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CASE REPORT

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A case of coronavirus disease 2019–infected liver transplant donor

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Coronavirus disease 2019 (COVID-19) is a novel infectious disease that continues to spread on a global scale. There has been growing concern about donor-derived transmissions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Herein, we present the case of a patient who underwent ABO-incompatible living donor liver transplantation without knowing that the liver donor was infected with COVID-19 during the donation procedure. In this case, the donor-derived transmission to the recipient was not identified, and the liver donor was found to be recovering from a COVID-19 infection. The donor-derived transmission was not identified.

KEYWORDS
COVID-19, liver transplantation

1 | INTRODUCTION

Coronaviruses frequently cause seasonal mild to moderate cold-like respiratory tract infections.[1,2] In December 2019, an outbreak of a novel coronavirus was detected in Wuhan, China. This virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes has been named coronavirus disease 2019 (COVID-19). The transmission of the virus has spread rapidly enough to be considered a pandemic, with the number of confirmed COVID-19 cases at 2 160 207 in more than 180 countries and regions as of April 18, 2020.[3] South Korea, in particular, had one of the largest outbreaks linked to certain religious services and nursing homes in the Daegu City metropolitan area in February 2020. As of March 2, 2020, almost 70% (2136/3081) of the cases in Daegu were related to a religious group, the Shincheonji church.[4]

The clinical spectrum of COVID-19 varies widely as it ranges from the asymptomatic carrier state to severe rapidly fatal pneumonia that affects not only the lungs but the liver and heart.[5,6] A recent study showed that 4 among 4955 blood donors in China were positive with SARS-CoV-2 RNA.[2] Another case series showed that serum SARS-CoV-S viral RNA was detected in at least 15% of patients infected with COVID-19.[7] Given that the asymptomatic or presymptomatic transmission of SARS-CoV-2 has been known,[8,9] there has been growing concern about donor-derived transmissions of SARS-CoV-2. However, there has been no reported case regarding donor-derived transmissions with COVID-19 through solid organ transplantation (SOT) until now. Here, we report the case of a patient who underwent living donor liver transplantation (LDLT) without knowing that the liver donor was infected with COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CT, computed tomography; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; MERS, Middle East respiratory syndrome; MERS-CoV, Middle East respiratory syndrome coronavirus; POS, positive; PT, posttransplant; rRT-PCR, real-time reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplantation.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

Study procedures were approved by the institutional review board (IRB) at Daegu Catholic University Medical Center (IRB approval number: CR-20-055).

2.2 | Case report

Three days after an ABO-incompatible LDLT, the donor was confirmed to have COVID-19. Following this, we observed whether a donor-derived transmission occurred or not. The clinical course of the donor and recipient is summarized in Figure 1.

2.3 | Donor

A 28-year-old female donor with no significant medical history was admitted to have her liver donated to her mother on February 17. She had a mild febrile illness without any respiratory or gastrointestinal symptoms for a day before admittance. Her blood pressure was 120/80 mm Hg, pulse rate was regular at 85 bpm, and temperature was 37.5°C. Both her appearance and breathing appeared normal.

Her white blood cell count was 7400/mm^3, with 79.4% neutrophils. Laboratory data were as follows: hemoglobin, 11.2 g/dL; platelets, 251 000/mm^3; C-reactive protein, 79.7 mg/dL; procalcitonin 0.18 ng/mL; and erythrocyte sedimentation rate, 52 mm/h. Electrolyte levels and kidney and liver function tests were normal. The electrocardiogram showed normal sinus rhythm, and the chest radiograph was normal.

On February 18, she had a successful liver donation. Two days later, she was informed by the health authorities that she was a close contact of a COVID-19–infected patient linked to the Shincheonji church. On February 21 (posttransplant [PT] day 3), she was confirmed COVID-19 positive via nasopharyngeal and oropharyngeal swab and sputum specimens using real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay. However, her blood specimen on PT day 4 revealed negative results of the SARS-CoV-2 PCR. We were unable to perform a PCR test of the blood at the time of transplantation as the blood sample was out of stock. She had a low-grade fever around 37.3°C without any symptom manifestation. Afterward, she was immediately moved to an isolated ward and given lopinavir plus ritonavir (500 mg twice daily, orally) as antiviral therapy, and ceftriaxone (2 g once daily, intravenously) to prevent secondary infection.

Histopathologically, the liver biopsy during donor operation was revealed as follows. The cord-sinus pattern of the liver was reserved without any architecture disorder, and there was no inflammatory infiltration in portal tracts. Although small fatty vacuoles were present in the lobules, there was notable hyperplasia of the Kupffer cells, which remain prominent and proliferated during a viral or bacterial infection or the presence of toxic material (Figure 2). As the PCR for SARS-CoV-2 from the live biopsy revealed negative results, there was no evidence of viral infection in the liver.

There was no adverse drug reaction for 10 days on antiviral therapy. During PT day 14, the patient was stable with a low-grade fever. Her chest radiograph and computed tomography (CT) were normal as well. The result of the COVID-19 PCR via nasopharyngeal and oropharyngeal swab was negative from PT day 7. She was observed until PT day 28 without any signs of the infection worsening.

2.4 | Recipient

A 57-year-old female was admitted on February 11, 2020, for an ABO-incompatible LDLT, with her 28-year-old daughter as her liver donor. She had no symptoms (eg, fever, etc), no history of travels abroad, and no exposure to COVID-19 positive patients. She and her daughter lived separately, and the 2 had not met for 2 weeks before the surgery. She has had chronic hepatitis B-related liver cirrhosis with a model for end-stage liver disease (MELD) score of 17 and

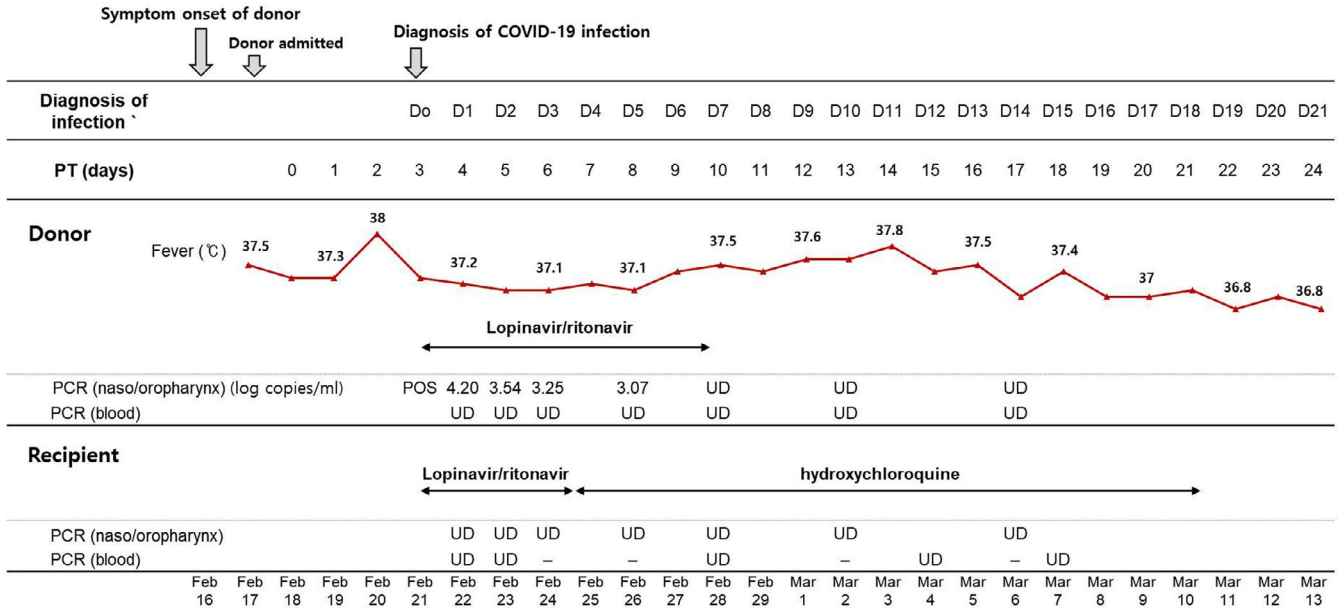

FIGURE 1 Clinical course of the transplant donor and recipient. POS, positive; PT, posttransplant; UD, undetected [Color figure can be viewed at wileyonlinelibrary.com]

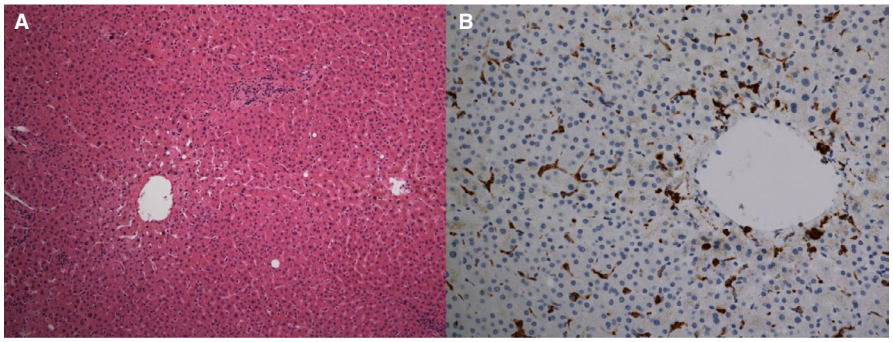

FIGURE 2 Kupffer cells. A, Kupffer cells (small spindle cells) along the sinusoids are prominent and hyperplastic (hematoxylin and eosin stain; ×100 magnification). B, Kupffer cells are stained in brown color (CD68 immunostain; ×200 magnification)

was treated with 300 mg/d tenofovir and 1 mg/d entecavir. Blood examination revealed a white blood cell count of 1200/mm^3 with 43.4% neutrophils, hemoglobin 12.3 g/dL, platelet count 32 000/mm^3, aspartate aminotransferase 38 U/L, alanine aminotransferase 22 U/L, total bilirubin 2.2 mg/dL, and serum creatinine 0.5 mg/dL. The chest radiograph on admission was normal. Afterward, she was administered a pretransplant therapeutic plasma exchange 5 times and basiliximab during the operation to reduce perioperative antibody titer. On February 19 (PT day 1), intensive treatment continued, and she was treated with an immunosuppressant agent such as methylprednisolone, tacrolimus, and mycophenolate mofetil. On PT day 3, upper and lower respiratory tract specimens from the recipient were collected to test for COVID-19 after the donor was diagnosed with COVID-19. The recipient's result was negative. In addition, her blood specimen on PT day 4 revealed negative results for SARS-CoV-2 PCR. To prevent donor-derived transmission, she was given lopinavir plus ritonavir (500 mg twice daily, orally). On PT day 6, the anti-B antibody titer was increased, and the total bilirubin was increased from 1.7 mg/dL to 3.4 mg/dL, plasma exchange was repeated, and the recipient's condition improved. Moreover, the trough level of tacrolimus sharply increased above 30 ng/mL on day 3 of the antiviral therapy. Lopinavir plus ritonavir was switched to hydroxychloroquine (400 mg once daily, orally) because ritonavir might increase the serum concentration of tacrolimus. For the next 14 days, the trough level of tacrolimus was kept at 5-15 ng/mL. Until PT day 14, her chest radiograph was normal, and the result of the serial COVID-19 rRT-PCR test via both nasopharyngeal swab and serum was still negative. Until PT day 69 (April 26, 2020), she has been hospitalized for the treatment of postoperative complications such as complicated intra-abdominal infection and hepatic artery occlusion without any COVID-19 symptoms or signs of infection.

3 | RESULTS AND DISCUSSION

During outbreaks, transplant recipients are exposed to several emerging illnesses, and unanticipated donor-derived infections could unexpectedly occur. In particular, ABO-incompatible LDLT requires strong immunosuppressants, and the recipient of such a process is also at a high risk of getting viral infections.[10] This paper discusses the case of a patient who inadvertently underwent ABO-incompatible LDLT from a COVID-19 positive donor in Korea just before the virus started to spread in the community. The recipient has not developed any signs or symptoms of COVID-19 infection so far.

Human coronaviruses are associated with the common cold and upper respiratory tract infection. Respiratory viruses, including influenza virus, parainfluenza virus, respiratory syncytial virus, rhinovirus, and coronavirus, are increasingly becoming recognized as major causes of respiratory illnesses after solid organ transplantation (SOT). Occasional outbreaks may occur, as exemplified by the SARS coronavirus, which caused fatal illnesses in some transplant recipients.[10] The coronavirus could be transmitted mainly through respiratory droplets like any other respiratory virus. The potential for the transmission of COVID-19 by SOT is unknown at this time. However, RNAemia was reported in at least 15% in 1 case series.[7] Coronaviruses are not known to be transmitted by SOT, and there have been no reported cases of transplant-transmitted coronavirus, especially in novel coronavirus infections such as the Middle East respiratory syndrome (MERS) and SARS.

However, in the case of SARS, some studies found a detectable coronavirus in the serum, sputum, stool, various tissues, including kidney and lung tissues, as well as bone marrow, from a patient with SARS. Guidelines for liver donor SARS screening were proposed during the outbreak of SARS because there is a high likelihood that the transmission of SARS through nonpulmonary organ transplantation is also possible.[11] Furthermore, recent studies have shown that liver injury due to COVID-19 infection, including elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation, has been reported, even though lung injury has been well known as the major damage caused by COVID-19 infection. Liver damage might be caused by a direct liver injury due to COVID-19, drug hepatotoxicity, and immune-mediated inflammation.[6]

In our case, the liver donor who was infected with COVID-19 was healthy and had mild symptoms without pneumonia. There was no evidence of viremia and viral infection on the donor liver biopsy, which had no obvious intranuclear or intracytoplasmic viral inclusions, suggesting that viremia may be short lived or of low titer. Notably, the angiotensin-converting enzyme 2 (ACE2) protein has been abundant in the human epithelia of the lungs and small intestines.[12] However, we could not overlook the possibility of transmission through transplants because the use of an organ from a donor

with COVID-19 (or under the virus' incubation period) could potentially infect organ recipients.[11] In outbreaks, a COVID-19 screening test should be considered for minimizing the risk of donor-derived transmissions.

There is neither definite therapy nor postexposure prophylaxis in a COVID-19 infection. Recently, hydroxychloroquine, lopinavir plus ritonavir, and remdesivir therapy has been proposed as a potential treatment option.[13] However, the efficacy of all such treatments is largely unknown. A previous study showed that health care workers with a high risk of exposure to the MERS coronavirus who received lopinavir/ritonavir as postexposure prophylaxis had a 40% decrease in the risk of infection.[14] In this context, we initially administrated prophylactic lopinavir/ritonavir to the LT recipient. However, because of the drug interaction of lopinavir/ritonavir, we switched to hydroxychloroquine. In line with this, it is unknown whether prophylactic lopinavir/ritonavir or hydroxychloroquine has any role in preventing the donor-derived transmission of SARS-CoV-2 in the recipient. This should be considered an urgent subject for further studies by researchers.

Beyond the donor and recipient, the researchers looked into the status of all hospital personnel who came into contact with them. All of the 32 health care workers (9 doctors, 21 nurses, 1 administrative staff, and 1 medical support employees) who were considered exposed to the donor were put into home quarantine for 2 weeks. They had undergone SARS-CoV-2 PCR testing twice by nasopharyngeal and throat swab both at the beginning and end of the 14-day home quarantine. All tested negative, and none of them developed COVID-19 symptoms. There was no nosocomial transmission to health care workers from unexpected COVID-19 exposure.

Our clinical findings in this case of unanticipated transplantation with a COVID-19–infected donor could provide new insights into the management of patients who undergo SOT in outbreaks. Strategies that would prevent unexpected donor-derived infectious diseases, such as the careful review of donors' charts and laboratory tests for COVID-19 infections, are crucial during outbreaks like the current COVID-19 pandemic. Further information on the disease pathogenesis and transmissibility of COVID-19 is thereby required.

DISCLOSURE

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

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