COVID-19 in Kidney Transplant Recipients

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To the Editor

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that began in Wuhan, China, has spread rapidly and has already taken on pandemic proportions.[1] After China, Italy is the country with the highest number of cases so far (41,035 confirmed cases according to Dipartimento della Protezione Civile as of March 19, and 3,405 deaths). In Northern Italy, where the current prevalence of confirmed cases has surpassed in some areas 2 per 1,000 people, kidney transplant patients are getting infected and starting to develop coronavirus disease 2019 (COVID-19).

There are only limited data on COVID-19 in transplant recipients.[2] Herein, we report the outcomes of two deceased-donor kidney transplant recipients with COVID-19 pneumonia admitted to the Hospital of Parma (Parma, Italy), between March 2 and 12, 2020. One was a

75-year-old male (patient #1) and the other a 52-yer-old female (patient #2), at 120 and 8 months after transplant, respectively (**Table**). Symptoms (cough, myalgia, and fever 38-39ºC) started 3 and 1 days before admission for patients #1 and #2, respectively. At the time of infection diagnosis, graft function was stable in patient #1, while patient #2 had developed acute kidney injury (AKI). Both patients were on tacrolimus (Tac), steroids, and mycophenolate mofetil. Both patients presented with fever (38-39° C) and dyspnea at admission. Lung CT scan at admission showed typical radiological findings of COVID-19 pneumonia, with extensive bilateral ground-glass opacities in both; specific treatment was started before arrival of nasopharyngeal swab test results (PCR, confirming SARS-CoV-2 infection on day 3 and 2 after symptoms' onset). Mycophenolate and Tac were discontinued on the day of admission and both patients received hydroxychloroquine (200 mg twice daily) in addition to lopinavir+ritonavir or darunavir+cobicistat. None of the patients were on ACE inhibitors or ARBs. Both patients required non-invasive ventilation, but no patient was transferred to the ICU. Patient #1 developed abrupt worsening of his respiratory conditions over a period of 24 to 38 hours and expired 5 days after admission before intubation. On day 6 after admission, patient #2 showed signs of systemic inflammation (plasmatic IL-6: 108.2 pg/ml; normal range 0-10 pg/mL; **Table**). After progressive worsening of respiratory conditions requiring non-invasive ventilation and being considered for intubation, the patient received colchicine (1mg on day 8, and 0.5mg/day thereafter) to reduce inflammation, due the unavailability of anti-IL-6 receptor mAb tocilizumab. Anti-retroviral therapy was stopped; 24hrs after colchicine administration, plasmatic IL-6 concentration decreased to 36 pg/ml, and respiratory conditions stabilized. At the time of writing (day 14 after initial symptoms), the patient is alert and stable on non-invasive ventilation positive airway pressure (PaO_2/FiO_2 114, respiratory rate 22 rpm, arterial blood pressure 150/90 mmHg, hear rate 105 rpm). Serum creatinine has returned to baseline levels (1.4 mg/dL) and liver function test are normal. Tacrolimus blood trough levels had initially increased to 39.9μg/L due to interaction with ritonavir and transient liver failure despite holding tacrolimus. On follow-up, Tac trough levels had returned to target range and Tac was resumed on day 12 (blood levels 5.4μg/L on Tac 0.5mg twice daily).

In kidney transplant recipients with COVID-19 who develop extensive pneumonia, which may require intubation, our current therapeutic approach includes stopping the immunosuppressive therapy (using steroids as the only antirejection drugs) to help promote the specific anti-viral immune response.

As the cytokine storm triggered by the coronavirus seems to be particularly responsible for morbidity of COVID-19, withdrawal of antirejection therapy can be associated with exacerbation of inflammatory response to viral infection. Therefore, IL-6 targeting therapies are being proposed to control acute respiratory distress syndrome (ARDS; currently being tested in a randomized trial in China; ChiCTR2000029765). A randomized controlled trial is testing the safety/efficacy of steroids (NCT04273321), but until results are available, broad use of steroids is discouraged.[3]

Viroporin E, a component of SARS-CoV, forms Ca2C-permeable ion channels and activates the NLRP3 inflammasome.[4] Colchicine prevents NLRP3 inflammasome assembly, thereby reducing the release of IL-1b and other interleukins, including IL-6.[5] In patient #2, colchicine therapy was associated with a fast decrease of IL6 levels.

In the presented kidney transplant recipients, the course of COVID-19 did not significantly differ from that of non-transplant individuals. Immunosuppression interruption combined to the anti-inflammatory effects of colchicine may have synergized with antiviral therapy and hydroxychloroquine to lower viral replication and minimize the cytokine storm triggered by SARS-CoV-2.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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Table. Patients characteristics at admission.

	Patients	
	#1	#2
Variables		
Sex	M	F
Age (*yrs*)	75	52
Race	White	White
Months post-Tx	120	8
Donors	Deceased	Deceased (DCD)
History		
Primary nephropathy	Pyelonephritis	Unknown
Flu vaccination	yes	yes
Lung disease	COPD	no
Heart disease	yes	no
Hypertension	yes	yes
Cancer	no	no
Obesity	yes	no
Vital signs		
Respiratory rate (rpm)	25	28
Heart rate (rpm)	101	93
Blood pressure (mmHg)	140/70	130/70
PO_2/fiO_2	276	247
Signs/symptoms		
Fever (T > 37.5°C)	yes	yes
Dyspnea	yes	yes
Diarrhea	no	yes
Myalgias	yes	yes
AKI	no	yes
CT (% of lung involvement)	40%	50%
Positive swab test	yes	yes
Biochemistry		

s-Creat (mg/dL); d0, d3, d7	2.2; 2.2; NA	2.4; 3.4; 2.9
(baseline creatinine)	(2.1)	(1.3)
PTL (x10^3/mmc)	164	386
WBC(x10^3/mmc)	6.56	2.54
Lymphocytes (cells/mmc)		
d0, d3, d7	880; 650; NA	110; 120; 50
Hb (g/dL)	11.7	11.6
d-dim (ng/mL)	NA	832
AST(IU/mL)	45	62
ALT (IU/mL)	25	26
LDH (IU/mL)	301	718
CPK (IU/mL)	82	197
CRP (mg/L); d0, d3, d7	180; >20; NA	158; 100; 43
Procalcitonin (ng/ml)	1.29	0.98
Concurrent/previous relevant therapy		
Induction therapy	Thymo	Thymo
Maintenance		
Immunosuppression	Tac, MMF, St	Tac, MMF, St
ACEi	no	no
ARB	no	no
Immunosuppression withdrawal		
Tac	yes	yes
MMF	yes	yes
Steroids	no	no
Antiviral/antibiotics		
Antibiotics	yes	yes
Hydroxychloroquine	yes	yes
Lopinavir/ritonavir	yes	no
Darunavir/cobicistat	no	yes

Remdesivir	no	no
Outcomes		
NIV	yes	yes
ICU	no	no
Death	yes	no
(days after admission)	(5)	(8)

Abbreviations: yrs, years; AKI, Acute Kidney Injury; CT Computerized Tomography; s-creat, serum creatinine; PTL, platelets; WBC, white blood cells; Hb, haemoglobin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDH, Lactate Dehydrogenase; CPK, Creatine Phosphokinase; CRP, C-reactive Protein; ACEi, ACE inhibitor; ARB, Angiotensin II Receptor blocker; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; St, steroids; NIV non-invasive ventilation; ICU, intensive care unit. NA, not available.