Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Liver Transplant in a Polymerase Chain Reaction−Positive COVID-19 Recipient: A Case Report

Keita Okubo[a,*], Sara Iqbal[b], Blanca Lizaola-Mayo[b], Bashar Aqel[b], Erin H. Graf[c], Juan C. Gea Banacloche[d], Andrew L. Singer[a], and Jack W. Harbell[a]

[a]Division of Abdominal Transplantation, Mayo Clinic, Phoenix, Arizona; [b]Transplant Center, Mayo Clinic, Phoenix, Arizona; [c]Laboratory Medicine and Pathology, Mayo Clinic, Phoenix, Arizona; and [d]Division of Infectious Diseases, Mayo Clinic, Phoenix, Arizona

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 coronavirus disease 2019 (COVID-19) global pandemic has ushered in an era of hesitation in performing transplants in affected patients. This stems from the paucity of data regarding the testing modalities, long-term implications, and uncertain prognosis in this group of patients. Current guidance from the Centers for Disease Control recommends assessing symptoms rather than polymerase chain reaction (PCR) positivity. In light of these recommendations, we describe a case of an orthotopic liver transplant in a patient infected with COVID-19 with persistent PCR positivity for 40 days before retransplant. The patient's perioperative and postoperative course was uncomplicated. Our experience leads us to advocate for liver transplants in patients who are PCR positive for COVID-19 after careful individualized and multidisciplinary evaluation regarding their liver disease and COVID-19 symptomatology.

SINCE the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, in December 2019, it has spread rapidly throughout the world. The disease caused by this virus, coronavirus disease 2019 (COVID-19), has affected more than 70 million people in 191 countries or regions, has killed more than 1.7 million people, and has been declared as a pandemic [1]. The American Society of Transplant Surgeons published guidelines in June 2020 to suspend organ transplants in symptomatic and asymptomatic infected individuals with a positive polymerase chain reaction (PCR) for SARS-CoV-2, because various studies have shown that surgery in these patients increases postoperative pulmonary complications and mortality [2,3]. Additionally, acquiring COVID-19 as a transplant recipient is reported to cause increased mortality (15%-30%), often atypical presentation, and a longer shedding phase with altered viral kinetics [4,5]. As a result, many patients positive for COVID-19 have lost the opportunity to attain a transplant [6]. However, the recent guidelines from the Centers for Disease Control (CDC) recommend formulating decisions regarding isolation on symptoms rather than on PCR [7]. This is because PCR may remain positive for weeks in the absence of viable virus [8]. We describe our first experience of a successful orthotopic liver transplant (OLT) in an asymptomatic patient with a persistently positive COVID-19 PCR prior to the transplant.

CASE

Presentation and Pretransplant Course

A 65-year-old man with a medical history significant for type 2 diabetes mellitus and nonalcoholic steatohepatitis cirrhosis complicated by ascites, nonbleeding esophageal varices, and hepatocellular carcinoma within the Milan criteria underwent OLT from a donation after circulatory death donor in March 2020. He was maintained on immunosuppression with tacrolimus, mycophenolate, and prednisone taper. During workup of persistently elevated liver enzymes, he underwent a liver biopsy that was consistent with biliary outflow impairment, along with periportal fibrosis without any features of rejection. Imaging studies confirmed biliary strictures, which led to multiple endoscopic retrograde cholangiopancreatographies with minimal improvement. His liver enzymes continued to rise with total bilirubin ranging up to 35 mg/dl, alkaline phosphatase of 1485 U/L, and aminotransferases ranging 2 to 3 times the upper limit of normal.

Because of the rapid progression to cholestatic graft failure, he was relisted for liver transplant in August 2020. He was

*Address correspondence to Keita Okubo, MD, PhD, Abdominal Transplant Surgery, Mayo Clinic, 5779 East Mayo Blvd, Phoenix, AZ 85054. Tel: 917-624-3845. E-mail: Okubo.Keita@mayo.edu

0041-1345/20
https://doi.org/10.1016/j.transproceed.2021.07.045

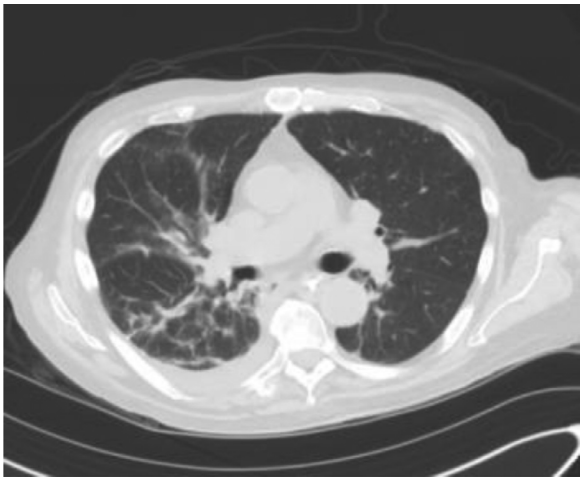

Fig 1. Chest computed tomography without intravenous contrast. Patchy ground-glass opacities with superimposed architectural distortion in the lung bases. Some mild fibrotic changes are thought to be related to COVID-19. COVID-19, coronavirus disease 2019.

continued on tacrolimus monotherapy while he waited for an organ offer. He was found to be SARS-CoV-2 PCR positive on August 13, 2020, while he was evaluated for a potential organ offer. The transplant was aborted owing to the concerns of active infection, and his listing was changed to status 7: inactive for transplant. The patient was completely asymptomatic with a stable physical examination maintaining normal oxygen saturation. He denied fever, cough, shortness of breath, diarrhea, or alterations in his sense of taste or smell. Chest x-ray (Fig 1) and computed tomography without intravenous contrast were performed (Fig 2), despite lack of symptoms, to ensure any signs of disease activity and showed patchy ground glass opacities along the peripheral aspects of the upper, as well as the left lower, lobe, in association with architectural distortion mild bronchiectasis in the right upper lobes and partly in the lower lobes. These findings were thought to represent pulmonary manifestations of COVID-19 pneumonia, and after further review with our infectious disease colleagues, consensus was made to check the SARS-CoV-2 PCR weekly, until negative, to make the patient stay active on the list. Serial testing over 40 days confirmed persistent positivity of the SARS-CoV-2 PCR, as summarized in Table 1 and Fig 3. All molecular testing was performed on nasopharyngeal swabs collected by a health care professional and in viral transport media. Two different emergency use authorized testing platforms were used over the course of this patient's repeated testing: the Abbott (Abbott park, IL) m2000 SARS-CoV-2 RealTime assay and the Cepheid (Sunnyvale, CA) GeneXpert SARS-CoV-2 PCR. As a result, cycle threshold values are not directly comparable between instruments, with the m2000 assay producing cycle threshold values typically 10 cycles lower than the GeneXpert assay. Of note, the patient was staying at a hotel with his wife and son who did not develop COVID-19 and were completely asymptomatic. Furthermore, detection of SARS-CoV-2 antibodies on September 9, 2020, suggested evidence of immunity and low transmissibility.

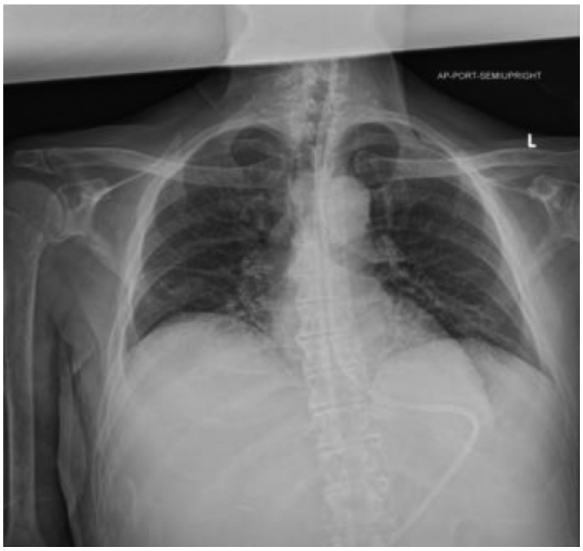

Fig 2. Chest x-ray. No focal consolidation, pleural effusion, or pneumothorax. Normal heart size. Bibasilar atelectasis, right greater than left, is shown. Bibasilar reticular opacities were consistent with the architectural distortion seen on prior computed tomography. Low lung volumes are shown.

The case was reviewed by the liver transplant multidisciplinary team, and in the setting of progressive liver disease, rising Model for End-Stage Liver Disease score, and lack of COVID-19 symptoms, the patient was re-activated for transplant. Two days after being activated on the transplant list, he underwent liver retransplant with a donation after brain death, public health service increased risk organ in late September.

OLT and perioperative management

The patient's surgery was performed in a negative pressure air cleaning system operation room. All the surgical staff had appropriate personal protective equipment (N-95 masks, gowns, hats, and shoe covers) for precaution. General endotracheal anesthesia was administered. Methylprednisolone 500 mg was given intravenously in the operating room prior to reperfusion following to the protocol. The donor liver was mounted in piggyback fashion by sewing the donor suprahepatic cava to the anterior wall of the recipient vena cava at the left, middle hepatic vein orifices. The portal vein was anastomosed to the recipient's portal vein. The recipient had the small replaced right hepatic artery. The hepatic arterial inflow was via an infrarenal aortic conduit using an iliac artery of the same donor and was anastomosed to the donor celiac artery, resulting in a good pulse. The biliary anastomosis was done as an Roux-en-Y hepaticojejunostomy. He tolerated the procedure well, and no complications occurred. Cold ischemic time was 6 hours and 20 minutes. The immediate postoperative ultrasound demonstrated good arterial flow with the patent portal vein and hepatic vein. His postoperative course was significant for acute blood loss anemia, which required a return to the operating room for a washout on postoperative day (POD) 1. A hematoma around

Table 1. Dates With SARS-CoV-2 (COVID-19) Testing

Date	8/13/20	8/17/20	8/28/20	9/2/20	9/8/20	9/15/20	9/22/20	9/25/20	9/26/20
SARS- CoV-2 PCR (rapid)	Detected								
SARS-CoV-2 PCR		Detected	Detected	Detected	Detected	Detected	Detected	Detected	
SARS-CoV-2 Ab				Positive					Negative

COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

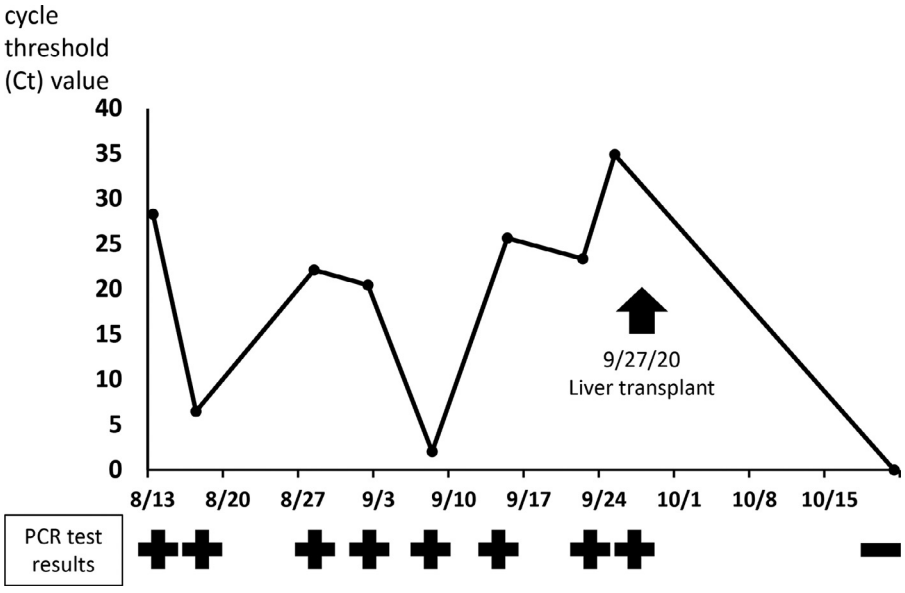

Fig 3. The timeline of Ct value in SARS-CoV-2 real-time PCR. Ct, cycle threshold; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the liver was identified without any major bleeding. He was weaned from mechanical ventilation on POD 2 without any respiratory complication. He was not kept in airborne isolation precautions post-transplant. Mycophenolate mofetil 2000 mg/d, weight-based tacrolimus, and a standard steroid taper were prescribed according to hospital protocol. We did not change our protocol especially to this patient. The rest of the postoperative course was unremarkable. He was discharged home with home health services on POD 10. The last follow-up visit was on POD 30 when his COVID-19 PCR was negative. He was in an excellent clinical status.

DISCUSSION

We report a case of an OLT in a patient with persistently positive SARS-CoV-2 PCR with no symptoms of COVID-19. The transplant was successful, and no viral transmission was documented. Our case helps shed light on the dearth of data concerning identifying the optimal time for transplantation in patients with positive SARS-CoV-2 PCR.

According to the latest American Association for the Study of Liver Diseases (AASLD) expert consensus for transplants in candidates who are SARS-CoV-2 positive, they should be delayed for at least 14 to 21 days after symptom resolution and for 1 or 2 negative SARS-CoV-2 diagnostic tests [9]. The likelihood of a replication-competent virus after 10 days of mild to moderate COVID-19 is very low [10,11]. In some cases of severe COVID-19 infection, mostly complicated by immunocompromised state, recovery of replication-competent virus has been reported beyond 10 days but it is usually undetectable 20 days after symptom onset [12]. The recovered patient can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks, even though there is no replication-competent virus and no reported secondary infections from such patients [13].

Since this transplant was performed, there have been reported cases of isolation of replication-competent virus for longer than 20 days in intensely immunosuppressed patients with cancer (viable virus isolated on days 21, 25, and 64) [14] and in a severely immunocompromised patient with lupus [15].

The CDC Guidelines for Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 emphasize that "disease severity factors and the presence of immunocompromising conditions should be considered in determining the appropriate duration for specific patient populations" [16]. Considering this, our patient seems to be a case of true asymptomatic SARS-CoV-2 infection, not a case of COVID-19.

The exact proportion of asymptomatic SARS-CoV-2 infections is not known, but recent estimates are up to 40% to 45% [17]. In the small but well-studied cohort of passengers of the Diamond Princess cruise ship, 33 of 104 patients followed for 14 days after diagnosis were completely asymptomatic

throughout the observation period [18]. Asymptomatic patients are sometimes conflated with "presymptomatic" patients, in part owing to difficulties with study design [11]. This makes it difficult to ascertain the degree of infectiousness of both categories, which may be biologically dissimilar. Of note, our patient never had any symptoms, and his wife and son, who were staying with him at close quarters in a hotel room, did not develop symptoms of COVID-19 either. Although a false-positive PCR result is conceivable, the persistently positive PCR, development of anti-nucleocapsid SARS-CoV-2 antibodies, and characteristic chest computed tomography findings support asymptomatic infection rather than a persistently false-positive PCR result.

In our case, continued immunosuppression since his previous transplant may have contributed to the persistent positivity of the SARS-CoV-2 PCR. Keeping this in mind, we roughly doubled the waiting period recommended by AASLD. This is also double the amount of time recommended by the CDC for severely immunocompromised patients who were asymptomatic throughout their infection [16].

Additionally, our patient had developed antibodies against SARS-CoV-2 3 weeks after the PCR was detected. The presence of antibodies indicates a previous infection and some level of immunity or protection against COVID-19 re-infection, albeit for an unknown duration [19]. A serum-neutralizing antibody titer of at least 1:20 has been independently associated with noninfectious SARS-CoV-2 [12]. Our patient's antibody titers were later found to be undetectable; hence he was advised to proceed with the COVID-19 vaccination when it became available to him. He has done phenomenally well since his transplant with no major complications.

We face an unusual challenge during the pandemic with the scarcity of empirical evidence to guide solid organ transplants for patients positive for COVID-19. Although there was a decrease in the number of organ transplants performed in the United States amid the COVID-19 outbreak, the number is beginning to increase [7]. The consensus in the transplant community has been the systematic use of PCR-based testing for both donors and recipients, and in cases where recipients have a suspicious or active SARS-CoV-2 infection, it is advised to defer the transplant for at least 4 weeks and after 2 negative tests at least 24 hours apart [20]; however, the optimal disease-free interval for a potential transplant recipient is not known. The decision should be individualized through a multidisciplinary approach to thoroughly evaluate all aspects of the case. The severity of SARS-CoV-2 infection as well as the appropriate use of quantitative viral load and serologic assays should be considered to assess patient eligibility. It is equally important to take into account the severity and progression of the underlying liver disease and the risk of mortality if the transplant is delayed.

CONCLUSIONS

It is encouraging to see increasing data revolving around outcomes in solid organ transplant recipients who acquired the SARS-CoV-2 infection. However, limited studies are available to provide evidence-based guidance regarding the time duration and eligibility of patients who get plagued by this disease before transplant. We hope this case report, with its very favorable outcome, serves to fill the void currently faced by the transplant society.

REFERENCES

[1] Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaieski DF, Yaffee AQ, et al. The 2019-2020 novel coronavirus (severe acute respiratory syndrome coronavirus 2) pandemic: a joint American College of Academic International Medicine−World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. J Glob Infect Dis 2020;12:47–93.

[2] Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020;21:100331.

[3] Jonker PKC, van der Plas WY, Steinkamp PJ, Poelstra R, Emous M, van der Meij W, et al. Perioperative SARS-CoV-2 infections increase mortality, pulmonary complications, and thromboembolic events: a Dutch, multicenter, matched-cohort clinical study. Surgery 2021;169:264–74.

[4] Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. COVID-19 and kidney transplantation. N Engl J Med 2020;382:2475–7.

[5] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant 2020;20:1800–8.

[6] Mamode N, Ahmed Z, Jones G, Banga N, Motallebzadeh R, Tolley H, et al. Mortality rates in transplant recipients and transplantation candidates in a high prevalence COVID-19 environment. Transplantation 2021;105:212–5.

[7] Centers for Disease Control and Prevention. HHS announces new organ transplant guidance, <https://www.cdc.gov/media/releases/2020/p0626-hhs-organ-transplant-guidance.html>; 2020[accessed 05.12.20].

[8] Wajnberg A, Mansour M, Leven E, Bouvier NM, Patel G, Firpo-Betancourt A, et al. Humoral response and PCR positivity in patients with COVID-19 in the New York City region, USA: an observational study. Lancet Microbe 2020;1:e283–9.

[9] Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020;72:287–304.

[10] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465–9.

[11] Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. New Engl J Med 2020;382:2081–90.

[12] van Kampen JJA, van de Vijver DAMC, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. Nat Commun 2021;12:267.

[13] Park YJ, Choe YJ, Park O, Park SY, Kim YM, Kim J, et al. Contact tracing during coronavirus disease outbreak, South Korea. CDC, <https://wwwnc.cdc.gov/eid/article/26/10/20-1315_article>; 2020 [accessed 03.12.20].

[14] Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. N Engl J Med 2020;383:2586–8.

[15] Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med 2020;383:2291–3.

[16] Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19), <https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html>; 2020 [accessed 05.01.21].

[17] Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Ann Intern Med 2020;173:362–7.

[18] Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, et al. Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. Lancet Infect Dis 2020;20:1043–50.

[19] Centers for Disease Control and Prevention. Information for laboratories about coronavirus (COVID-19), <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>; 2020 [accessed 03.12.20].

[20] Ritschl PV, Nevermann N, Wiering L, Wu HH, Moroder P, Brandl A, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: a by-proxy society recommendation consensus approach. Am J Transplant 2020;20:1826–36.