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Is Kidney Transplantation From a COVID-19–Positive Deceased Donor Safe for the Recipient?

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ABSTRACT

Introduction. In recent months, the number of kidney transplants from deceased donors has declined significantly. One of the reasons is the possibility of infection of the recipient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Determining the risk of transmission of coronavirus disease 2019 (COVID-19) with a donor organ is very important for developing a kidney transplantation policy during a pandemic.

Materials and method. We present cases of kidney transplantation from COVID-19–positive deceased donors to 2 dialysis patients 49 and 45 years old. One of them was on hemodialysis for 28 months; the other received continuous ambulatory peritoneal dialysis (CAPD). Both patients received only basic immunosuppression, including tacrolimus, methylprednisolone, and mycophenolic acid. No antilymphocyte agents were used for induction therapy.

Results. Cold ischemia time was 22 and 21 hours, respectively. One recipient had delayed graft function with increasing of urine output on day 8; another had immediate function. Both patients had no febrile and no other symptoms of acute respiratory disease during their hospital stay. No abnormalities on the chest x-ray were seen. No serum anti-SARS-CoV-2 IgM and IgG were detected before and during 6 weeks after surgery. Repeated nasopharyngeal swabs real-time reverse transcription polymerase chain reaction (rRT-PCR) were negative during the period. Both recipients were discharged 5 weeks after surgery with serum creatinine levels of 122 and 91 mcmol/L, respectively.

Conclusion. Today we have no evidence of the possibility of transmission of COVID-19 from a SARS-CoV-2 positive donor to a kidney recipient. We also have no reason to suspect kidney damage by COVID-19 in a deceased donor at normal serum creatinine level.

IN RECENT months, with the spread of coronavirus disease 2019 (COVID-19), the number of kidney transplants from deceased donors has declined significantly in most countries [1]. This is due to various reasons. First, this is due to the fact that many intensive care units were mainly aimed at assisting patients with severe respiratory failure. Second, stable patients can be on dialysis expecting transplantation for a long time. Third, the risk of transmission of COVID-19 to recipients during transplantation is unknown today.

At the same time, the risk of mutual infection of COVID-19 in hemodialysis centers is quite high, and the results of treatment of these patients are much worse compared to patients of the same age group without life-threatening chronic diseases [2].

Determining the risk of transmission of COVID-19 with a donor organ is important for clarifying the safety of transplantation and developing a kidney transplant policy during a pandemic. We present results of kidneys transplantation

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0041-1345/21
https://doi.org/10.1016/j.transproceed.2021.01.025

from COVID-19–positive deceased donors to 2 dialysis patients in single center.

MATERIAL AND METHOD

The deceased donor was a 45-year-old male patient with diabetes mellitus who was urgently hospitalized at a regional hospital on July 5, 2020, in a coma III. The examination revealed a hemorrhagic insult in the right vertebral-basilar zone, coma III. The patient was placed in the intensive care unit (ICU) and intubated, and mechanical ventilation was started. No signs of pneumonitis were seen on x-ray examination. The coma progressed; 3 days later, brain death was diagnosed. The transplant team was called. Because of hemodynamic instability, diabetes, electrolytes, and biochemical deviations, only kidney harvesting was done on October 5, 2020. The diagnosis of hemorrhagic insult was confirmed by postmortem pathologic examination. Serum creatinine level just before organ harvesting was 92.5 mcmol/L; urea was 8 mmol/L.

Some moderate biochemical deviations were noted: increased serum level of sodium (162 mmol/L), alanine aminotransferase (149 U/L), glucose (16 mmol/L), C-reactive protein (8 mg/L), D-dimer (0.6 FEU/mL). No other significant abnormalities were seen: hemoglobin was 159g/L, erythrocytes were 4.84×10^{12}/L, white blood cells were 10.9×10^{9}/L, lymphocytes were 1.20×10^{9}/L, and platelets were 240.0×10^{9}/L. Fibrinogen was normal at 3.9 g/L.

Nasopharyngeal swab real-time reverse transcription polymerase chain reaction (rRT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was ordered in the patient only for screening on admission to the hospital on July 5, 2020, and the analysis was performed only after the death of the donor on November 5, 2020. The test was positive for SARS-CoV-2. The result was reported to the ICU and then to the transplant center.

An autopsy confirmed the main cause of death: subarachnoid hemorrhage in the frontal lobes and cerebral edema; the competing disease was bilateral polysegmental pneumonia and pulmonary edema. Coronavirus infection caused by COVID-19 was confirmed by rRT-PCR test of autopsy material; RNA SARS CoV-2 was detected in the trachea and left bronchus.

Recipient 1 is a 49-year-old male patient with polycystic kidney disease. Hemodialysis was started in January 2018. Before that in January 2017, a left side open nephrectomy was done due to the unsuccessful treatment of renal cyst infection. The patient has a body mass index (BMI) = 35 and hypertension as a comorbidity. From the beginning of renal replacement therapy, arterial-venous fistula (AVF) thrombosis occurred 3 times, and operations for reconstruction or creation AVF were performed. During April 2020, difficulties with lack of AVF blood flow were noted again.

Recipient 2 is a 45-year-old male patient who also has polycystic kidney disease. Due to living in a faraway agricultural area, the patient's preference was kidney transplantation or continuous ambulatory peritoneal dialysis (CAPD). Because of the progression of renal failure in February 2020, a Tenckhoff was implanted to the patient, and CAPD was started. From the very beginning of peritoneal dialysis, the transport function of the peritoneum was not good (KT/V was 1.21). On the day of surgery, serum creatinine was 1400 mcmol/L, urea was 30 mmol/L, and BMI = 23.

RESULTS

ABO-compatible nonidentical (0-donor, B-recipient) kidney transplantation to the first recipient from this deceased donor (DDKT) was done at November 5, 2020. Cold ischemia time was 22 hours. A feature of the donor was 2 right renal arteries of almost the same diameter, located at a distance of about 5 cm from each other. During the back table, both arteries were cut off from the aortic patch and anastomosed side by side. During transplantation into the left iliac fossa, the common arterial orifice of the graft was anastomosed with the recipient's internal iliac artery "end-to-end" and the graft vein with the external iliac vein. The ureter was anastomosed with the ureter of the recipient (since the left kidney was removed earlier) after indwelling an internal stent.

The positive result for SARS-CoV-2 was received by the center approximately 2 hours after the completion of the operation. Despite the clinic's protocol, the use of antithymocyte globulin for starting immunosuppression in a mismatched ABO donor and recipient, in this case we preferred to avoid their use because of the potential possibility of COVID-19 transmission. The patient received only basic therapy, including tacrolimus (Tc; 15-14 mg/day with maintaining blood level 15.5 to 11.8 ng/mL), mycophenolic acid (1440 mg/day), and methylprednisolone (36 mg/day with rapid tapering 12 mg/day; Fig 1A).

There was delayed graft function with increasing urine output on day 8 post-transplant (Fig 1A). Serum creatine level was decreased from 630 mcmol/L (day 8) to 122 mcmol/L (day 25). glomerular filtration rate was 69 mL/minute × 1.73 m^2 at discharge time (sixth week).

On day 16 postsurgery, the patient revealed genital herpes, which was treated with valaciclovir 1000 mg/day for the next 3 weeks. No other symptoms of infection were seen during follow-up. Blood tests for DNA/RNA cytomegalovirus, Epstein-Barr, hepatitis B, hepatitis C, and HIV were negative.

No serum antibody to infections, including anti-SARS-CoV-2 IgM and IgG were detected on days 7, 14, 25, 35, and 42 post-transplant. Repeated nasopharyngeal swab rRT-PCR were negative on days 3, 9, 14, and 21 post-transplant. There were no abnormalities on the chest x-ray on days 2, 7, and 14 postsurgery.

There were no significant deviations in the results of standard biochemical analyses. Hemoglobin and blood cell count were within the normal ranges (hemoglobin: 82-118 g/L; erythrocyte count: $3.1\text{-}4.32 \times 10^{12}$/L; total leukocytes: $3.7\text{-}6.7 \times 10^{9}$/L; absolute lymphocytes: $0.9\text{-}2.5 \times 10^{9}$/L; platelets: $109\text{-}171 \times 10^{9}$/L). In addition to the standard biochemical parameters, C-reactive protein (0.26-4.34 mg/mL), ferritin (118.7-121.1 ng/mL), fibrinogen (2.03-3.89 g/L), D-dimer (0.3-0.37 FEU/mL), and procalcitonin (0.20-0.26 ng/mL) were determined.

Another DDKT from the same deceased donor was done to the second recipient (with HLA mismatch 5) on November 5, 2020, with a cold ischemia time of 21 hours (both surgeries were done simultaneously in next-door operating rooms). Graft function was immediate with a decrease in serum creatinine to 95 mcmol/L on post-operative day 25 (Fig 1B).

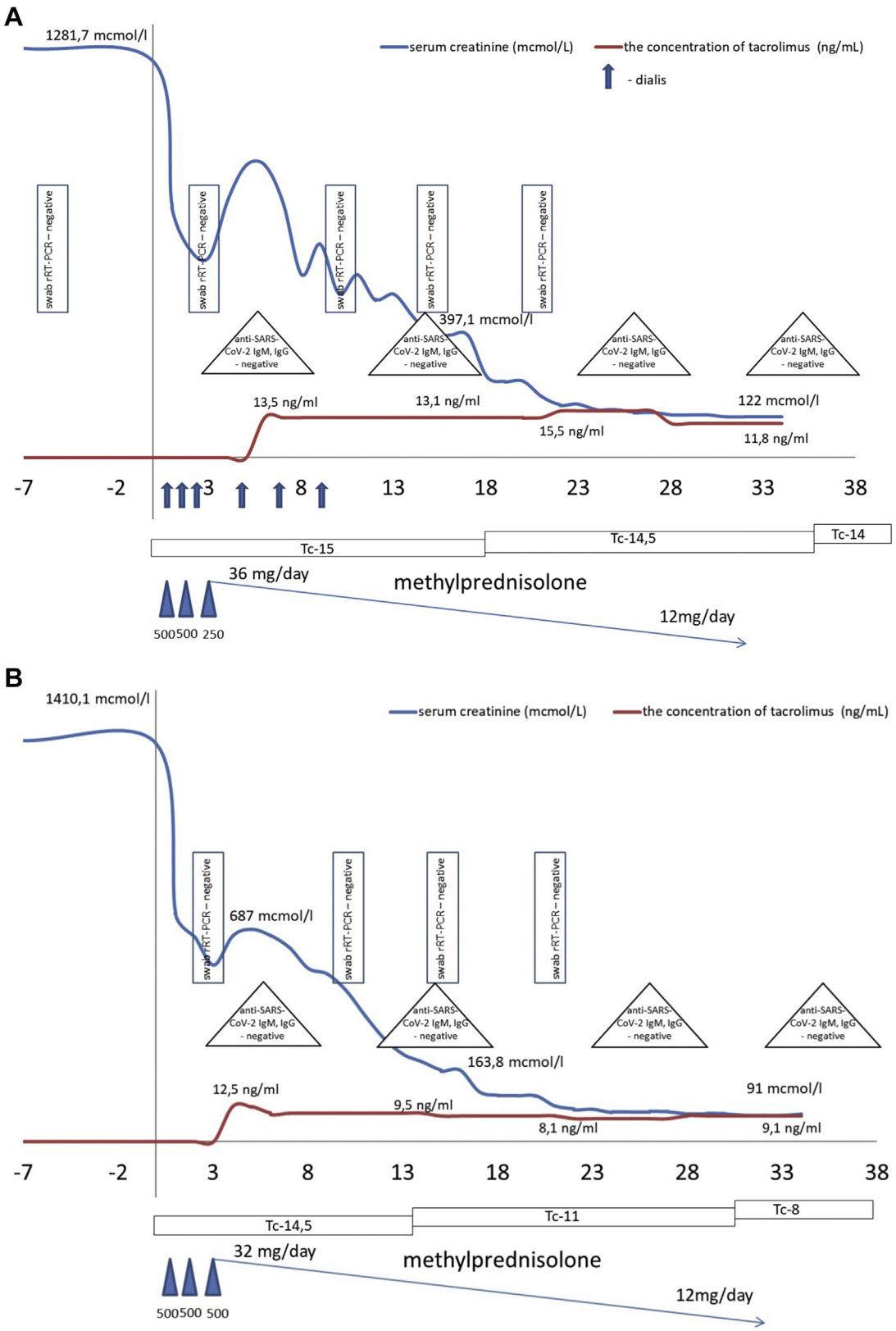

Fig 1. Timeline of the course of perioperative period with some basic biochemical and immunological parameters in patient 1 **(A)** and patient 2 **(B)**. DDKT, deceased living donor kidney transplant; rRT-PCR, real-time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Immunosuppression was started by using 500 mg of methylprednisolone during surgery and 500 mg next 2 days. Then patient also received only triple therapy including tacrolimus (0.2 mg/kg/day), mycophenolic acid (720 g/day), and methylprednisolone (0.3 mg/kg/day with rapid tapering to 12 mg/day). The tacrolimus dose was adjusted to maintain trough level of 10 to 8 ng/mL.

Main laboratory parameters, including hemoglobin (116-138 g/L), erythrocyte (3.98-4.64 $\times$ 10^{12}/L), total leukocyte (16.5-8.9 $\times$ 10^{9}/L), absolute lymphocyte (5.5-3.8 $\times$ 10^{9}/L), and platelet (182-246 $\times$ 10^{9}/L) count, showed no noticeable deviations. Additional laboratory indicators—C-reactive protein (0.7-2.2 mg/L), ferritin (223-305 ng/mL), fibrinogen (1.80-2.75 g/L), D-dimer (0.2-0.3 FEU/mL), and procalcitonin (0.22-0.32 ng/mL)—were also without significant features.

Peritoneal dialysis catheter and ureteral stent were removed 3 weeks after transplantation. The patient was discharged from hospital after 5 weeks with a serum creatinine level of 91 mcmol/L.

Immediately after the recovery room, both patients were placed in the same room with a separate bathroom, where they were all the time until discharge. To prevent contamination, patients left the room only once a day for a walk in the courtyard of the clinic. During the day, the patients were visited only by 1 nurse and once a day, or if necessary, by the attending doctor.

No deviations from the usual course were seen during the hospital stay. Both patients had no febrile and no other symptoms of acute respiratory disease during their hospital stay. The patient was discharged after 5 weeks to prevent out-of-hospital contamination of COVID-19, which would be difficult to differentiate from transmission infection. The patients were recommended to stay home for at least 2 weeks for further observation.

DISCUSSION

COVID-19 has quickly and dramatically changed the world. However, knowledge about SARS-CoV-2 infections in kidney transplant recipients and its impact on solid organ transplantation is limited to case reports and expert discussion [3,4]. We were able to find reports of 117 renal transplant patients infected with COVID19 in fast-published sources. Of these, only 7 recipients had an infection in the early post-transplant period [2,5–8].

There is no information about the transmission of COVID-19 from the donor to the recipient. The internal protocol of our center involves examining all patients on hemodialysis by nasopharyngeal swab rRT-PCR every 2 weeks. This is done to identify asymptomatic COVID-19–positive patients and to prevent contamination of other patients during the procedure. But the protocol does not provide for a strict periodic examination of patients on peritoneal dialysis because of their relative isolation from each other. In cases of urgent hospitalization, including for kidney transplantation, we additionally examine serum for specific IgM and IgG. We know that at the time of the operation, both recipients did not have antibodies to SARS-CoV-2, and the patient undergoing hemodialysis also had a negative swab rRT-PCR test. Both patients were retested weekly for 6 weeks for SARS-CoV-2 with nasopharyngeal swab rRT-PCR and serum IgM and IgG.

We can confidently state that there was no infection with SARS-CoV-2 in both our patients at the time of the operation and in the postoperative period. This is also confirmed by the absence of any clinical manifestations and immune response to COVID-19 (IgM, IgG) during further follow-up.

According to some reports, most common clinical features, including lymphopenia, high C-reactive protein, very high D-dimer, ferritin, and troponin levels, occurred in transplanted COVID-19 patients [5]. Both our patients were additionally examined on average twice a week for leukocytes, lymphocytes, ferritin, D-dimer, and C-reactive protein. Despite the absence of any clinical symptoms, an additional examination was carried out with the aim of early diagnosis of a possible disease and prevention of kidney damage.

Due to intensive immunosuppression, recent transplant recipients (< 3 months post-transplant) are at increased risk of developing severe disease due to COVID-19. They are also likely to have superadded or coinfections due to other pathogens during this early post-transplant phase [2]. Shingare et al described the clinical course of the first reported COVID-19 cases in 2 recent live donor kidney transplantation (LDKT) diagnosed on day 7 and 19 after operation [2]. The LDKT recipients had minimal symptoms and no allograft dysfunction after developing COVID-19. Other studies have reported 5 cases of COVID-19 in recent DDKT. A report from New York describes a poor outcome in 2 recent DDKT recipients [8]. In another report from London, 1 recent DDKT recipient required ventilator support and continuous renal replacement therapy, whereas another required a brief ICU stay [5]. One recent DDKT recipient in a report from China was discharged at day 31 and did not require an ICU stay [6].

A severe course of SARS-CoV-2 infection after deceased donor kidney transplantation (DDKT) could possibly be due to a higher dose of antithymocyte globulin, often used for induction immunosuppression, and could lead to lymphocyte depletion [2,9]. In the absence of understanding about the possibility of transmission of the infection from a COVID-19–positive donor, we preferred to minimize the factors that could affect the severity of the disease. Therefore, we completely abandoned any antilymphocyte agents, despite non-ABO identical (but compatible) transplantation in 1 of the recipients and delayed graft function. In both cases, we used only basic immunosuppression, including tacrolimus, methylprednisolone, and a mycophenolic acid (half of the usual dose for a patient with normal BMI). Calcineurin inhibitors tacrolimus and cyclosporine can diminish replication of SARS-CoV and SARS-CoV-2 [10,11].

Several studies address extrapulmonary abnormalities in COVID-19 infection [12–15]. Some papers provide evidence that SARS-CoV-2 specifically invades the kidneys [16].

The pathophysiology of acute kidney injury (AKI) currently relies mainly on unspecific mechanisms. Prolonged fever, tachypnea, and gastrointestinal troubles could lead to hypovolemia, heart failure, and subsequent prerenal AKI [17,18]. Nephrotoxic drugs can also be incriminated in AKI development, especially antibiotics, antiviral therapy, and radiographic contrast media used to investigate thromboembolic events.

According to Shingare et al, in a cohort of 99 critically ill patients with severe SARS-CoV-2 infection, 42.9% of patients have developed AKI, among them 74.4% severe AKI (kidney disease: improving global outcomes stage III), and 13.4% have required renal replacement therapy [2]. In contrast, Wang et al have found, in a case series of 116 noncritically ill patients from Wuhan, that only 10.8% experienced a small increase in serum creatinine or urea nitrogen within the first 48 hours of hospital stay [19].

Despite some evidence suggesting the tropism of the virus to the kidney parenchyma, it seems that renal injury occurs only with a prolonged progressive course of the disease. In any case, an increase in serum creatinine is a reliable and rather early criterion of kidney damage. This is an important question because the SARS-CoV-2 rRT-PCR test using throat swab specimens can be often falsely negative, possibly due to the sampling techniques, viral load of the upper respiratory tract, and mutations of the virus gene [6].

With the rapid progression of COVID-19 or a fatal concomitant pathology, as in the case we described, it may not have time to develop severe renal damage. This is confirmed by the normal level of serum creatinine in the donor in the premortal period, as well as the relatively rapid repairing of graft function in both recipients, even despite the use of nephrotoxic calcineurin inhibitor. There were no significant deviations during the follow-up period in both recipients. Graft function progressively improved in both recipients; by the time of discharge, serum creatinine was 122 mcmol/L and 91 mcmol/L, respectively.

CONCLUSION

Today, we have no evidence of the possibility of transmission of COVID-19 from a SARS-CoV-2–positive donor to a kidney recipient. We also have no reason to suspect kidney damage by COVID-19 in a deceased donor at normal serum creatinine level.

Avoiding the use of antilymphocyte drugs for induction of immunosuppression may also reduce the risk of developing COVID-19 after transplantation. A careful collection and analysis of such dates is necessary to develop modern practical recommendations for transplant centers.

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