Osmotic Tubulopathy in a Patient With COVID-19 Treated With Remdesivir

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has posed unique challenges to nephrology. COVID-19–associated acute kidney injury occurs in as high as 36.6% of patients,[S1] with the most common etiology being acute tubular injury due to hemodynamic changes and a proinflammatory milieu. In addition to acute tubular injury, patients with COVID-19 can also develop a variety of glomerular pathologies, including primary podocytopathies and immune-mediated glomerular diseases (membranous nephropathy, lupus nephritis, anti–glomerular basement membrane disease).[1] Here, we report another pattern of tubular pathology related to COVID-19, osmotic injury associated with antiviral therapy.

CASE PRESENTATION

A 33-year-old African American obese man with past medical history of poorly controlled type 2 diabetes mellitus and hypertension presented with left-sided abdominal pain for 2 days. His nasopharyngeal swab polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 was positive. He was febrile, 38.1 °C (100.6 °F), tachycardic, 106 beats per minute, and blood pressure of 140/79 mm Hg. Respiratory rate of 18 per minute, and oxygen saturation of 98% on room air. He was not in acute distress and was noted to have dry mucous membranes, clear respiratory sounds, and no pedal edema. Computed tomography showed ground glass opacities in both lung bases compatible with COVID-19. Initial laboratory values showed acute kidney injury and hyponatremia

(Table 1). The patient was admitted for management of COVID-19 pneumonia and acute kidney injury.

Hospital Course

After fluid resuscitation, creatinine further rose to 1.98 mg/dl, and hyponatremia worsened to 123 mmol/dl (127 mmol/dl, corrected with glucose). Urine studies suggested the syndrome of inappropriate antidiuretic hormone secretion (Table 2). The 24-hour urine collection confirmed the nephrotic range proteinuria: total protein of 12.8 g, with 8.6 g being albumin. The patient was obese (body mass index 34.1) and had poorly controlled diabetes type 2 since age 20; hemoglobin A1c on admission was 12.1%, but his urine microalbumin was 677 mg/g creatinine 1 year before the admission, with associated baseline creatinine of 1.58 mg/dl. Renal ultrasound showed bilateral echogenic cortices with slightly enlarged kidneys (right kidney at 13.1 cm and left kidney at 13.4 cm) without evidence of hydronephrosis, and renal arteries and veins were patent.

On hospital day 6, the patient developed worsened bilateral opacities on chest radiograph with associated hypoxemia. A course of remdesivir and dexamethasone was started. Remdesivir 200 mg was given i.v. for 1 dose, followed by 100 mg i.v. per day for 4 additional doses. Dexamethasone (10 mg per day i.v.) was given concomitantly for 6 doses. Blood glucose during the hospitalization was well-controlled by insulin. Additional laboratory values revealed total complement >95 unit/ml (reference 42–95 units/ml), C3 115 units/ml (reference 90–180 units/ml), C4 56 units/ml (reference 10–40 units/ml). Serology for anti-neutrophil cytoplasmic antibodies, anti-myeloperoxidase, anti-

Table 1. Laboratory values on admission and during the hospital course

Laboratory	Reference range	Unit	Hospital day 0	Hospital day 5	Hospital day 7
Sodium	136–145	mmol/l	131	123	130
Potassium	3.4–5.1	mmol/l	4.6	4.9	4.7
Chloride	98–107	mmol/l	93	89	95
Bicarbonate	22–31	mmol/l	25	23	22
Urea	6–23	mg/dl	30	31	38
Creatinine	0.5–1.2	mg/dl	1.86	1.98	2.38
Glucose	70–100	mg/dl	488	355	198
eGFR	>59	ml/min per 1.73 m^2	46	43	35
Calcium	8.8–10.7	mg/dl	9	8.1	8.5
Magnesium	1.7–2.6	mg/dl	1.8		
Albumin	3.5–5.2	g/dl	3.8	2.8	2.8
Total bilirubin	0.0–1.0	mg/dl	0.4	0.3	0.2
AST	10–50	U/l	12	96	191
ALT	10–50	U/l	17	130	200
ALP	35–130	U/l	85	70	78
Ferritin	30–400	μg/l	291		1881
LDH	135–225	U/l	186		
D-dimer	<500	ng/ml	276		536
PT-INR	0.9–1.1	-	1.1		
Serum osmolality	280 – 296	mOsm/kg water		278	
Hemoglobin	13.5–18.0	g/dl	11.2	10.4	11
Hematocrit	40.0–54.0	%	33.9	30.4	31.7
White blood cell	4–10	K/μl	5.59	4.47	4.7
Platelet	150–450	K/μl	213	193	201
Abs neutrophil	1.92–7.6	K/μl	3.88	3.99	3.99
Abs lymphocyte	0.72–4.10	K/μl	0.91	1.37	1.37

Abs, absolute; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; PT-INR, prothrombin time and international normalized ratio.

proteinase-3, anti-PLA2R antibodies, HIV, hepatitis B surface antigen, and hepatitis C virus antibodies were all negative. Serum protein electrophoresis did not reveal evidence of M-spike. The serum-free light chain (FLC) ratio was 1.08 (kappa FLC 101.2 mg/l, lambda FLC 93.5 mg/l). The patient did not receive osmotic agents that are associated with osmotic tubulopathy, such as, but not limited to, i.v.Ig, mannitol, low-molecular weight dextrans, radiologic contrast media, hydroxyethyl starch, excess glucose, methanol, and gelatin.

A kidney biopsy was performed to determine the etiology of proteinuria.

Kidney Biopsy

The sample consisted of renal cortex with 31 glomeruli, of which 3 were globally sclerosed, 2 were segmentally sclerosed, and 11 were hypoperfused. The nonsclerosed glomeruli were enlarged. Although a classic example of a collapsing lesion is not seen on multiple levels examined, 2 glomeruli showed features strongly suggestive of segmental capillary collapse, with proliferating epithelial cells filling the Bowman space (Figure 1a). The mesangium was found to be expanded by the extracellular matrix, with few periodic acid–Schiff–positive Kimmelstiel-Wilson nodules. Nonatrophic tubules were enlarged and showed mild

distension of the lumen. The tubular epithelium was focally flattened with multifocal loss of the brush border of the proximal tubular epithelium. Tubular epithelial cells revealed diffuse prominent vacuolization (Figure 1b). Several tubules contained necrotic cellular debris and periodic acid-Schiff–positive organizing casts. The interstitium contained mild inflammation in areas of atrophy, which were composed of mononuclear cells and rare eosinophils, neutrophils, and plasma cells. Approximately 70% of the renal cortex showed tubular atrophy and interstitial fibrosis.

Ultrastructural examination revealed near-global and diffuse effacement of glomerular visceral epithelial cell foot processes (Figure 1c) and prominent cytoplasmic vacuolization of many proximal tubular epithelial cells (Figure 1d). Immunofluorescence and electron microscopy showed no evidence of paraprotein or immune complex deposition.

The immunohistochemical stain for severe acute respiratory syndrome coronavirus 2spike protein was negative in the kidney (Figure 1e).

Follow-up

The patient's oxygen requirement improved, and creatinine continued to improve to 1.65 mg/dl during

Table 2. Urine analysis and urine chemistry

Laboratory	Reference range	Unit	Hospital day 0	Hospital day 5	Hospital day 7
Bilirubin	Negative		Negative		
Blood	Negative		2+		
Clarity	Clear		Clear		
Color	Yellow		Yellow		
Glucose	Negative		3+		
Ketones	Negative		Negative		
Leukocyte esterase	Negative		Negative		
Nitrites	Negative		Negative		
pH	4.5–8.0		5		
Protein	Negative		3+		
Specific gravity	1.003–1.035		1.013		
Urobilinogen	Negative		Negative		
Red blood cell	0–2	/hpf	3		
White blood cell	<10	/hpf	1		
Bacteria	Negative	/hpf	1+		
Squamous cells	Negative	/hpf	Negative		
Hyaline casts	0–2	/lpf	6		
Granular casts	none	/lpf	4		
Urine osmolality	150–1150	mOsm/kg water		304	
Urine sodium		mmol/l		30	
Urine protein	0–15	mg/dl		648	715
Urine albumin	0.0–2.0	mg/dl		394	479
Urine creatinine		mg/dl		52	
UPCR		g/g		12.5	
UACR		mg/g		7576	
Total urine protein	0–165	mg/24 h			12,870
Total urine albumin	0–30	mg/24 h			8622
Urine volume		ml/24 h			1800

hpf, high-power field; lpf, low-power field; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.

the course of i.v. remdesivir therapy. The patient declined genetic testing of *APOL1* risk alleles.

DISCUSSION

Our case highlights 2 histopathologic findings developing in the setting of severe acute respiratory syndrome coronavirus 2 infection: collapsing glomerulopathy and osmotic tubulopathy. Collapsing glomerulopathy is one of the characteristic glomerular pathologies reported in COVID-19, as seen also in other viral illnesses, such as HIV and parvovirus B19, with Apolipoprotein L1 risk alleles being one of the risk factors (see Supplementary discussion).[S2-S5] In our patient, although the kidney biopsy showed a significant nodular diabetic glomerulosclerosis, the extent of proteinuria (12 g/d) was much more than what could be explained solely by the progression of diabetic kidney disease. The patient had only 677 mg/g of albuminuria 1 year before this presentation, and COVID-19 infection likely worked as a second hit to cause diffuse podocyte injury, which resulted in massive proteinuria.

Osmotic tubulopathy is a finding characterized by cytoplasmic vacuolization, seen when proximal tubules become overwhelmed by the load of indigestible carbohydrates, such as sucrose, dextrans, hydroxyethyl starch, mannitol, and iodinated contrast media.[2] Remdesivir is a nucleotide analog that is used to treat patients with COVID-19 both in severe and mild disease. Due to its limited water solubility, remdesivir formulation contains sulfobutylether-β-cyclodextrin (SBECD) as a solubilizing carrier agent, and we postulate that this contributed to osmotic tubulopathy in our patient.

First-generation cyclodextrin carrier agents, α- and β-cyclodextrin, are cyclic oligosaccharides consisting of a macrocyclic ring of glucose subunits joined by α-1,4 glycosidic bonds, and are exclusively excreted by the kidney. Due to their cyclic structure, they are resistant to hydrolysis by amylases and are associated with renal toxicity due to osmotic tubulopathy.[3]

SBECD is a second-generation cyclodextrin, engineered to enhance ionization properties by adding a sulfobutyl ether group.[4] Preclinical animal study suggested that, although cytosolic vacuolation in kidney tubular epithelial cells was observed at as low as 160 mg/kg in rats, serum creatinine remained normal, and the histologic changes were reversible within 1 month
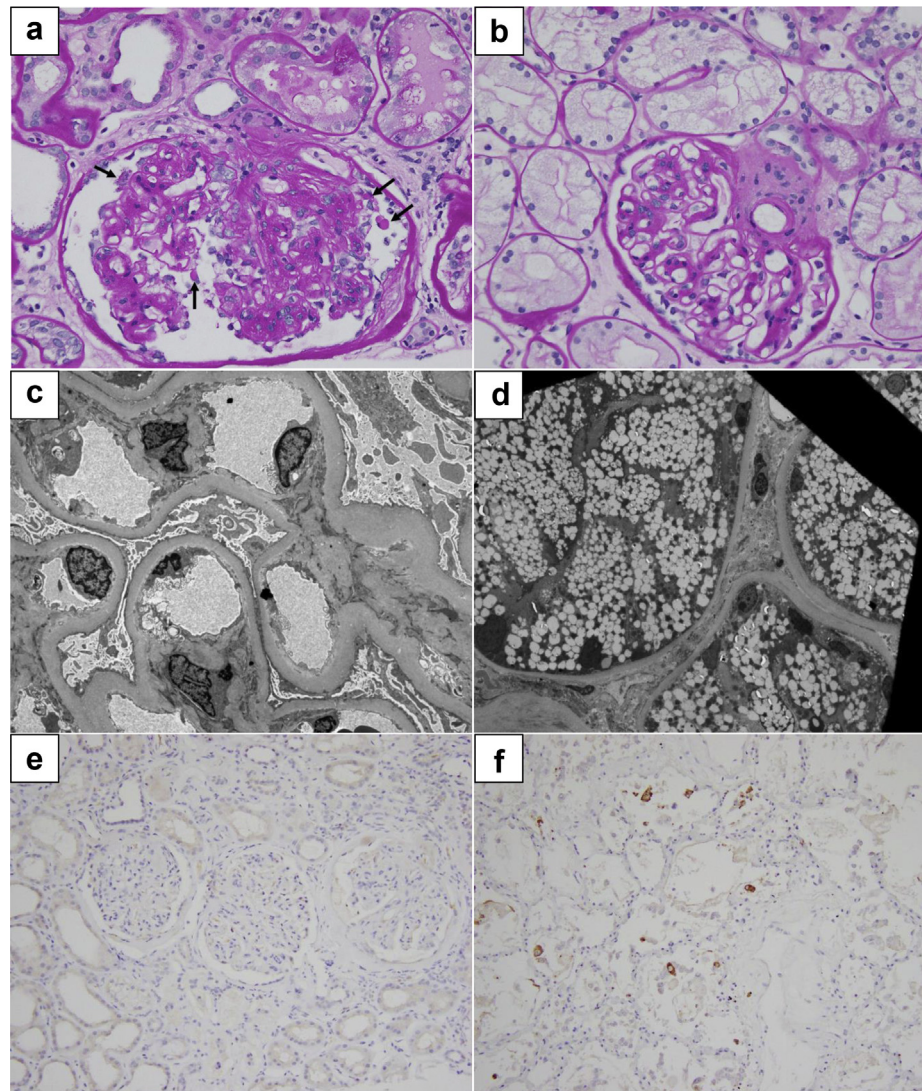
Figure 1. (a) Glomerulus with features suggestive of collapsing glomerulopathy; there is segmental collapse of capillaries and increased number of epithelial cells within the Bowman space. Several epithelial cells also reveal coarse protein reabsorption granules (arrows) (periodic acid-Schiff, original magnification ×40). (b) Proximal tubules with diffuse microvesicular degeneration. The glomerulus reveals moderate expansion of the mesangium by matrix (periodic acid-Schiff, original magnification ×40). (c) The electron microscopy reveals markedly thickened glomerular basement membranes and diffuse effacement of podocyte foot processes (original magnification ×4100). (d) Proximal tubular epithelial cells show extensive vacuolization of the cytoplasm (original magnification ×1640). (e) The renal cortical tissue is negative for severe acute respiratory syndrome coronavirus 2 antigens by immunoperoxidase staining (original magnification ×20). (f) Positive control for severe acute respiratory syndrome coronavirus 2 antigens by immunoperoxidase staining. Lung tissue obtained at autopsy from a patient who died of Coronavirus Disease 2019 (original magnification ×20).

after the last dose.[5] In a clinical safety study, healthy male volunteers received up to 200 mg/kg of SBECD without acute kidney injury.

The post-marketing studies of voriconazole provide the best available real-world safety data of SBECD, as its i.v. formulation contains 3.2 g of SBECD per 200 mg voriconazole. Pharmacokinetics studies in patients receiving renal replacement therapy showed that standard loading dose of voriconazole with SBECD up to 192 mg/kg per day did not accumulate while on dialysis or continuous renal replacement therapy (further discussion in Supplementary Material).[6-8]

Currently, there are 2 formulations of remdesivir available for clinical use. The solution form and lyophilized form contain 6 g and 3 g of SBECD per 100 mg of remdesivir, respectively. Given our patient's low

Table 3. Teaching points

○ Treatment of Coronavirus Disease 2019 with remdesivir containing sulfobutylether-β-cyclodextrin could be associated with osmotic tubulopathy.
○ Risk and benefit of using remdesivir need to take into account this consideration, especially when the patient has acute kidney injury and advanced chronic kidney disease.

estimated glomerular filtration rate of 43 ml/min per 1.73 m^2, we chose the lyophilized form of remdesivir, and he received a total of 600 mg of remdesivir, corresponding to a cumulative 18 g of SBECD over 5 days before the kidney biopsy. The exposure of 3 to 6 g of SBECD per day is well below the safety threshold of 250 mg/kg per day (i.e., for our patient, 25 g/d). A recent study looked at the safety of remdesivir in 11 patients with severe acute kidney injury, and reported no significant increase in serum creatinine after remdesivir treatment,[S6] and another study also suggested the safety of remdesivir in 20 patients with estimated glomerular filtration rate <30 ml/min.[9]

Our patient's serum creatinine continued to improve after initiation of remdesivir; however, the significant vacuolization in proximal tubules is a clear and unmistakable structural sign of tubular injury. The differential diagnoses of vacuolar change seen in this case include the Armanni-Ebstein lesions characterized by larger cytoplasmic vacuolation in proximal tubules in the outer medullary regions, seen in the setting of extremely high glucosuria, and changes due to toxic or ischemic injury. Our patient had poorly controlled diabetes and had significant glucosuria at the time of presentation, which could have been a contributory factor for osmotic tubular injury. Creatinine did not seem to serve as a sensitive enough biomarker for tubular injury in our case, or hyperfiltration mechanism might have compensated and masked the tubular injury.[S7]

CONCLUSION

In addition to collapsing glomerulopathy, the treatment of COVID-19 infection with remdesivir may be associated with osmotic proximal tubulopathy (Table 3). The precise mechanism of the osmotic tubulopathy is unclear in our case, but is probably multifactorial, and clinicians should remain cautious in the use of remdesivir in patients with severe acute kidney injury or advanced chronic kidney disease.

DISCLOSURES

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

AUTHOR CONTRIBUTIONS

All authors participated in the clinical care and assembling of the data and contributed to the intellectual content and the writing of the case report. The authors reviewed and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary References
Supplementary Discussion

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