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Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York

The Columbia University Kidney Transplant Program*

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ABSTRACT

Background The novel SARS-CoV-2 virus has caused a global pandemic of coronavirus disease 2019 (COVID-19). Although immunosuppressed individuals are thought to be at an increased risk of severe disease, little is known about their clinical presentation, disease course, or outcomes.

Methods We report 15 kidney transplant recipients from the Columbia University kidney transplant program who required hospitalization for confirmed COVID-19, and describe their management, clinical course, and outcomes.

Results Patients presented most often with a fever (87%) and/or cough (67%). Initial chest x-ray most commonly showed bilateral infiltrates, but 33% had no acute radiographic findings. Patients were managed with immunosuppression reduction and the addition of hydroxychloroquine and azithromycin. Although 27% of our patients needed mechanical ventilation, over half were discharged home by the end of follow-up.

Conclusions Kidney transplant recipients with COVID-19 have presentations that are similar to that of the general population. Our current treatment protocol appears to be associated with favorable outcomes, but longer follow-up of a larger cohort of patients is needed.

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Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, first spread to the United States in January 2020, with the first case in New York City diagnosed at the end of the following month.[1,2] Since that time, the New York metropolitan area has become the epicenter of COVID-19 in the United States, with approximately 40% of confirmed COVID-19 cases and 25% of all reported COVID-19 deaths as of March 28, 2020. Given that the metropolitan area is home to nine major academic transplant centers, there is significant concern regarding the susceptibility, presentation, and ideal management of organ transplant recipients who develop COVID-19. International data regarding the management and prognosis for kidney transplant recipients with COVID-19 has been limited to case reports.[3,4] Here, we describe 15 consecutive cases of COVID-19 among kidney transplant recipients at our center, Columbia University Medical Center, who required hospitalization through March 27, 2020.

CASE SERIES

The 15 patients included in this series had a median age of 51 (interquartile range, 28–72) years and were predominantly men (65%) and deceased donor kidney recipients (80%), with a median time since transplant of 49 (interquartile range, 38–118; range, 0–232) months (Table 1). All but one patient were taking tacrolimus at the time of COVID-19 diagnosis, and most (80%) were also taking either mycophenolate mofetil or mycophenolic acid. Despite our status as an early steroid withdrawal center for most transplants, ten patients (67%) were taking prednisone at the time of COVID-19 diagnosis. The underlying cause of ESKD varied.

Patients reported symptom onset ranging from 1 day to nearly 3 weeks before admission. The most common presenting symptom was fever, which was reported in 13 (87%) cases, followed by cough, which was present in nine (60%) cases (Table 1). Only one patient had neither fever nor cough as a presenting symptom, and instead reported exertional dyspnea and malaise. Three patients (20%) reported diarrhea, and

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*For a full list of Columbia University Kidney Transplant Program members see the Supplemental Material.

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Table 1. Characteristics of kidney transplant recipients with COVID-19

Characteristics	All Patients, *n*=15
Baseline characteristics	
Age, yr	51 (IQR, 28–72; range, 21–78)
Female, *n* (%)	5 (33)
Time since transplant, mo	49 (IQR, 38–118; range, 0–232)
Deceased donor, *n* (%)	12 (80)
Multiorgan recipient, *n* (%)	2 (13)
Maintenance immunosuppression, *n* (%)	
Tacrolimus	14 (93)
Mycophenolate mofetil or mycophenolic acid	12 (80)
Belatacept	2 (13)
Leflunomide	1 (7)
Azathioprine	1 (7)
Prednisone	10 (67)
Clinical presentation, *n* (%)	
Fever	13 (87)
Cough	9 (60)
Fatigue/malaise	4 (27)
Dyspnea (exertional or rest)	4 (27)
Diarrhea	3 (20)
Myalgia	2 (13)
Hemoptysis	1 (7)
Emesis	1 (7)
Laboratory tests on diagnosis[a]	
White blood cell count, ×1000/μl (*n*=13)	4.8 (range, 2.1–12.7)
Absolute lymphocyte count, /μl (*n*=11)	800 (range, 110–1410)
Ferritin, ng/ml (*n*=12)	471 (range, 93–1963)
Lactate dehydrogenase, U/L (*n*=12)	275 (range, 113–450)
Procalcitonin, ng/ml (*n*=13)	0.46 (range, 0.08–18.7)
Erythrocyte sedimentation rate, mm/h (*n*=12)	40.5 (range, 0–75)
C-reactive protein, mg/L (*n*=13)	104 (range, 0.3–232)
IL-6, pg/ml (*n*=12)	24 (range, <5–120)
Initial chest x-ray, *n* (%)	
Multifocal/bilateral patchy opacities	7 (47)
No acute findings	5 (33)
Left lower lobe opacities	1 (7)
Right lower lobe opacity	1 (7)
Report not available	1 (7)

Data are displayed as *n* (%), median (IQR), or median (range). COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a]*n*<15 because of some patients being diagnosed at outside hospitals or as outpatients, or inconsistent laboratory test ordering upon admission.

Significance Statement

Currently, the clinical presentation, optimal management strategy, and outcomes for patients with kidney transplants who develop COVID-19 infection remain unknown. The description of our cohort represents the first cohort of patients with kidney transplants and COVID-19 infection and includes clinical features, markers of inflammation, and a strategy for management that includes both immunosuppression reduction and the use of adjuvant therapy, including hydroxychloroquine, azithromycin, and tocilizumab. This approach appears to have resulted in favorable outcomes in our cohort of hospitalized kidney transplant patients and provides an effective treatment strategy for the management of these patients

only two patients (13%) reported myalgias. Two patients were in the hospital for 6 and 7 days, respectively, before developing a fever and being tested for COVID-19.

About half of our patients had bilateral/multifocal opacities noted on initial chest x-ray, whereas two patients (13%) had lobar opacities and five patients (33%) had unremarkable radiographs initially (Table 1). Among patients for whom laboratory data obtained at the time of diagnosis were available, median white blood cell count was $4.8\times10^3/\mu l$ (range, 2.1–12.7) and median absolute lymphocyte count was 800/μl (range, 110–1410). We observed wide variation in admission values for ferritin (median, 471 ng/ml; range, 93–1963), lactate dehydrogenase (median, 275 U/L; range, 113–450), procalcitonin (median, 0.46 ng/ml; range, 0.08–18.70), erythrocyte sedimentation rate (median, 40.5 mm/h; range, 0–75), C-reactive protein (median, 104 mg/L; range, 0.3–232), and IL-6 (median, 24 pg/ml; range, <5–120).

The primary change in immunosuppression in the majority of patients was complete cessation of antimetabolites or leflunomide (ten out of 14, 71%) while continuing the tacrolimus (with a goal trough of 4–7 ng/ml) and the baseline prednisone in those individuals who were on maintenance prednisone (Table 2). One patient who was on a regimen of tacrolimus and high-dose prednisone was switched to a regimen of prednisone 20 mg only, as was a patient who had just completed a course of thymoglobulin induction therapy (6 mg/kg) after a deceased donor transplantation. Two patients were also on maintenance belatacept, including one patient who was on a four-drug regimen and a second patient whose dose was deferred because of their severe ongoing hypoxemia. (Tables 3 and 4).

As per the Columbia University COVID-19 protocol, in addition to holding the antimetabolite, 13 (87%) patients received hydroxychloroquine, including nine that received it with adjunctive azithromycin. Hydroxychloroquine therapy was not used for the recent transplant recipient and for the patient first admitted to another institution. A single dose of tocilizumab was given to the patient whose

Table 2. Clinical management and outcomes of kidney transplant recipients with COVID-19

Clinical Management and Outcomes	All Patients, *n*=15 (%)
Change in immunosuppression	
Discontinued only MMF/MPA/AZA/leflunomide	10/14 (71)
Prednisone decreased	1/10 (10)
Belatacept infusion postponed	1/2 (50)
Discontinued all immunosuppression	2 (14)
Replaced tacrolimus and MMF with prednisone	1 (7)
No change	1 (7)
Anti–COVID-19 therapies	
Hydroxychloroquine without azithromycin	4 (27)
Hydroxychloroquine plus azithromycin	9 (60)
Tocilizumab	1 (7)
Outcomes	
AKI	6 (40)
Intubation required	4 (27)
Days between admission and intubation (*n*=4)	5 (range, 0–9)
Hospitalization disposition	
Died	2 (13)
Discharged	8 (53)
Days between admission and discharge (*n*=8)	4.5 (range, 0–9)
Hospitalization ongoing	6 (40)
Days between admission and end of follow-up (*n*=6)	7 (range, 3–11)

Data are displayed as *n* (%) or median (range). COVID-19, coronavirus disease 2019; MMF, mycophenolate mofetil; MPA, mycophenolic acid; AZA, azathioprine.

immunosuppression was reduced to prednisone alone shortly after intubation for acute respiratory distress syndrome. This patient has since been successfully been extubated on day 5 of mechanical ventilation.

Six patients (40%) had AKI, although none had a kidney biopsy performed to determine the cause. Four patients (27%) required intubation and mechanical ventilation between 0 and 9 days after admission (Table 2), of whom three remain on mechanical ventilation and two died because of severe acute respiratory distress syndrome, including one who declined mechanical ventilation. Patients who required mechanical ventilation were intubated between days 5 and 7 after the onset of symptoms (Table 4). In addition, one patient developed symptoms during an inpatient stay while being treated for an acute antibody-mediated rejection with high-dose steroids and plasmapheresis, which were stopped, and another patient developed symptoms after completion of a course of thymoglobulin induction therapy after a deceased donor transplantation. Both of these patients, who are in their first-year post transplant, remain intubated and on mechanical ventilation at this time. Among the patients who developed AKI, only two patients, both of whom were intubated, required RRT. One of these patients was experiencing delayed graft function at the time of COVID-19 diagnosis, and the other patient had a failing allograft at the time of diagnosis. At the end of follow-up, an additional three patients remain hospitalized outside of the intensive care unit, and eight have been discharged home at a median of 4.5 (range, 0–9) days after admission. Available high-sensitivity C-reactive protein trends for patients are shown in Figure 1.

DISCUSSION

The sudden and rapid spread of COVID-19 throughout the globe has resulted in early uncertainty in the identification and management of this disease. Although the general understanding of the clinical presentation of COVID-19 is improving, information about select patient groups who may warrant special consideration, such as transplant recipients, remains limited. Here, we present a series of 15 cases of COVID-19 in kidney transplant recipients at our center who required hospitalization.

The most common presenting symptom we observed was fever, followed by cough, similar to larger reports from general population cohorts.[1,5] Clinical presentation in our patients was consistent with those seen in case reports of kidney transplant recipients from Spain and Wuhan, where patients presented with fever that preceded a dry cough by several days, or cough, dyspnea, and chest tightness.[3,4] We should note that the majority of the patients in our cohort were on prednisone at the time of diagnosis despite our status as an early steroid withdrawal center for most kidney transplant recipients, perhaps suggesting that the greater immunosuppression associated with the use of an immunosuppressive three-drug regimen may predispose patients to a more severe infection requiring hospitalization.

The ideal treatment for kidney transplant recipients with COVID-19 remains uncertain at present. Although the Columbia University COVID-19 protocol is to withdraw the antimetabolite and introduce hydroxychloroquine (with azithromycin in the absence of QT interval prolongation), the true efficacy of this approach remains unclear given the relatively small number of adverse outcomes to date. In both previously published case reports of COVID-19 in kidney transplant recipients, maintenance immunosuppression was also reduced. The patient reported from Wuhan recovered after cessation of immunosuppression and treatment with methylprednisolone, intravenous

Table 3. Detailed description of individual cases, including individual cases and select laboratory tests at admission

Case	Age, yr	Sex	Months since Transplant	Presenting Symptoms	Symptom Duration before Admission	Initial Chest X-Ray Findings	WBC Count, ×1000/ul	Absolute Lymphocyte Count	Ferritin, ng/mL	LDH, U/L	Procalcitonin, ng/mL	ESR, mm/hr	CRP, mg/L	IL-6, pg/mL
1	70	M	60	Fever, cough, fatigue	2–3 wk	No acute findings	4.8	500	155	409	0.34	16	100	89.5
2	64	M	232	Fever, cough, fatigue	4 d	Bilateral mid and lower lung reticular opacities and hazy bibasilar opacities								
3	28	M	42	Fever, cough, myalgia	1 d	Bilateral haziness and patchy opacities (left greater than right)	11.7	860	187	193	17.05	60	173	<5
4	51	M	118	Fever, cough	9 d	Bilateral multifocal patchy opacities	2.8	370	1514	231	0.86	64	129	120
5	32	F	14	Fever, dyspnea, diarrhea	Same day	Right lower lobe hazy opacity	5.7	1160	173	338	0.26	27	134	13
6	21	M	46	Fever, fatigue, diarrhea	4 d									
7	36	M	38	Fever, myalgia	2 d	Left lower lobe opacities	3.4	850	879	113	0.15	75	11	8
8	72	F	49	Fever, cough, dyspnea	2–3 d	No acute findings	3.6	790			0.08		0	
9	51	F	9	Fever, cough	1 d	Diffuse multifocal opacities	3.8	110	760	450	3.66	0	55	51
10	76	M	136	Fever, diarrhea	1 d	No acute findings	8.1	810	93	205	0.13	38	6	120
11	61	M	0	Fever, cough	1 d	No acute findings	3.6		1963	419	18.69	43	130	34
12	22	M	34	Fever, exertional dyspnea	2 d	No acute findings	2.1	230	821	231	3.93	31	104	16
13	78	M	117	Exertional dyspnea, malaise	1 wk	Bilateral patchy opacities	5.7	860	453	318	0.46	38	208	10
14	72	F	120	Fever, cough, hemoptysis	3–4 d	Diffuse interstitial airspace opacities with upper lobe predominance	5.5	1410	467	330	0.14	50	74	32
15	25	F	80	Cough, diarrhea, emesis	1 wk	Bilateral hazy opacities	12.7	390	476	224	0.62	52	232	5

WBC, white blood cell; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; M, male; F, female.

Table 4. Detailed description of treatment of individual cases and their outcomes at last follow-up

Case	Admission Immunosuppression	Immunosuppression Change	Anti–COVID-19 Therapy	Mechanical Ventilation Required	AKI	AKI Outcome	RRT Required	Symptoms to Intubation	Hospitalization Outcome
1	Belatacept, MPA, prednisone	Held MPA, postponed belatacept	Hydroxychloroquine, azithromycin		Yes	Resolved			Deceased
2	Tacrolimus, MMF, prednisone	Held MPA	Hydroxychloroquine, azithromycin						Discharged home
3	Tacrolimus, azathioprine, prednisone, adalimumab	Held azathioprine	Hydroxychloroquine, azithromycin		Yes	Ongoing			Discharged home
4	Tacrolimus, MMF, prednisone	Held MPA	Hydroxychloroquine, azithromycin		Yes	Resolving			Discharged home
5	Tacrolimus, MMF, prednisone	Held MMF	Hydroxychloroquine						Discharged home
6	Tacrolimus, MMF	No change							Discharged home
7	Belatacept, tacrolimus, MMF, prednisone	Held MMF	Hydroxychloroquine						Discharged home
8	Tacrolimus, MPA	Held all immunosuppression	Hydroxychloroquine, azithromycin						Discharged home
9	Tacrolimus, MMF, prednisone	Held MMF	Hydroxychloroquine	Yes				6	Remains intubated (day 8 of mechanical ventilation)
10	Tacrolimus, leflunomide	Held leflunomide	Hydroxychloroquine						Discharged home
11	Tacrolimus, MMF	Held tacrolimus and MMF, started prednisone		Yes	Yes	Ongoing	yes	5	Remains intubated (day 6 of mechanical ventilation)
12	Tacrolimus, prednisone	Decrease prednisone and tacrolimus	Hydroxychloroquine, azithromycin, tocilizumab	Yes			yes	5	Extubated on day 5
13	Tacrolimus, MMF, prednisone	Held MMF	Hydroxychloroquine, azithromycin	Yes	Yes	Resolving		7	Deceased
14	Tacrolimus, MMF	Held MMF	Hydroxychloroquine, azithromycin						Remains hospitalized
15	Tacrolimus, MMF, prednisone	Held MMF	Hydroxychloroquine, azithromycin		Yes	Ongoing			Remains hospitalized

Patients 2 and 6 were admitted to other hospitals, as a result, admission lab data are not available. The remaining empty cells in the table are missing information. COVID-19, coronavirus disease 2019; MPA, mycophenolic acid; MMF, mycophenolate mofetil.

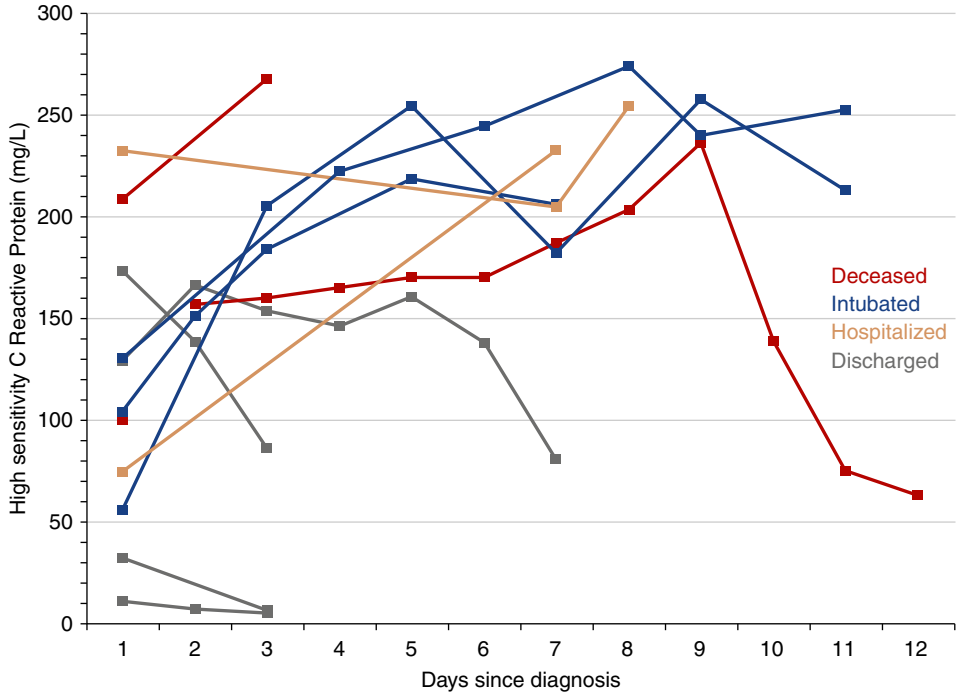

Figure 1. Heterogeneity in high-sensitivity C-reactive protein measurements at admission and subsequently during the course of hospitalization.

Ig, and IFNα.[4] For the Spanish patient, maintenance tacrolimus and everolimus were both stopped, and treatment was initiated with lopinavir/ritonavir and hydroxychloroquine.[3] IFNβ was eventually added when the patient's hypoxia worsened and they subsequently required intubation.

Unfortunately, there are many questions pertaining to the management of kidney transplant patients with COVID-19 that currently rely on expert opinion because of the paucity of evidence. The management of transplant recipients with mild symptoms as outpatients *via* telemedicine is a strategy that we have used on a case-by-case basis. However, attempting to identify patients who are likely to progress is currently a challenge, and relies on the relatively insensitive subjective assessment of worsening dyspnea on exertion and self-reported vital signs, along with the usual recommendations for self-isolation. This approach is not without risks, particularly in those individuals thought to be at significantly increased risk, given the rapid nature of decompensation seen among patients who eventually go on to develop acute respiratory distress syndrome, and needs further study to determine the optimal strategy.[6]

Although more than half of our patients have been successfully discharged, the optimal timing of the reintroduction of immunosuppressive agents is not yet clear. Current estimates are that viral shedding can occur for up to 2 weeks or more after improvement of symptoms, but there is also considerable variation (maximum observed shedding of 37 days).[7–9] There is also an association between severity of illness and peak viral loads, which may in turn influence the duration of subsequent viral shedding.[10] Thus, given the present uncertainty, our current clinical practice has been to delay reintroduction of these agents for up to 2 weeks after discharge, recognizing that prolonged reduction of immunosuppression increases the risk of allograft rejection.

We observed that 27% of our cases required intubation, a proportion that is similar for cases in New York City overall. Over half of the patients in our series were discharged home by the time this manuscript was prepared, and only two had died. Despite concerns about a possible biphasic nature of the illness, to date, none of the discharged patients have been readmitted with worsening disease. Although these findings are encouraging regarding the prognosis of transplant recipients who develop COVID-19 and require hospitalization, the large number of patients who remain hospitalized makes it impossible to draw any conclusions in this patient population regarding the overall rate of respiratory failure requiring intubation, or death. In addition to these 15 hospitalized patients, at least eight additional kidney transplant recipients in our program have tested positive for SARS-CoV-2 infection, but to date have not required hospitalization. Additionally, the limited availability of COVID-19 testing in New York City makes it likely that mild cases of the disease have remained unrecognized among other transplant recipients at our center.

In conclusion, among 15 kidney transplant recipients at our center with COVID-19, overall presentation was similar to that reported for the general population. Although many of our patients experienced a favorable outcome with our current treatment strategy, the small cohort and

varied additional therapies makes it difficult to draw any conclusions beyond that of short-term safety and tolerability of our protocol. Longer-term follow-up is required to better understand the prognosis and sequelae of COVID-19 in immunosuppressed kidney transplant recipients.

DISCLOSURES

Dr. Hardy reports grants from NHLBI, outside the submitted work. Dr. Husain reports grants from NCATS, during the conduct of the study. Dr. Ratner reports personal fees from Natera, personal fees from CSL Behring, personal fees from Sanofi, outside the submitted work; and I own a small amount of stock in Hansa BioPharma. Dr. Cohen reports personal fees from Natera, other from Alexion Pharmaceuticals, outside the submitted work. Dr. Mohan reports grants from NIDDK/NIH, during the conduct of the study; grants and other from Angion Pharmaceuticals, personal fees from Kidney International Reports, outside the submitted work.

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See related editorial, "The Immunocompromised Transplant Recipient and SARS-CoV-2 Infection," on pages 1147–1149.