Received: 16 February 2021 | Accepted: 21 February 2021

DOI: 10.1111/tid.13598

CASE REPORT AND REVIEW OF THE LITERATURE

WILEY

Successful management of T-cell mediated rejection in a recent kidney transplant recipient with COVID-19 associated severe acute respiratory syndrome

Maha Mohamed[1] | Jeannina Smith[2] | Sandesh Parajuli[1] | Neetika Garg[1] | Fahad Aziz[1] | Didier Mandelbrot[1] | Arjang Djamali[1] | Weixiong Zhong[3]

[1]Department of Medicine, Division of Nephrology, University of Wisconsin School of Medicine, Madison, WI, USA

[2]Department of Medicine, Division of Infectious Disease, University of Wisconsin School of Medicine, Madison, WI, USA

[3]Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine, Madison, WI, USA

Correspondence
Maha Mohamed, University of Wisconsin School of Medicine and Public Health, 4165 Medical Foundation Centennial Building, 1685 Highland Avenue, Madison, WI 53705, USA.
Email: mmohamed2@wisc.edu

Funding information
The authors received no financial support for the research, authorship, and/or publication of this article.

Abstract

COVID-19-associated vasculitis has been reported as a defining feature of systemic disease including acute kidney injury. However, the understanding of COVID-19 kidney transplant-related injuries is still evolving. We report a case of AKI with isolated vasculitis (v2 lesion) in a new kidney transplant recipient with COVID-19 pneumonia.

KEYWORDS

COVID-19, Kidney Transplant, microvascular injury, T-cell Mediated Rejection

1 | CASE REPORT

1.1 | Hospital course

A 35-year-old White woman with past medical history of End Stage Kidney Disease secondary to congenital single kidney and biopsy-proven minimal change disease, non-ischemic cardiomyopathy, and mitral valve repair on warfarin, obstructive sleep apnea, and failed living-related kidney transplant underwent deceased donor kidney transplant after being tested negative for SARS-CoV-2 (rT-PCR) 17 hours prior to the surgery. Donor upper respiratory SARS-CoV-2 rT-PCR was also negative twice prior to transplant. Pre-transplant virtual cross-match was negative for Donor Specific Antibodies (DSA) (cPRA 80%, KDPI 72%, Cold Ischemia time ~7.5 hours). CMV and EBV sero-status for donor and recipient were both positive. The patient received a deceased donor kidney transplant on August 25, 2020 with rabbit Anti-thymocyte globulin induction therapy (4.5 mg/kg total dose) and was started on triple immunosuppression with tacrolimus (12 hours trough goal 8 - 10 ng/ml), mycophenolate 720 mg twice daily and prednisone 30 mg followed by taper. Post-perfusion biopsy identified 20 glomeruli, three were sclerosed in the frozen section, otherwise none of those had sclerosis (Figure 1). The

Abbreviations: ah, arteriolar hyalinosis; AKI, Acute Kidney Injury; BiPAP, Bilevel Positive Airway Pressure; C4d, complement protein 4d; cg, glomerular double contour; ci, interstitial fibrosis; CMV, Cytomegalovirus; COVID-19, 2019 novel Corona Virus Disease; cPRA, calculated Panel Reactive Antibody; ct, tubular atrophy; cv, vascular fibrous; EBV, Epstein-Barr Virus; Fio2, fraction inspiration of oxygen; g, glomerulitis; H&E, Hematoxylin and eosin stain; i, interstitial inflammation; IFTA, Interstitial Fibrosis and Tubular Atrophy; i-IFTA, interstitial inflammation in areas of interstitial fibrosis and tubular atrophy; KDPI, Kidney Donor Profile Index; mm, mesangial matrix; PAM, Programmable Array Microscopy; PAS, periodic acid–Schiff; PCO2, partial pressure of carbon dioxide; PCR, polymerase chain reaction; pO2, partial pressure of oxygen; ptc, peritubular capillaritis; rT-PCR, Real time Polymerase Chain Reaction; SARS-Cov-2, Sever Acute Respiratory Syndrome Corona virus 2; SpO2, oxygen saturation; t, tubulitis; ti, total inflammation; v, intimal arteritis.

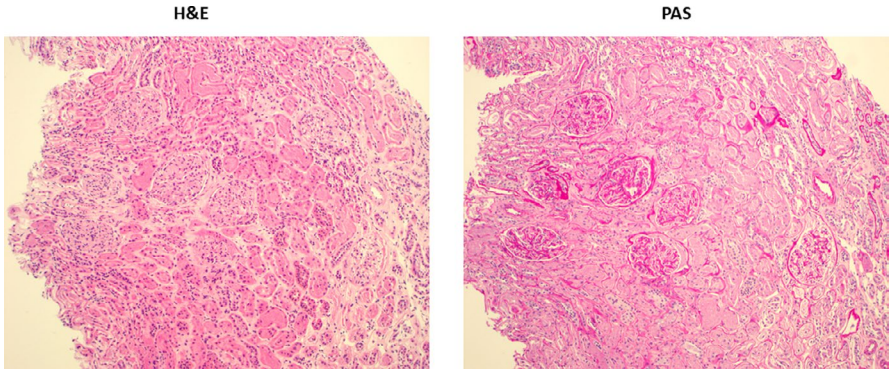

FIGURE 1 Post-reperfusion biopsy

TABLE 1 SARS-CoV-2 Laboratory Results

	Hospitalization days			
Laboratory values	1	5	13	44
White Blood cells (K/ul)	**11.7**	**11**		**5.4**
Hematocrit (%)	**23**	**26**		**30.8**
Hemoglobin (g/dl)	**7.6**	**8.7**	**7.6**	**9.7**
Creatinine (mg/dl)	**2.5**	**1.5**	**3.25**	**1.42**
eGFR (ml/min/1.73 m^2)	**27**	**44**		**48**
UPC (mg/mg)	**2.35**		**7.9**	**0.458**
B2MG (mg/L)	**14.2**	**11.8**		
Urine WBC/hpf)	**11 - 20**		**6 - 10**	**0 - 2**
Urine RBC/hpf	**> 50**		**3 - 5**	**0 - 2**
CRP	**22**	**11.9**		
LDH (U/L)	**844**	**679**		
INR	**2.3**	**1.8**	**1.1**	
Tacrolimus trough (ng/ml)	**8**		**<2**	**11.8**

TABLE 2 Post-transplant course

	17-hrs pre-surgery	Post-operative day								
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 Admission**
COVID-19 rt-PCR Nasopharyngeal	Neg									
COVID-19 Ab, IgG										
Remdesivir (mg)										
Convalescent Plasma										
Dexamethasone IV (mg)										
Tacrolimus		X	X	X	X	X	X	X	X	X
Myfortic (mg) BID		720	720	720	720	720	720	720	720	720
Prednisone (mg)		X	X	X	X	X	X	X	X	x
IVIG 500 mg/kg										
Thymoglobulin 4.5 mg/kg		X	X	X						
Creatinine mg/dl	8.2	8.2	6.8				3.2			2.19
UPC mg/mg									2.3	
Urine RBC /hpf									FF	
Allograft biopsy										
DSA	Neg									
Mechanical Ventilation										

Abbreviations: Ab, Antibodies; BID, twice daily; dl, Deciliter; DSA, Donor Specific Antibodies; FF, full filed; hpf, high power field; IgG, Immunoglobulin G; IV, Intravenous; IVIG, Intravenous Immunoglobulin; Kg, Kilogram; mg, Milligram; Neg, negative; Pos, Positive; UPC, Urine Protein/creatinine ration.

glomeruli were normal and focal few atrophic tubules with minimal interstitial fibrosis were identified, as shown in Figure 1. The patient was discharged on post-operative day 6, with a serum creatinine of 2.2 mg/dl.

On post-operative day 8, the patient complained of shortness of breath, pulse-oximetry (SpO2) ranging from 55 - 78% with the use of BIPAP. She denied cough, sore throat, rhinorrhea, loss of smell or taste, fever and she had no new gastrointestinal symptoms. On September 2, 2020, the patient was admitted for hypoxia and tachypnea with labored breathing and found to have 2 plus pitting edema. Vital signs were: respiratory rate 43 per minute, blood pressure 121/76 mmHg, pulse 79 beats per minute, temperature 97 °F, SpO2 96% on 100% FiO2 and 10/5 BiPAP. Admission arterial blood gas on 85% FiO2 was pO2 85 mm Hg, SpO2 93.6%, oxygen content 10.7 ml/dl, pH 7.47, pCO2 38 mm Hg, bicarbonate 27.5 mmol/L and nasopharyngeal swap rT-PCR for SARS-Cov-2 turned positive. On admission, her serum creatinine was 2.19 mg/dl, INR 2.3 and D-Dimer 0.89 mcg/ml (Table 1).

Admission chest x-ray showed new diffuse airspace opacities in a pulmonary edema pattern compared to the August 24, 2020 chest x-ray. The patient's respiratory status continued to worsen and on hospital day 2 she was transferred to the intensive care unit, where she underwent endotracheal intubation and mechanical ventilation. 2-dimensional echocardiography demonstrated multiple segmental motion abnormalities and an ejection fraction of 55%. She was started on dexamethasone 6 mg IV daily and she received COVID-19 convalescent plasma and a 5-day course of remdesivir in addition to azithromycin and piperacillin/tazobactam for possible hospital acquired pneumonia. Because of the noticeably short incubation period, rapid progression of the COVID-19 related respiratory failure, recent induction with rabbit-antithymocyte globulin, reported high rate of mortality among hospitalized patients with chronic kidney disease and kidney transplant, we decided to hold tacrolimus and mycophenolate sodium.[1-4]

The patient was extubated 7 days after intubation and transferred to the COVID-19 unit, where she continued requiring 4 - 6 litters oxygen by nasal cannula. On day 11 of this admission urine, the protein/creatinine ratio increased from 2.6 mg/mg on post-operative day 7 to 7.9 mg/mg. On day 13 of the admission she developed non-oliguric AKI with peak creatinine of 3.25 mg/dl (Table 2). Urinalysis showed persistent but improved hematuria and E. Faecium bacteriuria which was treated with daptomycin, given the recent transplant and presence of ureteric stent. Repeat DSA test was negative for de novo DSA. A diagnostic kidney transplant biopsy on day 14 after re-admission was performed and showed severe intimal arteritis and hyperplasia (Figures 2 and 3). Only low density mononuclear cells and no neutrophils were seen in the i-IFTA scored area. Multiple small arteries and few arterioles showed severe endothelial cell hyperplasia or swelling, some of which also showed mild or moderate intimal arteritis. Intravascular fibrin thrombi were not seen. Electron microscopy from two glomeruli recovered from the paraffin block was examined (Figure 4). The glomeruli showed normo-cellularity, no basement membrane alterations, and no electron-dense deposits (Figure 4A and 4B). There was minimal foot process effacement.

9	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**31**
Pos																		
												Pos						
200	100	100	100	100														
X																		
6	6	6	6	6	6	6	6	6	6	6	6	50	50	44	38	30	24	
Discontinued															X	X	X	X
Discontinued										360	360	360	360	360	360	360	360	360
																		30
												X						
			1.5				1.14		1.6		2.38	3.25	2.9					1.2
										7.9								
												3–5						
												X						
										Neg								
X	X	X	X	X	X	X	X											

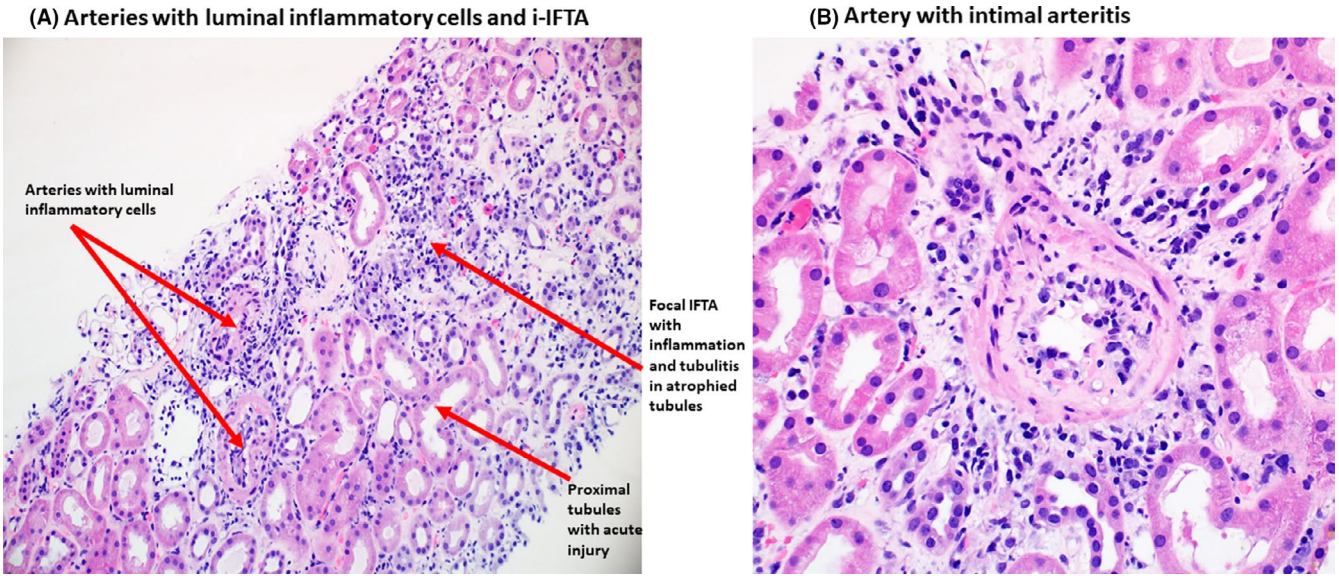

FIGURE 2 (A and B): Acute kidney transplant injury biopsy (H&E stain)

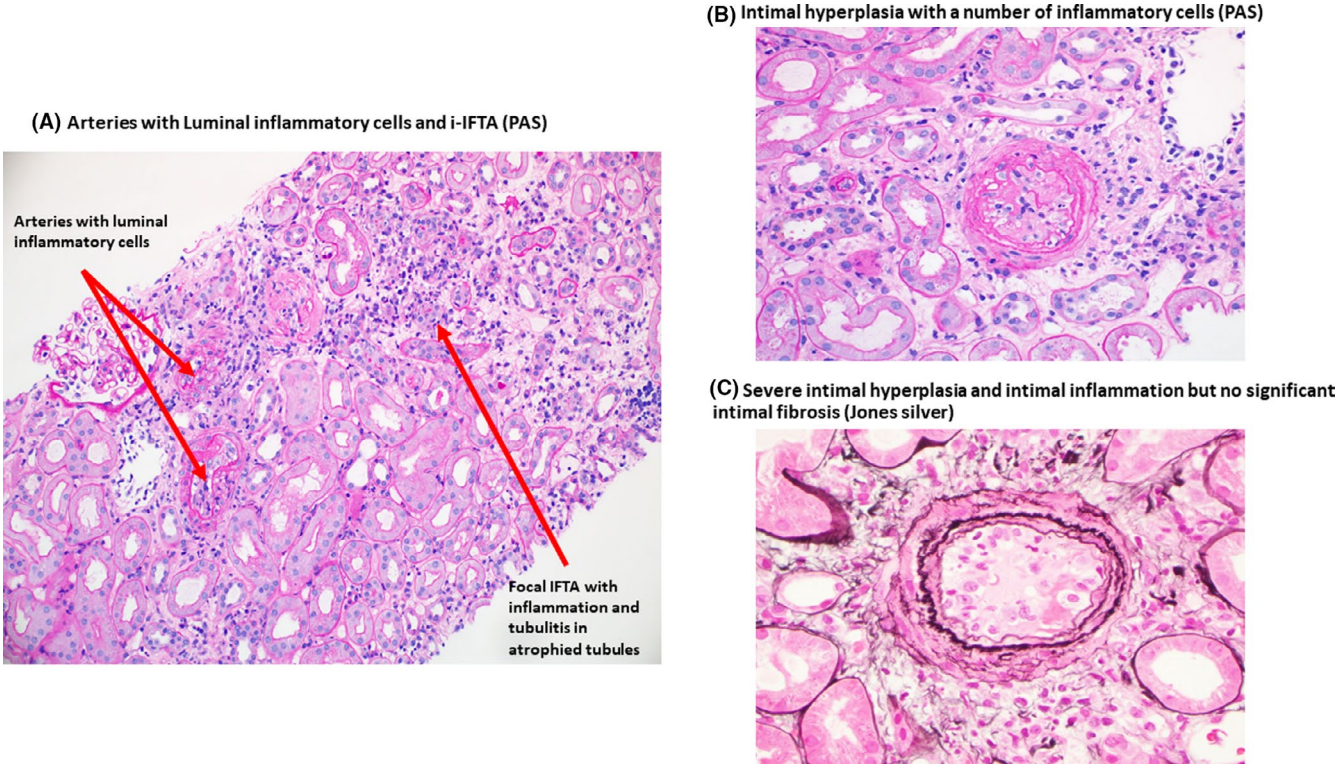

FIGURE 3 (A, B and C): Acute kidney transplant injury biopsy (PAS and Jones Silver stain)

Small arteries and arterioles showed endothelial cell swelling or hyperplasia (Figure 4C). COVID-19 virus particles were not identified. Peritubular capillaries were normal.

The patient was considered to have either T cell mediated rejection (TCMR) or virus related endothelial injury. Accordingly, the patient was treated relatively conservatively with pulse steroids (dexamethasone 50 mg) and taper. Her tacrolimus and mycophenolate sodium were resumed and she was discharged home 17 days after re-admission with a SpO2 of 94% on room air and a serum creatinine of 2.07 mg/dl. On the patient's most recent follow-up on January 14, 2021, laboratory testing demonstrated negative DSA, serum creatinine of 1.4 mg/dl and allograft follow-up biopsy showed mild interstitial fibrosis and tubular atrophy (Figure 5). She remains on mycophenolate sodium 540 mg twice daily, prednisone 5 mg daily and tacrolimus 0.5 mg twice daily with 12 hour tacrolimus trough levels of 6 - 7 ng/ml.

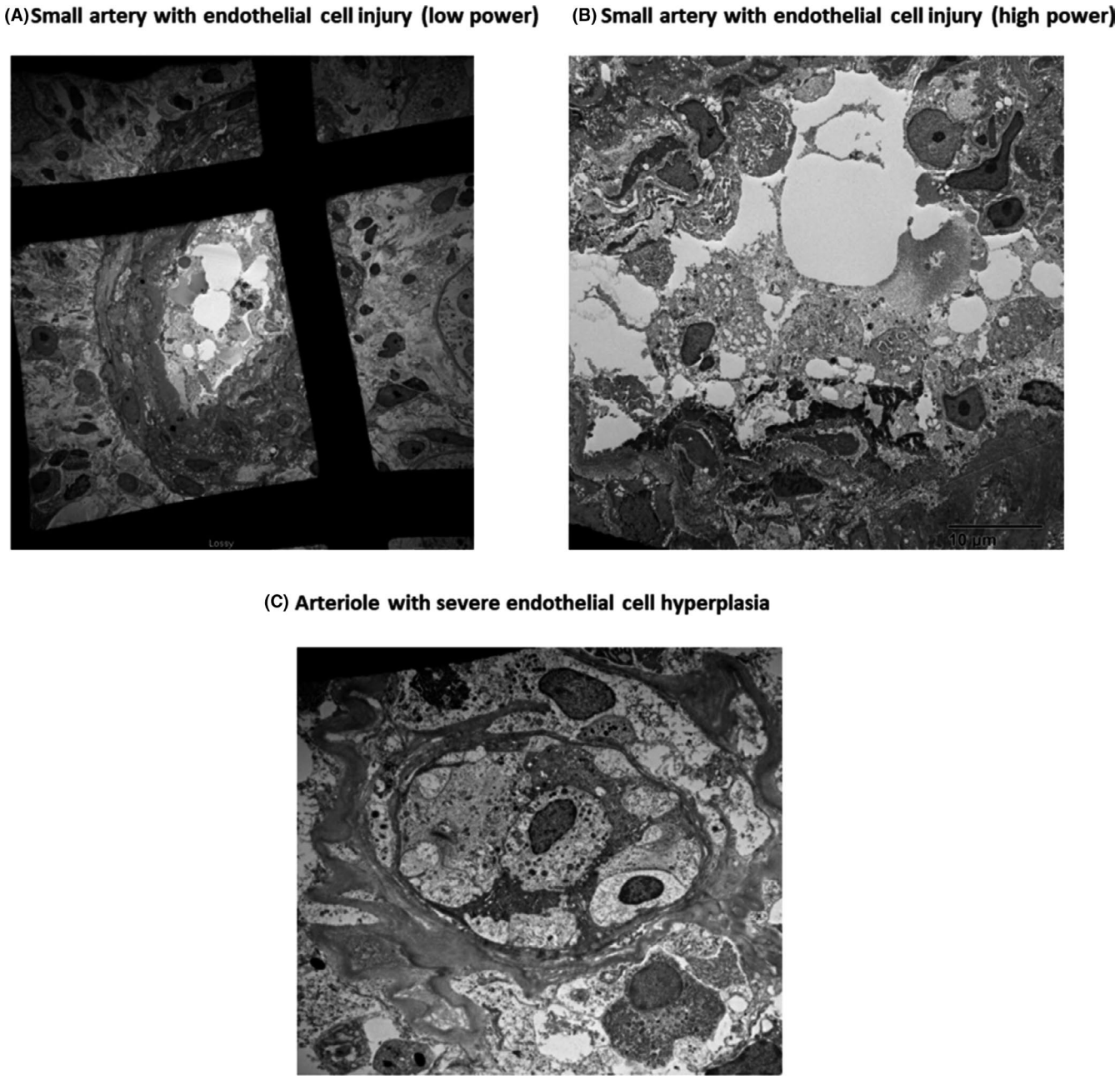

FIGURE 4 (A and B): Acute kidney transplant injury, small artery with endothelial cell injury (high and low power E&M). C, Acute Kidney transplant injury, sever endothelial cell hyperplasia (E&M)

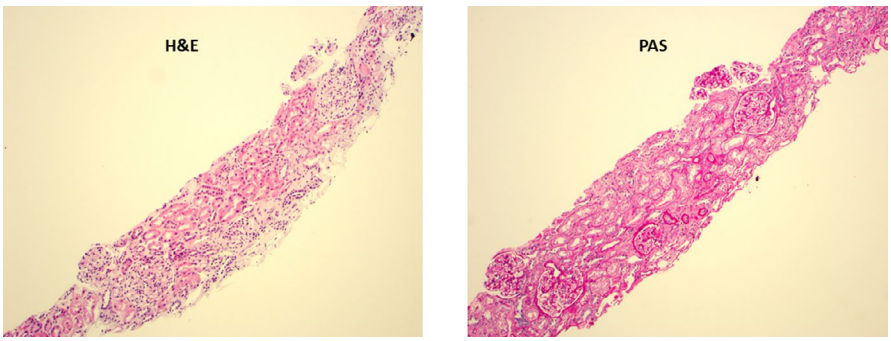

FIGURE 5 4 months follow-up biopsy

2 | DISCUSSION

We report a case of AKI and predominantly v2 lesion involving small arteries and arterioles in a kidney transplant recipient with COVID-19 pneumonia within 1 month after transplantation. At the time of biopsy, we were unable to clearly determine whether this pathological finding was related to TCMR or COVID-19 infection. However, as the patient responded to high dose IV steroids, the diagnosis of TCMR became more plausible.

Isolated intimal arteritis may be seen in rejection and typically involves medium-sized arteries, commonly in grade II TCMR and occasionally in ABMR. The biopsy in our case showed unusual pathological changes with predominantly endothelial cell hyperplasia involving multiple small arteries and arterioles which coexisted with inflammation in the i-IFTA area.[5] Covid-19 infection has been reported to cause vasculitis and vasculopathy directly through tissue tropism, indirect innate immunity related inflammatory response, and leukocyte debris.[6] Therefore, differential diagnosis in our patient includes acute TCMR and Covid-19-associated vasculitis. Tubular injury is most likely secondary to vascular changes. However, the clinical course and progression timeline which included immunosuppression minimization, response to pulse steroids with gradual maximization of the immunosuppressive regimen, and absence of viral inclusion bodies on the biopsy support that the AKI was more likely secondary to TCMR.

Banff i-IFTA2 or 3 score is an essential component of chronic active TCMR. However, it is not sufficient to make a diagnosis of chronic active TCMR as it also requires at least ti2 and t2 lesions involving cortical tubules other than severely atrophic tubules.[5,7] i-IFTA itself is not a specific lesion and is seen in the context of tissue injury because of many causes other than TCMR, including BK virus nephropathy and ABMR.[7] Arteritis with epithelial hyperplasia instead of intimal hyperplasia would favor acute TCMR, grade IIB if COVID-related vasculopathy can be ruled out, but it is not a feature of chronic TCMR. The presence of i-IFTA soon after transplant and in the setting of recent COVID-19 infection and the absence of neutrophils raises the question of whether i-IFTA is a feature of COVID-19 allograft infection and ongoing disease or a sequela of recent TCMR.[8] However, the absence of viral inclusion bodies goes against COVID-19 related allograft endothelial cell inflammation, apoptosis and dysfunction occurrence with COVID-19 infection.[6,9,10]

Kidney transplant recipients receiving depleting induction agents and additional immunosuppressive therapy are at high risk of severe illness from COVID-19 infection.[11] Multiple studies reported high mortality rates among kidney transplant recipients with COVID-19 infection compared with general population patients with COVID-19 infection (20 - 28% vs 1 - 5%).[12] Accordingly, the balance between timing, effective and safe utilization of induction therapy and maintenance immunosuppression and the intensity of the regimen plays a pivotal role in the management of these patients so as to achieve allograft survival without compromising the recipient survival.[11,13] Our case highlights the possibility of TCMR in recently transplanted patients whose immunosuppression is reduced in the context of severe COVID pneumonia. We further report that TCMR may be safely managed with pulse steroids in patients with early post-transplant COVID-19 pneumonia.

CONFLICT OF INTEREST

The authors of this case report certify that they have no conflict of interest to disclose as described by the Transplant Infectious Disease Journal.

AUTHORS' CONTRIBUTION

Mohamed: concept, design, data collection, analysis, manuscript preparation and editing; Smith: analysis and editing; Parajuli: analysis and editing; Garg: analysis and editing; Aziz: analysis and editing; Mandelbrot: analysis and editing; Djamali: analysis, manuscript preparation and editing; Zhong: analysis, manuscript preparation and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Maha Mohamed https://orcid.org/0000-0002-7517-8407
Jeannina Smith https://orcid.org/0000-0001-9379-6332
Sandesh Parajuli https://orcid.org/0000-0003-1667-7465
Neetika Garg https://orcid.org/0000-0002-7001-2168
Fahad Aziz https://orcid.org/0000-0001-8230-3889
Didier Mandelbrot https://orcid.org/0000-0003-3326-8583
Arjang Djamali https://orcid.org/0000-0001-7675-6128
Weixiong Zhong https://orcid.org/0000-0002-4937-1764

REFERENCES

1. Azzi Y, Parides M, Alani O, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. *Kidney Int*. 2020;98(6):1559-1567.
2. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ*. 2020;369:m1996.
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA*. 2020;323(20):2052-2059.
4. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829-838.
5. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18(2):293-307.
6. Becker RC. COVID-19-associated vasculitis and vasculopathy. *J Thromb Thrombolysis*. 2020;50(3):499-511.
7. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. A 2018 reference guide to the banff classification of renal allograft pathology. *Transplantation*. 2018;102(11):1795-1814.

8. Mengel M. BK virus nephropathy revisited. *Am J Transplant*. 2017;17(8):1972-1973.
9. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. *J Thromb Thrombolysis*. 2020;50(1):54-67.
10. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418.
11. Mirjalili M, Shafiekhani M, Vazin A. Coronavirus Disease 2019 (COVID-19) and Transplantation: Pharmacotherapeutic Management of Immunosuppression Regimen. *Ther Clin Risk Manag*. 2020;16:617-629.
12. Elias M, Pievani D, Randoux C, et al. COVID-19 Infection in kidney transplant recipients: disease incidence and clinical outcomes. *J Am Soc Nephrol*. 2020;31(10):2413-2423.
13. Fernandez-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transplant*. 2020;20(7):1849-1858.

How to cite this article: Mohamed M, Smith J, Parajuli S, et al. Successful management of T-cell mediated rejection in a recent kidney transplant recipient with COVID-19 associated severe acute respiratory syndrome. *Transpl Infect Dis*. 2021;23:e13598. https://doi.org/10.1111/tid.13598