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Case Report

Successful Kidney Transplantation of Two Patients with Donors Positive for Severe Acute Respiratory Syndrome Coronavirus Infection

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Abstract

Despite preventative measures, including vaccination, severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection may result in severe illness, particularly in immunosuppressed transplant recipients. This has had a negative impact on organ donation and transplantation rates. However, the risk of transmission from SARS-CoV-2 positive donors to kidney transplant recipients is unknown. We describe 2 cases of successful kidney transplantation from SARS-CoV-2 positive donors. Case 1: 38-year old unvaccinated female, established on haemodialysis for 1 year, with underlying reflux nephropathy. Donor tested SARS-CoV-2 positive on polymerase chain reaction testing with a cycle threshold (CT) value of 29 initially. Sequential testing demonstrated a rise in CT value (37.8), aiding the decision to proceed. The recipient was high immunological risk and received a controlled category 3 donation after circulatory death (DCD) kidney transplant. She had immediate graft function and did not develop SARS-CoV-2 infection. Case 2: 63-year old female, with diabetes mellitus and hypertension. She was low immunological risk and for pre-emptive transplantation. The

donor was SARS-CoV-2 positive with a CT value of 41.5 and was subsequently negative. Decision was made to proceed with a donation after brainstem death (DBD) transplant. The recipient had immediate graft function and did not develop SARS-CoV-2 infection. We report 2 cases of successful transplantation from SARS-CoV-2 positive donors, without severe infection, with no transmission seen in the recipients post-operatively. Decisions to proceed were primarily made on clinical grounds with assistance from RT-PCR CT values, making this a useful additional tool in determining suitability of organ donation in people who are SARS-CoV-2 positive.

Keywords
Renal transplantation; Covid-19; SARS-CoV-2; cycle threshold value

1. Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection results in a wide spectrum of illness ranging from mild to severe respiratory disease to multi-organ involvement. Despite vaccination and new medications, immunosuppressed patients such as transplant recipients, with SARS-CoV-2 infection are at increased risk of severe infection and death [1, 2]. Accordingly, the coronavirus disease (Covid-19) has had a significant effect on organ donation and transplantation rates, with consideration required for donor selection, timing of transplantation and clinical management post-transplant [3].

The risk of transmission from a SARS-CoV-2 positive donor to recipient in kidney transplantation is unknown. National Health Service Blood and Transplant (NHSBT) UK recommended respiratory polymerase chain reaction (PCR) testing for all donors for Covid-19 and advice against organ donation if positive within the last 28 days [4]. However, a recent amendment of the guideline on 30th March 2022 (POL304/3) supports organ donation from selected donors with positive or indeterminate SARS-CoV-2 PCR results and this guidance is supported by growing experience in USA and Europe with the transplantation of organs (other than lungs) from selected SARS-CoV-2 PCR positive donors without any evidence of transmission to the recipients [4]. This is a welcome change as SARS-CoV-2 PCR swab results may stay positive even when the patient is no longer infectious. Identification of these cases may be aided by PCR cycle threshold (CT) values.

We describe two cases of kidney transplantation, including one unvaccinated recipient, where donors had tested SARS-CoV-2 PCR positive.

2. Case Report

2.1 Case 1

A 38-year old Caucasian woman with end-stage kidney disease secondary to reflux nephropathy who had been established on haemodialysis (HD) for more than one year. She had a past medical history of hypertension and sphincter dyssynergia during childhood with previous intermittent urinary catheterisation. Her transplant workup was unremarkable with good cardiac function. She had a body mass index (BMI) of 21.0 kg/m^2. She was high immunological risk with a human leukocyte

antigen (HLA) antibody calculated reaction frequency (CRF) of 79% (i.e. highly sensitized) and donor specific antibody negative with a negative cross match. She was on the national waiting list for over 4 years. She decided against having Covid-19 vaccinations. She reported never having COVID-19 infection. Her SARS-CoV-2 PCR test was negative at the time of current admission for renal transplant.

The donor was a 27-year old controlled (category 3) donation after circulatory death (DCD), who had withdrawal of life sustaining treatments following a traumatic intracranial hemorrhage. There was no significant past medical history and the donor had good kidney function with an eGFR >90 ml/min/1.72 m^2. The donor had received two COVID-19 vaccinations with the 2^{nd} dose more than 6 months back. The donor had positive lateral flow test 38 days prior to current admission with a negative lateral flow test one week later. The donor was SARS-CoV-2 PCR test negative at the time of admission to hospital. He developed hospital acquired SARS-CoV-2 infection with positive PCR a week following his admission. He remained SARS-CoV-2 PCR positive until the time of donation. CT value was 29.1 a day before donation with value of 37.8 on the day of organ retrieval (Table 1). There was no clinical evidence of Covid-19 pneumonia and his Chest x-rays remained unremarkable throughout.

Table 1 Summary of recipients and donors with corresponding cycle threshold values.

	Case 1	**Case 2**
Recipients		
Recipient age and sex	38 years, female	63 years, female
Body Mass Index (kg/m^2)	21.0	25.2
Aetiology of kidney disease	Reflux Nephropathy	Diabetes mellitus, Hypertension
Covid-19 vaccination status	No	3 doses
SARS-CoV-2 PCR test on admission	Negative	Negative
Waiting time, days	1518	1537
HLA mismatch	2-1-1	2-1-2
HLA Antibody calculated reaction frequency, %	79%	0%
Date of Transplantation	March 2022	March 2022
Donors		
Donor age and sex	27 years, male	47 years, male
Donor type	Donation after circulatory death	Donation after brainstem death
Donor vaccination status	X2 doses (9 m and 6 m prior)	X2 doses (timing unknown)
Admission SARS-CoV-2 PCR	Negative	Negative
Nose and throat swab-CT value 48 hours pre-donation	29.1	-
Endotracheal aspirate-CT value within 48 hours pre-donation	40.4	-

Nose and throat swab-CT value 24 hours pre-donation	37.8	41.5
Endotracheal aspirate-CT value within 24 hours pre-donation	34.4	44.5

Respiratory polymerase chain reaction (PCR) for SARS-CoV-2 was performed with corresponding cycle threshold (CT) values calculated using "Cepheid GeneXpert" for Donor A and "Cepheid Multiplex Cartridge – N2 and E, gene target" for Donor B respectively. Abbreviations: Covid-19 = Coronavirus disease 2019; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; PCR = Polymerase chain reaction; HLA = human leukocyte antigen; CT = cycle threshold.

The recipient consented to proceed with transplantation after detailed discussion with clinical team. The transplant surgery was performed in March 2022 (prior to the updated guidance) and was uneventful with primary graft function. She was given Basiliximab induction followed by Tacrolimus, Mycophenolate Mofetil and Prednisolone. The recipient was discharged home on day 4 post-transplant. She remained COVID-19 free during hospital stay and during subsequent 6-month follow-up period. The graft function has remained excellent (Creatinine 93 µmol/L, eGFR 67 mL/min at 6 m post-transplant) with no proteinuria. A routine SARS-CoV-2 PCR done 3 weeks post transplantation prior to ureteric stent removal was negative.

2.2 Case 2

A British Asian 63-year old woman with end-stage kidney disease secondary to diabetes mellitus and hypertension. She was a pre-emptive recipient with eGFR of 9 ml/min/1.73 m^2. Her transplant workup was satisfactory. She had a BMI of 25.2 kg/m^2. She was low immunological risk with a HLA antibody calculated reaction frequency (CRF) of 0% and was on the transplant waiting list for over 4 years. She was fully vaccinated with three doses of Pfizer-BNT162b2 messenger ribonucleic acid (RNA) vaccine. Her SARS-CoV-2 PCR test pre-admission was negative.

The donor was a 47-year old male donation after brainstem death (DBD), who died of subarachnoid haemorrhage. There was no significant past medical history and eGFR was >90 ml/min/1.72 m^2. The donor was fully vaccinated (2 doses) with the 2nd dose over 8 months ago. He had a positive lateral flow test 15 days prior with flu-like symptoms. Initial PCR for SARS-CoV-2 from nose, throat and endotracheal aspirate was intermittently positive with CT value of 41.5. The second sample done same day showed negative PCR however the following day at time of retrieval SARS-CoV-2 PCR test was positive again with a CT value of 44.5. There were no clinical or radiological features of Covid-19 pneumonia.

Following discussion with the patient a decision was made to proceed with transplantation, which was performed in March 2022 (prior to the updated guidance). She had Basiliximab induction with Tacrolimus and Mycophenolate Mofetil as maintenance immunosuppression therapy. Prednisolone was withdrawn on day 7 post-transplant, as per our low immunological risk protocol. The graft function was immediate. She remained Covid-19 negative at 6 weeks post-operatively. She has remained well 5-month post-transplant with no Covid-19 infection and excellent graft function (Creatinine 94 µmol/L, eGFR 56 mL/min, no proteinuria). A SARS-Cov-2 PCR done 3-week post-transplant prior to elective ureteric stent removal was negative.

3. Discussion

As the world adjusts to life with Covid-19, transplant centres need to balance the risk of infection, including donor-derived, versus the need for continuing with organ transplantation. Current guidelines remain understandably cautious with potential SARS-CoV-2 positive donors, resulting in the loss of potentially viable organs. We report 2 cases of successful transplantation from SARS-CoV-2 PCR positive donors, with no transmission seen in the recipients post-operatively; an outcome which has been replicated in other centres around the world [5].

Although SARS-CoV-2 viral ribonucleic acid (RNA) is predominantly found in the lungs, there is evidence of these viral RNA in other organs including the kidneys [6]. Acute kidney injury is a common pathology in SARS-CoV-2 infections, with the likely pathophysiology ranging from pre-renal, iatrogenic, direct viral injury via tropism, endothelial injury and coagulopathic dysfunction with thrombotic microangiopathy [7, 8]. In addition, podocyte injury leading to proteinuria with focal segmental glomerulosclerosis/collapsing glomerulopathy like lesions on renal biopsy has been reported [9]. So far, there has been no convincing evidence in the literature to prove the presence of SARS-CoV-2 virus within the kidney. However, the potential presence of viral RNA in the kidneys remains a concern. However, there are no reports of transmission of SARS-CoV-2 to kidney transplant recipients from positive donors, although this is limited by the low numbers of positive donors used.

In the two cases that we have presented, SARS-CoV-2 infection was an incidental finding in both donors and there was no evidence of Covid-19 pneumonia. Both had PCR testing, which tests for fragments of the of SARS-CoV-2 genome, which may or may not represent viable replicating virus. Correlation with onset of symptoms where possible and clinical evidence of Covid-19 pneumonia is very important in assessing the risk of infectivity.

Cycle threshold (CT) values are being utilized in order to determine infectivity risk. Standard PCR tests identify infection by isolating and amplifying viral RNA. The CT value is the number of cycles of amplification required to produce a detectable amount of RNA. Therefore, lower cycle threshold value are associated with higher viral load which is often associated with increased infectivity risk [10]. One study found that 70% of patient samples with CT values less than 25 could be cultured, compared to 20% with CT values of 30 and less than 3% for values above 35 [11]. Using PCR CT values in addition to the clinical course and examination findings, should allow more informed decisions to be made regarding Covid-19 positive organ donation. Although serial PCR CT values will be of more value as they would demonstrate a trend of either worsening or improving infectivity, this would still be of value in uncontrolled DCDs as a very high PCR CT value, would suggest lower infectivity at that specific timepoint. Interestingly, there are also reports of successful kidney transplantation from donors with terminal Covid-19 related lung disease with no evidence of transmission [12], suggesting that kidneys from donors with severe disease can be potentially utilized for transplantation without the risk of transmission.

Reported outcomes from SARS-CoV-2 infection in the early renal post-transplant period vary from mild symptoms managed in an outpatient setting to more severe multi-organ illness, requiring intensive care [5, 13, 14]. It is worth noting that as the pandemic has evolved, the proportions of those requiring intensive treatments has decreased, likely related to a combination of improved treatments (both preventative and active) and potentially reduced virulence (as an evolutionary trade-off for increased infectivity) in subsequent variants of a rapidly mutating virus [15]. Other

factors which increase mortality risk are immunosuppression, old age and comorbidities, such as diabetes mellitus, hypertension, obesity and pre-existing lung disease. Therefore, careful selection of potential recipients is important to mitigate risk with SARS-CoV-2 positive donors.

Both of our patients had standard protocol immunosuppression regimens based on their immunological risk. Induction was with Basiliximab. We do not use lymphocyte depleting antibody treatments for induction unless there is a current donor specific antibody in the recipient. Maintenance in the first 3 months is with Tacrolimus, Mycophenolate mofetil and a weaning Prednisolone regimen. For Case 1, who was stratified as high immunological risk this involves a gradual taper over 3 months. For Case 2, who was low immunological risk, Prednisolone was withdrawn on day 7 as per our protocol. Basiliximab, is an interleukin-2 receptor antagonist, preventing T-cell proliferation and has been described to reduce risk of developing SARS-CoV-2 infection in solid organ transplant patients [8]. However, Anti-thymocyte globulin, which results in T-cell depletion and can also be used at kidney transplant induction, is associated with a potential increase risk of SARS-CoV-2 infection [8].

We used the clinical details of the donor and PCR CT value in conjunction with virological advice to decide to transplant. Spike antibody testing was not performed with our patients at the time of transplantation or during post-transplant follow up visits as they are not currently recommended as a routine screening test to assess immune competence against the virus. In the UK, we are currently using serum spike antibody tests to assess eligibility for therapies such as monoclonal antibodies against SARS-CoV-2 virus in patients with clinically relevant Covid-19 infection. However, there is evidence that solid organ transplant patients may have negative or lower spike antibody titres compared to the general population after vaccination and that lower titres may be correspond to higher risk of infection and it may become a routine practice to test for Spike antibodies in recipients prior to implanting a kidney from SARS-CoV-2 positive donor and/or following transplantation at regular intervals [16].

Although not used in our patients, the role of prophylactic treatments, including monoclonal antibodies such as Bamlanivimab, has been reported to reduce the risk of developing SARS-CoV-2 infection in non-transplant patients [17, 18]. Further investigation is underway to assess the efficacy in transplant patients, such as TIXSI-TRANS trial, which is assessing Tixagevimab/Cilgavimab for Covid-19 prophylaxis in solid organ transplant recipients (clinical trials identifier: NCT05234398) [19], as this combination is currently recommended for pre-exposure prophylaxis in the UK and United States of America to individuals who are unable to mount an adequate immune response (e.g. moderate to severe immunocompromise or unable to be vaccinated) [20, 21]. Further review of spike antibody testing and additional prophylactic treatments may be warranted in order to reduce anxiety of transplanting SARS-CoV-2 positive donor organs. However, it is reassuring to see very low risk of donor-derived Covid-19 in recipients receiving kidneys from SARS-CoV-2 positive donors based on current literature and experience of transplanting centres across the world. Recent data from United Network for Organ Sharing database has reported 281 kidney transplants from 193 Covid-19 positive donors who had tested PCR positive for the SARS-CoV-2 virus within 14 days of implantation [22]. The 30-day patient and graft survivals were comparable to outcomes from Covid-19 negative donors [22].

The donors of both of our recipients had a positive PCR test for SARS-CoV-2 virus within 48 hours of organ retrieval but neither had clinical Covid-19 pneumonia and the PCR CT values were high suggesting low viral load and low risk of infectivity. Based on clinical and virological assessments, it

was deemed that the infection risk was very low and we proceeded with transplantation. Although our first patient was unvaccinated for Covid-19, she had been on the kidney transplant waiting list for over 4 years. The risk versus benefit discussions favoured transplantation in her case as the donor was young with excellent kidney function at retrieval and had high CT values with no radiological features of SARS-CoV-2 infection suggesting a lower risk of infectivity.

The outcomes of two patients reported along with similar experience from other centres is encouraging and supports use of kidneys from selected SARS-CoV-2 positive deceased donors after obtaining virological advice and appropriate consent from suitable recipients.

4. Conclusion

In the United Kingdom, the updated NHSBT/ODT guidelines support utilizing kidneys from SARS-CoV-2 PCR positive deceased donors provided there is no clinical evidence of Covid-19 pneumonia. Appropriate informed consent along with clinical assessment and virological advice is essential to determine the risk of infection. Decisions need to be made on case-by-case basis with thorough consideration given to quality of the donor organ, recipient risk profile and waiting period on transplant waitlist. In summary, early results of kidney transplantation from SARS-CoV-2 PCR positive deceased kidney donors with no clinical evidence of Covid-19 pneumonia are supportive of utilising these kidneys for transplantation.

Author Contributions

DB conceived the idea. The manuscript was written by RG with support from MP and AG. All authors reviewed and edited the final manuscript.

Competing Interests

All the authors have declared no competing interest.

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