	3.7	
Total bilirubin	0.1-1.2	mg/dL	1	1	0.9	1.1	
AST	13-47	U/L	23	24	33	42	
ALT	9-64	U/L	14	13	23	43	
ALP	37-113	U/L	86	77	66	69	
Ferritin	8-180	ng/mL			1,038	971	739
LDH	125-256	U/L			512	550	437
D-Dimer	<0.6	ng/mL			0.8	1.45	0.7
CRP	<0.9				6.62	1.1	0.6
INR/PTT	PTT 11.5-14.4	s				1.1/13.9	
Hemoglobin	11.6-15.2	g/dL	9.5	9.2	8.3	8.7	7.6
Hematocrit	34.9%-45.2%	%	29.6	28.2	27	28.1	24.5
White blood cell	4.16-9.95	k/μL	2.96	3.61	3.39	4.80	5.78
Platelet	143-398	k/μL	89	82	125	150	143
Abs neutrophil	1.80-6.90	k/μL	1.47	2.48	1.39	2.29	3.28
Abs lymphocyte	1.30-3.40	k/μL	0.44	0.64	1.23	1.43	0.9
Lipase	9-63	U/L	398				
Amylase	310-124	U/L	222				
Tacrolimus trough		ng/mL		9.8	11.3	12.5	2.7
CMV	Not detected				<137		
TSH				1.3			

Abbreviations: Abs, Absolute; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CMV, cytomegalovirus; CO_2, carbon dioxide; CRP, C-Reactive protein; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, prothrombin time; TSH, thyroid stimulating hormone.

The biopsy specimen (Fig 1) was composed of cortical tissue containing 49 glomeruli (13 globally sclerotic). At least 30% of the patent glomeruli and focal arterioles exhibited segmental luminal fibrin and platelet thrombi. Most uninvolved glomeruli exhibited variable ischemic changes. Proximal tubules displayed diffuse coarse to isometric cytoplasmic vacuolization. There was acute tubular injury and 20%-25% interstitial fibrosis/tubular atrophy. There was no significant interstitial inflammation, tubulitis, peritubular capillaritis, or glomerulitis. Arteries exhibited moderate to severe intimal sclerosis. Arterioles exhibited mild intimal hyalinosis without nodular medial hyalinosis. No oxalate crystals were present. Immunofluorescence studies demonstrated fibrinogen staining of focal glomerular thrombi, segmental granular mesangial C3 staining (2-3+), and negative C4d. Ultrastructural studies demonstrated numerous enlarged distended lysosomes filled with lucent material with proximal tubule cytoplasm. Glomerular capillary loops were corrugated, consistent with ischemia, and displayed mild endothelial cytoplasmic swelling. Occasional tubuloreticular inclusions were present. There were no double contours or viral particles. There were segmental small mesangial electron dense deposits. Peritubular capillary basement membranes were normal.

The kidney biopsy interpretation was acute thrombotic microangiopathy (TMA), acute tubular injury with osmotic tubulopathy, and low-grade glomerular C3 deposition, possibly infection-related.

Additional diagnostic testing for etiologies of thrombotic microangiopathy was obtained: ADAMTS13 (von Willebrand factor protease) activity, 118% (reference value, ≥67%); haptoglobin, 10 mg/dL (reference range, 21-210 mg/dL); C3, 91 mg/dL (reference range, 76-165 mg/

Table 2. Urine analysis

	Reference Range	Unit	2 mo Prior Admission	Hospital Day 0	3 mo After Discharge
Urine color			Yellow	Yellow	Yellow
Specific gravity	1.005-1.030		1.021	1.011	1.015
pH, urine	5.0-8.0		5.5	5.5	6.0
Blood	Negative		2+	3+	Negative
Bilirubin	Negative		Negative	Negative	Negative
Ketones	Negative		Negative	1+	Negative
Glucose	Negative		Negative	Negative	Negative
Protein	Negative		Negative	1+	1+
Leukocyte esterase	Negative		Negative	1+	Negative
Nitrite	Negative		Negative	Negative	Negative
RBC per μL	0-11	cells/μL	48	>1,000	5
WBC per μL	0-22	cells/μL	3	56	6
RBC per HPF	0-2	cells/HPF	10	>210	1
WBC per HPF	0-4	cells/HPF	1	11	1
Bacteria	Absent			Present	
Squamous epithelial cells	0-17	cells/μL		3	3
Sodium, random urine		mg/dL		82	
Creatinine, random urine		mg/dL		93.2	
Urea nitrogen, random urine				430	
Urine albumin to creatinine ratio	<30	μg/mg		63	
Urine protein to creatinine ratio	0.0-0.4			0.3	

Abbreviations: HPF, High-power field; RBC, red blood cell; WBC, white blood cell.

dL); C4, 37 mg/dL (reference range, 14-46 mg/dL), and complement activity alternative pathway, 136 % (reference value, >59%). Peripheral smear did not show schistocytes.

During her hospitalization, tacrolimus dose was adjusted because of the supratherapeutic tacrolimus level attributed to CYP3A4 inhibition by remdesivir. The

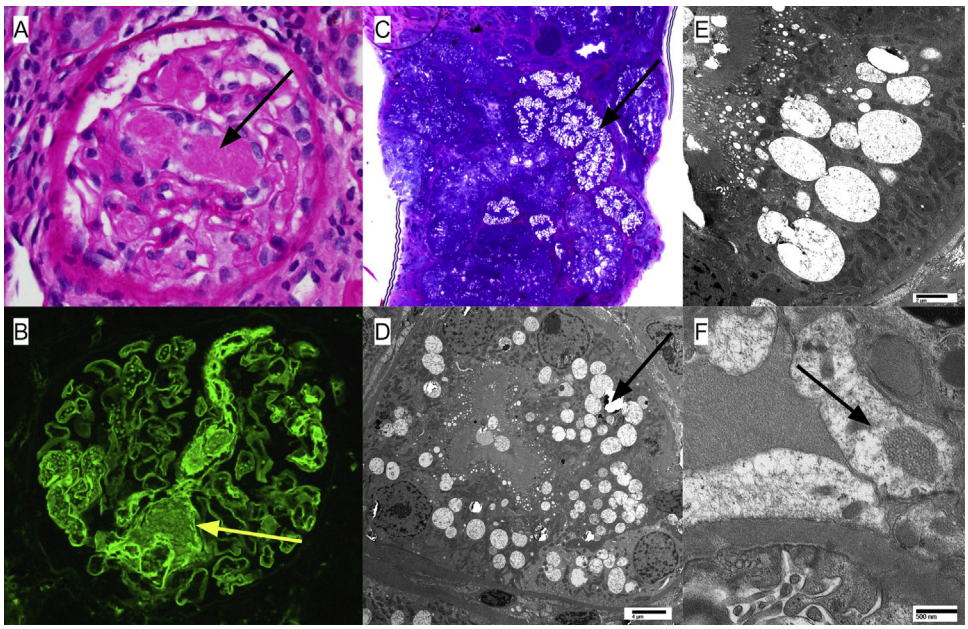

Figure 1. Acute glomerular predominant thrombotic microangiopathy and osmotic tubulopathy. Glomeruli with luminal thrombi (A) periodic acid–Schiff stain (original magnification, ×400), (B) fibrinogen staining of fibrin thrombus (original magnification, ×400). Arrows point to thrombi. (C) Prominent tubular cytoplasmic vacuolization (toluidine blue stain; original magnification, ×400). Arrow points to tubular cytoplasmic vacoulization. (D and E) Electron micrograph of proximal tubule with cytoplasmic vacuoles. Arrow points to tubular cytoplasmic vacuolization. (F) Tubuloreticular inclusion (arrow) in glomerular endothelial cells.

patient's kidney function started to improve on hospital day 9. The serum creatinine level was 5.91 mg/dL before discharge and 3.34 mg/dL 1 week after discharge. The most recent serum creatinine level was 3.42 mg/dL, which was 2 months after her admission.

DISCUSSION

TMA associated with COVID-19 has been previously reported.[2] Evidence suggests that severe acute respiratory syndrome coronavirus 2 infection leads to cytokine storm–mediated kidney injury through the activation of the alternative pathway of the complement rather than direct viral infection of the kidney.[4] The presence of low-grade C3 deposition within the glomerulus seen in this case may further implicate the alternative complement activation or, possibly, a concurrent low-grade infection–related glomerulopathy. Interestingly, COVID-19–associated kidney diseases, including TMA, often occur even with mild pulmonary and systemic COVID-19 disease.[2]

Etiologies for TMA are diverse, and there are no specific findings on kidney biopsy specimens that can discriminate among them. Alternative differential diagnoses for TMA in this case include tacrolimus-induced TMA and active antibody-mediated rejection. The patient's tacrolimus trough was in the 7-9 ng/mL range for at least 1 year before presentation, and her serum creatinine level was stable until the severe acute respiratory syndrome coronavirus 2 infection. The patient also had multiple prior allograft biopsies without evidence of acute or chronic tacrolimus effects. Tacrolimus trough 3 days before presentation was 7.1 ng/mL, and the thrombocytopenia was improving during her hospital stay despite development of slightly supratherapeutic tacrolimus trough levels. Thus, tacrolimus-induced TMA is a less likely etiology for the patient's AKI or pathologic findings. Because this patient had no other evidence for antibody-mediated rejection (eg, no microvascular inflammation, C4d negative, or serum donor-specific antibodies), the possibility of antibody-mediated rejection associated TMA was thought to be unlikely.

Other less likely etiologies of TMA, such ADAMTS13 deficiency, other infections, antiphospholipid antibodies, and drug-associated TMA, were also ruled out. An underlying complement-mediated TMA with COVID-19 as a trigger is also a possibility; however, a more extensive complement system evaluation (eg, genetic studies) was not performed because the patient's kidney function improved after COVID-19 resolution.

Osmotic tubulopathy describes a morphologic pattern, with vacuolization and swelling seen when proximal tubules are overwhelmed by a load of indigestible carbohydrates. Injury is favored to be because of pinocytosis with uptake into lysosomes.[5] Osmotic tubulopathy is generally associated with mannitol, low-molecular-weight dextrans, intravenous radiologic contrast media, hydroxyethyl starch, excess glucose, methanol, and gelatin.[6] Our patient did not receive any of these agents. The patient's blood glucose was normal or near normal, and urine glucose was negative at the time of admission. Additionally, no reports suggest that casirivimab/imdevimab causes AKI, tacrolimus interaction, or pathologic changes on kidney biopsy, and it has been tolerated by kidney transplant patients.[7,8]

Remdesivir is a nucleotide analog that inhibits viral ribonucleic acid–dependent ribonucleic acid polymerase.[9] Remdesivir formulation contains sulfobutylether-β-cyclodextrin as a solubilizing carrier agent, and we postulate that this contributed to osmotic tubulopathy in our patient. At least 1 prior case of remdesivir osmotic tubulopathy has been reported.[10] Sulfobutylether-β-cyclodextrin is a large, cyclic oligosaccharide that is predominantly excreted through glomerular filtration.[11] A preclinical animal study suggested that reversible cytosolic vacuolation in kidney tubular epithelial cells was observed at as low as 160 mg/kg in rats.[10] Each 100 mg of lyophilized powder and solution of remdesivir contain 3 and 6 g of sulfobutylether-β-cyclodextrin, respectively, and our patient received a total of 600 mg of the lyophilized form of remdesivir. The use of remdesivir with decreased kidney function is relatively safe. Although 11.7 % of kidney transplant recipients reported elevated levels of serum creatinine after remdesivir therapy, none required discontinuation of therapy.[12]

The primary differential diagnosis of the tubular vacuolar change seen in this case is calcineurin inhibitor toxicity, which is characterized by isometric vacuolization and may be indistinguishable from osmotic tubulopathy. The tubular cytoplasmic vacuolization observed in our case was diffuse and variably coarse, which is not typical for acute calcineurin inhibitor toxicity, which usually shows focal fine isometric vacuolization. Other convincing morphologic features of calcineurin inhibitor nephrotoxicity (eg, myocyte cytoplasmic vacuolization and dropout, focal nodular hyalinosis) were not present.[13] Thus, we believe that the osmotic tubulopathy was mostly likely because of remdesivir therapy. Interestingly, remdesivir is a weak CYP3A4 inhibitor that may lead to increased tacrolimus levels and could explain the slightly supratherapeutic tacrolimus trough levels that developed during the patient's admission.[14]

In summary, the patient's clinical course and kidney biopsy findings support that this patient's AKI was most likely secondary to a COVID-19–associated TMA, possibly exacerbated by an osmotic tubulopathy secondary to remdesivir therapy. This case illustrates that severe COVID-19–associated kidney disease can occur even with an otherwise mild severe acute respiratory syndrome coronavirus 2 infection and that novel treatments such as remdesivir may result in renal biopsy histologic perturbations.

ARTICLE INFORMATION

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