Received: 18 May 2020 | Accepted: 27 May 2020

DOI: 10.1111/tid.13359

CASE REPORT

WILEY

COVID-19 in pancreas transplant recipients

Geoffrey K. Dube[1] | S. Ali Husain[1] | Kasi R. McCune[2] | P. Rodrigo Sandoval[2] | Lloyd E. Ratner[2] | David J. Cohen[1]

[1]Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA

[2]Department of Surgery, Columbia University Irving Medical Center, New York, New York, USA

Correspondence
Geoffrey K. Dube, 622 West 168th St, PH4-124, New York, NY 10032.
Email: GKD4@cumc.columbia.edu

Abstract

Coronavirus disease 2019 (COVID-19) has become a pandemic since first being described in January 2020. Clinical manifestations in non-transplant patients range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome, multiorgan system failure, and death. Limited reports in kidney transplant recipients suggest similar characteristics in that population. We report here the first case series of COVID-19 infection occurring in pancreas transplant recipients.

KEYWORDS

coronavirus, COVID-19, pancreas transplant, SARS-CoV-2

1 | INTRODUCTION

SARS-CoV-2, a novel coronavirus first reported in December 2019, rapidly developed into a global pandemic, with more than 1.8 million cases and 100 000 deaths reported worldwide.[1] Clinical manifestations of COVID-19, the disease caused by SARS-CoV-2, range from asymptomatic infection to mild upper respiratory tract symptoms or viral pneumonia. The most severe cases of COVID-19 can lead to respiratory failure, multiorgan system failure, and death.[2,3] Mortality rates between 2% and 3% have been reported in the general population.[4] Death is more common in those with preexisting conditions, including hypertension, diabetes, and cardiovascular disease.[4]

Due to chronic immunosuppression, transplant recipients are at increased risk both of acquiring infections and developing more severe clinical disease. Additionally, there is a high burden of comorbid disease in the transplant population. Several case reports and single-center series have described COVID-19 in transplant patients, with most series describing kidney transplant patients who were sick enough to require hospitalization.[5-9] To date, there have been no reports of COVID-19 in pancreas transplant (PT) recipients. We report here our experience with COVID-19 in four PT recipients in New York, the epicenter of the outbreak in the United States.

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; PT, pancreas transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPK, simultaneous pancreas-kidney.

2 | CASES

Four simultaneous pancreas-kidney (SPK) transplant recipients, representing 4.3% of all patients with functioning PT followed by our program, were diagnosed with COVID-19 between March 22, 2020, and April 11, 2020. Three patients tested positive by nasopharyngeal swab for SARS-CoV-2after presenting to the hospital for evaluation. The fourth patient received a clinical diagnosis of COVID-19 based on symptoms; due to a critical shortage of testing supplies during the epidemic, outpatient confirmatory testing was not able to be offered. Cases are described below and summarized in Table 1; case 4 was also included in a large multicenter cohort that was previously reported but did not include patient-level data.[9] This study was approved by the Columbia University Medical Center Institutional Review Board.

2.1 | Case 1

A 53-year-old man end-stage renal disease (ESRD) secondary to type 1 diabetes presented to an outside hospital for evaluation 107 months after receiving his second SPK. His immunosuppression regimen was tacrolimus monotherapy. Presenting symptoms included fever and cough. Creatinine on presentation was 0.9 mg/dL; other laboratory results are not available. He tested positive for SARS-CoV-2. Due to normal oxygen saturation, he was discharged home with outpatient monitoring. His tacrolimus was held for two days, and he was prescribed azithromycin. He did not develop dyspnea at home, and

TABLE 1 Patient demographics and laboratory parameters

Case number	1	2	3	4
Age, y	53	40	60	36
Sex	Male	Male	Female	Female
Race	White	Hispanic	White	Asian
Comorbidities	Hypertension, atrial fibrillation, coronary artery disease	Hypertension	Hypertension, coronary artery disease	Hypertension
Duration of diabetes pre-transplant, years	26	21	57	23
Time from transplant, months	107	20	8	3
Induction immunosuppression	Thymoglobulin, rapid steroid withdrawal	Thymoglobulin, rapid steroid withdrawal	Thymoglobulin, rapid steroid withdrawal	Thymoglobulin, rapid steroid withdrawal
Maintenance immunosuppression	Tacrolimus	Tacrolimus, mycophenolate	Tacrolimus, mycophenolate	Tacrolimus, mycophenolate
SARS-CoV-2 PCR	Positive	Not performed	Positive	Positive
Hospitalized	No	No	Yes	yes
Baseline Laboratories				
Hemoglobin A1c (%)	5.2	4.8	5.4	4.9
Creatinine (mg/dL)	0.9	1.14	1.05	1.8
Lipase (U/L)	39	28	18	351
Laboratories on Presentation				
Creatinine (mg/dL)	0.9		0.96	1.9
Lipase (U/L)				351
Lactate dehydrogenase (U/L; reference range 135-214)			276	440
C-reactive protein (mg/L; reference range 0-10)			8.8	9.56
Ferritin (ng/mL; reference range 13-150)			1118	4492
D-dimer (ng/mL; reference range < 0.8)			1.4	0.56
COVID-19 treatments	Azithromycin	None	Hydroxychloroquine, azithromycin	Hydroxychloroquine, azithromycin
Immunosuppression change	Tacrolimus held × 2 d	Mycophenolate held	Mycophenolate held	Mycophenolate held
Duration of symptoms, days	18	15	Not resolved	18

his symptoms gradually resolved over 18 days. He monitored his fingerstick glucose intermittently at home and never developed hyperglycemia. Five weeks after initial symptom resolution, he remains asymptomatic with normal fingersticks. Outpatient laboratories have not been rechecked due to his desire to avoid healthcare settings.

2.2 | Case 2

A 40-year-old man with ESRD secondary to type 1 diabetes presented for telehealth evaluation 20 months after receiving an SPK. His immunosuppression regimen was tacrolimus and mycophenolate. Post-transplant course was notable for uncontrolled hypertension, for which he had undergone angioplasty of the transplant renal artery three weeks earlier, during the first week of the COVID-19 outbreak in New York. Presenting symptoms included fever, headache, anosmia, chest pain, diarrhea, and myalgias. A clinical diagnosis of COVID-19 was made. Due to the absence of respiratory symptoms, he was not referred to the emergency department and did not receive confirmatory testing for SARS-CoV-2 infection. Mycophenolate was discontinued, and he was monitored at home with daily telehealth check-ins. Outpatient laboratories were not checked during this period. His fevers persisted at home for 15 days before his symptoms resolved completely. He did not monitor his fingerstick glucose during his illness but reported no symptoms of hyperglycemia. His mycophenolate was resumed five days after

symptom resolution. Five weeks later, he remains asymptomatic, with normal glucose readings. His creatinine is 1.24 and lipase 42 U/L.

2.3 | Case 3

A 60-year-old woman with ESRD secondary to type 1 diabetes presented for telehealth evaluation 8 months after receiving an SPK. Her immunosuppression regimen was tacrolimus and mycophenolate. Presenting symptoms included fever, cough, dyspnea, headache, anosmia, and diarrhea. Her mycophenolate was discontinued, and she was monitored at home with frequent check-ins. Glucose readings over the next 10 days were 120-130, similar to her baseline. Due to worsening dyspnea and the development of hypoxia 10 days after symptom onset, she was referred to her local hospital. Her room air oxygen saturation was 89%, and she was started on supplemental oxygen. She tested positive for SARS-CoV-2. Admission laboratories were notable for white blood cells 1.3×10^3, absolute lymphocyte count 200, creatinine 0.96 mg/dL, and random glucose 118 mg/dL; pancreas enzymes were not checked. Other values are shown in Table 1. Chest X-ray showed bilateral infiltrates. She was treated with hydroxychloroquine, azithromycin, and methylprednisolone. Glucose while on methylprednisolone ranged from 71 to 206. She had hypoxic respiratory failure 22 days after symptom onset and died 3 days later. Creatinine was 0.6 prior to the respiratory arrest.

2.4 | Case 4

A 36-year-old woman with ESRD secondary to type 2 diabetes presented to our hospital three months after receiving an SPK. Her immunosuppression regimen was tacrolimus and mycophenolate. Presenting symptoms included fever, cough, and myalgias. She tested positive for SARS-CoV-2. Admission laboratories were notable for white blood cells 6.24×10^3, absolute lymphocyte count 310, creatinine 1.9 mg/dL, random glucose 114 mg/dL, and lipase 351 U/L. Other values are shown in Table 1. Chest x-ray showed bilateral hazy opacities in the lower lung fields. Her room air oxygen saturation was 94%-100%, and she did not require supplemental oxygen during her 7-day hospital stay. Her fevers resolved after 1 week and her cough was slowly resolving after 2 weeks. During her admission, her creatinine ranged from 1.9 to 2.2 mg/dL, her glucose ranged from 71 to 114 mg/dL, and her lipase ranged from 248 to 351 I/L. She was restarted on mycophenolate 1 week after her last fever. Five weeks later, she remains asymptomatic, with fingersticks 95-110, creatinine 1.34, lipase 211 U/L, and hemoglobin A1c 5.3%.

3 | DISCUSSION

We present here the first four cases of COVID-19 reported in PT recipients, with one case being a presumptive diagnosis based on suggestive symptoms and known nosocomial exposure in the absence of confirmatory PCR testing for SARS-CoV-2. Our cases show several notable findings and raise several key management questions. First, the main presenting symptoms in our PT recipients (fever in 100%, cough in 75%) were similar to what is reported in the non-transplant population.[2,3] Diarrhea is reported in <5% of non-transplant patients, but was found in two of our patients, including one without respiratory symptoms. Diarrhea may be more commonly reported in transplant patients with COVID-19 than in the general population.[9] Whether this finding is due to the concurrent use of transplant medications known to cause diarrhea or other factors is unclear. Second, similar to the non-transplant population, PT recipients presented with a spectrum of disease severity ranging from mild illness managed at home to more severe disease requiring hospitalization and need for supplemental oxygen.[4] Three of our four patients had mild-moderate disease, characterized by no pneumonia or mild pneumonia, which is similar to the 74% rate of mild-moderate disease reported in solid organ transplant recipients and the 80% rate of mild disease reported in the non-transplant population.[4,9] One patient initially had mild disease but developed respiratory failure 10 days after initial symptom onset and expired. This symptom progression is similar to the biphasic disease course described in non-transplant patients, in whom worsening respiratory status can develop around 7-10 days after symptom onset.[10,11] Third, in patients for whom glucose levels were available, there was no change in glycemic control compared with their premorbid glucose control. Finally, the duration of symptoms in the three cases that have resolved was 14-18 days.

The clinical deterioration of patient 3 after 10 days highlights the importance of close monitoring of suspected or confirmed COVID-19 in PT recipients followed in the outpatient setting until complete symptom resolution. As the pandemic worsened in New York, most patients without dyspnea or hypoxia were not admitted due to the surge in hospitalized patients. Ambulatory clinics were reduced due to staff redeployment and transition to telemedicine to support social distancing policies, making follow-up challenging. We managed our outpatient COVID-19 PT recipients with frequent check-ins to discuss symptom progression and review vital signs, including pulse oximetry when available. Patients with worsening dyspnea or hypoxia were referred to the emergency department for inpatient management.

In all three of our PT patients who have recovered from COVID-19 infection, symptoms lasted for at least 2 weeks. Despite persistence of symptoms, none of these patients experienced worsening respiratory status. Transplant providers caring for PT recipients with COVID-19 should be aware that a prolonged disease course in these patients does not imply that a clinical deterioration is inevitable. Due to uncertainty regarding the duration of viral shedding and infectivity in recovered transplant patients, to avoid exposing COVID-negative patients and staff in our transplant center to the virus, we have limited follow-up for our COVID-19 PT recipients to either video visits or in-person visits scheduled for hours that our transplant center has dedicated specifically to follow-up for COVID-19

patients. Unfortunately, due to limited availability of testing, we were unable to perform serial SARS-CoV-2 RNA tests to document time to resolution of viral shedding. We have reached out to the three surviving patients to arrange for testing for the development of anti-SARS-CoV-2 antibodies.

Management of immunosuppression in the setting of COVID-19 infection remains challenging. Immunosuppression is usually decreased in the setting of other systemic infections, typically with dose reduction or elimination of the antimetabolite. When our patients informed us of symptoms consistent with COVID-19 infection, we held mycophenolate in three of our patients and temporarily held tacrolimus in one patient on monotherapy, a strategy similar to that employed in other solid organ transplant recipients at our center. The effect of commonly used antirejection medications on SARS-CoV-2 is unknown, although both tacrolimus and mycophenolate have been shown to inhibit the growth of other coronaviruses.[12,13] Mycophenolate, in combination with interferon-ß, was shown to limit viral replication in vivo but was associated with higher levels of viral shedding in vivo.[14,15] It is unknown whether reduction of immunosuppression at disease onset will affect the likelihood of developing cytokine storm syndrome nor is it known when it is safe to reintroduce immunosuppression in patients who recover from COVID-19 infection. We restarted mycophenolate in two patients 5-7 days after resolution of fevers, without any recurrence of symptoms over the next 5 weeks.

At the time these cases were diagnosed, there were limited data on the efficacy of various antiviral therapies against SARS-CoV-2, including hydroxychloroquine and azithromycin, both of which had been used as adjunctive therapy in COVID-19 infection.[12] Three of our patients treated with hydroxychloroquine and/or azithromycin. Two of these patients were treated at hospitals away from our center, and decisions as to whether and which adjunctive agent to use were made based on institution-specific protocols in place at the time of presentation. Subsequent studies have suggested an absence of benefits of these adjunctive agents against SARS-CoV-2, and we have stopped using these agents in our PT and other solid organ transplant recipients.[9,16] Whether there is a role for other potential therapies, such as remdesivir or convalescent plasma, in the treatment of SARS-CoV-2, remains unknown. Ongoing studies of these therapies are being conducted at our hospital, and we have enrolled solid organ transplant recipients when eligible.

ACE2, the receptor which SARS-CoV-2 uses to enter cells, is expressed in the small intestine, pancreas, and kidney, and autopsies from non-transplant patients with SARS-CoV-2 have found virus particles in the kidney.[17-19] It is not known whether the virus may also be found in the donor duodenum or pancreas of PT recipients. Although glucose and laboratory monitoring were not uniform in our patients, we did not observe any change in either glycemic control or pancreas enzymes during their infection or on follow-up, suggesting stable allograft function in the short-term. To date, there have been no reports of acute rejection in other solid organ transplant recipients.

In conclusion, PT recipients with COVID-19 infection present with symptoms and clinical courses similar to what is reported in other solid organ transplant patients. Transient reduction in immunosuppression was associated with a mild disease course in three out of four patients, although the optimal management of antirejection medications remains uncertain. Longer follow-up of PT recipients with COVID-19 infection is needed to determine if there are long-term sequelae on allograft function.

CONFLICT OF INTEREST

The authors declare that that have no financial conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Geoffrey K. Dube, MD: made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and involved in drafting and revising the manuscript. S. Ali Husain, MD MPH: made substantial contributions to analysis and interpretation of data and involved in drafting and revising the manuscript. Kasi R. McCune, MD: made substantial contributions to analysis and interpretation of data and involved in drafting and revising the manuscript. P. Rodrigo Sandoval, MD: made substantial contributions to analysis and interpretation of data and involved in drafting and revising the manuscript. Lloyd E. Ratner, MD MPH: made substantial contributions to analysis and interpretation of data and involved in drafting and revising the manuscript. David J. Cohen, MD: made substantial contributions to analysis and interpretation of data and involved in drafting and revising the manuscript.

ORCID

Geoffrey K. Dube https://orcid.org/0000-0003-0206-5652
S. Ali Husain https://orcid.org/0000-0002-1823-0117
Kasi R. McCune https://orcid.org/0000-0001-6482-8665
P. Rodrigo Sandoval https://orcid.org/0000-0003-4833-3974
Lloyd E. Ratner https://orcid.org/0000-0002-1564-9617
David J. Cohen https://orcid.org/0000-0003-1227-3252

REFERENCES

1. WHO. Coronavirus disease 2019 (COVID-19) Situation Report - 85. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200414-sitrep-85-covid-19.pdf?sfvrsn=7b8629bb_2. Published 2020. Accessed April 15, 2020
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020.382(18):1708–1720.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet*. 2020;395(10223):497-506.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: summary of a report of 72314 cases from the Chinese Center for disease control and prevention. *JAMA*. 2020.https://doi.org/10.1056/NEJMoa2012410
5. Columbia University Kidney Transplant P. Early description of Coronavirus 2019 Disease in Kidney Transplant Recipients in

New York. *J Am Soc Nephrol*. 2020.31(6):1150–1156. https://doi.org/10.1681/ASN.2020030375
6. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant*. 2020.https://doi.org/10.1111/ajt.15869
7. DE Alberici F, Manenti C, Econimo L, et al. A single center observational study of the clinical characteristics and short-term outcomes of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020.97(6):1083–1088. https://doi.org/10.1016/j.kint.2020.04.002
8. Banerjee DPJ, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int*. 2020.97(6):1076–1082. https://doi.org/10.1016/j.kint.2020.03.018
9. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020.https://doi.org/10.1111/ajt.15941
10. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130:2620-2629.
11. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis*. 2020;20(6):697-706.
12. Ahmadpoor P, Rostaing L. Why the immune system fails to mount an adaptive immune response to a Covid -19 infection. *Transpl Int*. 2020.https://doi.org/10.1111/tri.13611.
13. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res*. 2015;115:9-16.
14. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect*. 2013;67(6):606-616.
15. Chan JF, Yao Y, Yeung ML, et al. Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *J Infect Dis*. 2015;212(12):1904-1913.
16. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020.https://doi.org/10.1056/NEJMoa2012410.
17. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637.
18. Su HYM, Wan C, Yi LX, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020.https://doi.org/10.1016/j.cgh.2020.04.040.
19. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clin Gastroenterol Hepatol*. 2020.

How to cite this article: Dube GK, Husain SA, McCune KR, Sandoval PR, Ratner LE, Cohen DJ. COVID-19 infection in pancreas transplant recipients. *Transpl Infect Dis*. 2020;22:e13359. https://doi.org/10.1111/tid.13359