Serological response and disease-specific neutralizing antibodies in kidney transplant recipients with SARS-CoV-2 infection – a case series

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Case Report

Keywords: COVID-19, kidney transplantation, SARS-CoV-2, immunosuppression, case report

Posted Date: November 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-110295/v1>

Abstract

Background Since SARS-CoV-2 is a highly contagious virus without an available disease-specific medication, the hope is focused on a sustained immunity after SARS-CoV-2 infection and a near-term successful vaccination therapy. A sufficient anti-SARS-CoV-2 antibody production with neutralizing antibodies is crucial to prevent further viral spreading and for protection against prospective reinfection. Kidney transplant recipients may have a potentially aggravated risk for COVID-19 complications as well as a reduced vaccine response due to the allograft protecting immunosuppressive therapy. However, little is known about the strength and duration of their immunological response upon SARS-CoV-2 infection.

Case presentation Here we report on 4 kidney transplant recipients proven to have SARS-CoV-2 infection by positive PCR testing, focusing on their immunological response with the production of disease-specific neutralizing antibodies. All kidney transplant recipients developed a sufficient antibody response including specific neutralizing antibodies against SARS-CoV-2 within 2 to 3 weeks after the first onset of symptoms that sustained during the follow-up of 15 weeks. After 6 weeks, the virus was eliminated in all patients. Most important, the serological response and viral shedding were achieved and sustained in the presence of immunosuppression. Acute kidney graft deterioration was common but reconstituted in all transplant recipients during follow-up.

Conclusions Immunocompromised kidney transplant recipients showed a functional serological response with disease-specific neutralizing antibodies upon SARS-CoV-2 infection, a basic prerequisite for a prospective successful vaccination response.

Background

The clinical presentation of coronavirus disease 2019 (COVID-19) is diverse, ranging from asymptomatic infection to a multisystem disorder with a cytokine storm-like clinical syndrome [1]. Angiotensin converting enzyme 2 (ACE2) receptor facilitates entry and replication of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in various cell types, including endothelial cells where it leads to recruitment of perivascular lymphocytes and severe endothelial injury [2]. Generalized endothelialitis followed by microthrombosis, besides acute respiratory failure, frequently induces multi-organ disease involving kidneys (acute kidney injury, AKI), heart and brain. Thus, the high mortality of COVID-19 patients is attributable to both, pulmonary and extrapulmonary complications.

Kidney transplant recipients are at particular risk for severe COVID-19 complications and acute deterioration of kidney function. These patients are immunocompromised and, in addition, have numerous comorbidities that favor a severe course of COVID-19 disease [3]. Although transplant recipients constitute a high-risk subgroup, reported outcomes are conflicting [4]. The impact of immunosuppression on the course and outcome of a COVID-19 infection is unknown. Whether the immunosuppressive therapy is a driver of COVID-19 disease or, on the contrary, whether it alleviates the symptoms of endothelialitis and cytokine storm-like clinical syndrome in critically ill COVID-19 transplant

recipients is not finally clarified. Immunosuppressive drugs applied to kidney transplant recipients may also prevent seroconversion.

Here we report on 4 kidney transplant recipients who were treated at Heidelberg University Hospital, focusing on their immunological response to infection with SARS-CoV-2 and especially viral shedding and antibody production against SARS-CoV-2 with a follow-up of 15 weeks.

Case Presentation

At the Heidelberg University Hospital, we have seen 4 cases of kidney transplant recipients with COVID-19, proven to have SARS-CoV-2 infection by positive PCR testing in March and April 2020. Distinct courses of viral shedding and serological response upon SARS-CoV-2 infection, including neutralizing antibodies, with a follow-up of 15 weeks are shown in Figure 1. Patient baseline characteristics and outcomes are summarized in Table 1 and Table 2. Biochemical parameters and kidney graft function are illustrated in Figure S1.

Case 1

A 56-year-old woman was admitted to our hospital 29 months after deceased donor kidney transplantation, with a two-day history of fever and cough as the first symptoms of COVID-19. She had no other comorbidities apart from arterial hypertension. She tested positive for SARS-CoV-2 RNA by nasal and throat swabs, and chest x-ray showed a slight bi-pulmonary ground-glass opacity. Immunosuppression with ciclosporin A and prednisolone was continued, while mycophenolate mofetil was discontinued on admission. The prophylactic antibiotic, antifungal and immunoregulatory therapy is given in Table 1. During hospitalization she was in good clinical condition but developed a reversible AKI with a maximum serum creatinine level of 1.1 mg/dL (Figure S1A, Table 2). In addition, she was diagnosed with asymptomatic induced Brugada syndrome. After 7 days she showed a complete recovery and was discharged in good general condition and with reconstituted kidney transplant function. Viral shedding was observed for four weeks and antiviral antibodies including neutralizing antibodies against SARS-CoV-2 were detectable 2 weeks post infection and the antibody-titer was sustained during the follow-up of 15 weeks (Figure 1).

Case 2

A 70-year-old man developed shortness of breath without cough or fever 15 months after deceased donor kidney transplantation and was admitted with a positive SARS-CoV-2 RNA detection in nasal swab 3 days after the first symptoms appeared. Relevant comorbidities were coronary heart disease and arterial hypertension. On admission the patient was hypoxic with a peripheral oxygen saturation of 88% and a respiratory rate of 25 breaths/min. He was immediately transferred to the Intensive Care Unit where

oxygen was administered through a high-flow nasal cannula. The immunosuppression was reduced to 20 mg prednisolone only (Table 1). Chest radiographs showed moderate bilateral patchy consolidation, and the patient had clinical and laboratory signs of both AKI and heart failure (Figure 2A and Figure 2H-I). Inflammation and immune activation parameters were enormously elevated with a serum ferritin of 2841 ng/mL and serum IL-6 of 74.8 ng/L (Figure S1B-G). On day 10 after admission, the patient developed a suspected bacterial superinfection of COVID-19 pneumonia, and antibiotic therapy was extended from tazobactam/piperacillin to meropenem and azithromycin. After 12 days on the intensive care unit, both general condition and kidney transplant function improved significantly and oxygen supplementation was no longer required. The patient was finally discharged after 44 days post-admission with a negative SARS-CoV-2 RNA nose and throat swab. The SARS-CoV-2 IgG seroconversion appeared strongly positive even before negative swab detection after 4 weeks and the neutralizing antibody titer was as high as 1:1280 after 10 weeks (Figure 1).

Case 3

A 64-year-old man was admitted to the hospital with COVID-19 129 months after deceased donor kidney transplantation. First symptoms like dry cough and shortness of breath appeared 2 days before admission. He was tested positive for SARS-CoV-2 RNA by nasal and throat swabs. The chest X-ray showed a severe bi-pulmonary ground-glass opacity. He had several comorbidities such as atrial fibrillation, factor V Leiden mutation and chronic kidney transplant failure with an initial eGFR of only 26 mL/min/1.73m². Tacrolimus and mycophenolate mofetil were discontinued and prednisolone 16 mg was administered. The patient initially required high-flow nasal cannula oxygen therapy but deteriorated rapidly and was therefore intubated and mechanically ventilated 3 days after admission. He developed a severe acute respiratory distress syndrome (ARDS), and therefore had to be ventilated in prone position. The kidney transplant function decreased and hemodialysis was necessary due to the progressive volume overload. Biochemical parameters showed a cytokine storm-like clinical syndrome (Figure S1D-G) combined with severe cardiac involvement with a maximum NT-pro BNP level of 33,598 pg/mL. Prednisolone 100 mg was administered in addition to standard of care anti-infective and immunoregulatory therapy to prevent hyperinflammation (Table 1). After 2 weeks, the patient's general condition gradually recovered, hemodialysis was stopped (Figure S1A) and mechanical ventilation was no longer necessary. After 27 days the SARS-CoV-2 nose and throat swab became negative and the patient could be discharged after 37 days. The seroconversion appeared strongly positive one week post admission with a neutralizing antibody titer of 1:640 at week 10 of follow-up (Figure 1).

Case 4

A 54-year-old male deceased donor kidney transplant recipient, who had been transplanted 33 months ago, was admitted with cough and fever only one day after the onset of symptoms, and was tested

positive for SARS-CoV-2. The x-ray showed only discrete bi-pulmonary ground-glass opacity. Immunosuppressive therapy with cyclosporine A and prednisolone was unchanged while mycophenolate mofetil was discontinued on the day of admission. Although the clinical course was mild and the proinflammatory biochemical parameters were nearly unchanged (Figure S1B-G), the patient developed AKI with a highest serum creatinine level of 2.1 mg/dL (Figure S1A). He fully recovered during the inpatient stay and was discharged after 13 days. The SARS-CoV-2 nose and throat swab was negative after 41 days. Despite the mild clinical course of COVID-19 in this patient, the seroconversion remained strongly positive during follow-up and neutralizing antibodies developed during follow-up albeit with only a lower titer of 1:80 (Figure 1).

Discussion And Conclusions

A sufficient anti-SARS-CoV-2 antibody production with neutralizing antibodies is crucial to prevent further viral spreading and for protection against prospective reinfection. Since SARS-CoV-2 is a highly contagious virus causing a disease for which a specific medication is not available, one major goal is focused on a successful prophylactic vaccination therapy. To what extent the pronounced immunopathology in severe COVID-19 cases will have an influence on the success of this approach is currently difficult to predict. Kidney transplant recipients may have a potentially aggravated risk for COVID-19 infection and reduced vaccine response due to the allograft protecting immunosuppressive therapy.

Although several case reports and case series of kidney transplant recipients with COVID-19 have previously been reported, little is known about their immunological response upon SARS-CoV-2 infection [4,5]. Herein, we describe for the first time a strong and sustained serological response with neutralizing antibodies in immunocompromised kidney transplant recipients. All patients developed a sufficient antibody response within 2 to 3 weeks after the first onset of symptoms of SARS-CoV-2 infection that sustained during the follow-up of 15 weeks. After 6 weeks, the virus was eliminated in all patients.

A recent study observed a lower level of IgM response in mildly-ill COVID-19 patients compared to patients with a severe disease activity [6]. Notably, a review showed that nearly all of the current literature focused on the results obtained using serologic testing in symptomatic patients [7]. The definition of antibody responses in individuals with subclinical or mild disease is still obscure. In our cohort, however, even patient 1 and patient 4 with only a mild COVID-19 course, revealed an immunological response albeit with a lower neutralizing antibody titer, compared to patient 2 and patient 3 with severe disease activity, requiring mechanical ventilation, and cytokine storm-like clinical syndrome. Neutralizing antibodies play an essential role in prevention of infection and viral clearance and are a critical immune player for protection against viral diseases as COVID-19. Although there are reports, that up to 30% of patients with mild disease activity generated a deficient neutralizing antibody titer, all patients of our

study developed anti-SARS-CoV-2 antibodies during follow-up [8]. Notably, despite a high viral load early after infection and a high antibody titer measured by ELISA, patient 4 developed a markedly lower neutralizing antibody titer compared to other patients of the study group. However, if the mild clinical course accompanied by a weak immune response with almost standard values of ferritin and IL-6 (Figure S1F-G, Figure 1) might be responsible, remains hypothetical.

The strength and duration of immunity after SARS-CoV-2 infection and vaccination, respectively, are key issues for a prospective herd immunity [8]. According to recent reports, there is increasing evidence for a decrease of IgG levels and neutralizing antibodies within 2-3 months after infection [9]. Another analysis of the dynamics of neutralizing antibody titers in eight convalescent patients with COVID-19 also showed decreased neutralizing antibodies approximately 6–7 weeks after disease onset [10]. At least during our follow-up of 15 weeks, the titers did not decline in all kidney transplant recipients but long-term observations are pending.

Our study has several limitations with only 4 kidney transplant recipients reported. Clearly, the observations made in this report are preliminary and further larger scaled studies have to confirm our data. Nevertheless, our presented data provide a first in-depth look into the kinetics and specificity of the serological response in kidney transplant recipients.

In conclusion, we report a functional serological response with SARS-CoV-2 specific neutralizing antibodies in immunocompromised kidney transplant recipients upon SARS-CoV-2 infection, a basic prerequisite for a prospective successful vaccination response.

Abbreviations

ACE2- angiotensin converting enzyme 2

AKI- acute kidney injury

COVID-19- coronavirus disease 2019

eGFR- estimated glomerular filtration rate

PCR- polymerase chain reaction

SARS-CoV-2- severe acute respiratory syndrome coronavirus 2

Declarations

Ethics approval and consent to participate

Informed consent of the patient has been given and every precaution taken to protect the privacy and confidentiality of the patient has been taken, in line with the World Medical Association Declaration of Helsinki.

Consent for publication

Written consent for publication has been given by the patient and is available upon request.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No authors have any competing interests to declare.

Funding

No authors are receipt of any grants or other sources of funding to support this work.

Author contributions

CS, UM and CSo designed the study; CS, PS, TG, CM, MZ, UM and CSo drafted and wrote the manuscript; AP and RB carried out experiments; CS, CM and CSo drafted the figures; FK, CN and MZ revised the manuscript; all authors approved the final version of the manuscript.

Acknowledgement

This study was conducted with resources provided by the DZIF transplant cohort e.V. (<https://www.dzif.de/en/working-group/transplant-cohort>), support code TTU 07.701.

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Tables

Table 1

Baseline characteristics of transplanted COVID-19 patients

Patient	1	2	3	4
Age (years)/sex	56/f	70/m	64/m	54/m
Months since Tx	29	15	129	33
Baseline SCr (mg/dl)	0.7	2.1	2.5	1.4

Comorbidities	HT	CHD, HT	AF, FVL	HT
ACEI or ARA	-	-	+	-
Baseline IS	CsA/MMF/P	Tac/MMF/P	Tac/MMF/P	CsA/MMF/P
IS during disease	CsA/P 4mg	P 20mg	P 16mg	CsA/P 4mg
Onset to diagnosis (d)	2	3	2	1
Onset to admission (d)	2	4	2	1
Initial symptoms				
Fever	+	-	-	+
Cough	+	-	+	+
Dyspnea	-	+	+	-
Diarrhea	-	-	-	-
Chest CT findings	mild	moderate	severe	mild
(mild, moderate, severe)				
Antibiotic therapy	Ceftriaxon	Pip/taz	Pip/taz	Pip/taz
	Azithromycin	Azithromycin	Azithromycin	
	Meropenem	Meropenem		
Antifungal therapy	Caspofungin	Caspofungin	Caspofungin	Caspofungin
Immunomodulatory therapy	+	+	+	+

Oxygen support

HFNC (d)	-	+ (7)	+ (3)	-
Invasive ventilation (d)	-	-	+ (15)	-
Admission to ICU	-	+	+	+
Time in ICU (d)	0	12	34	3
Onset to discharge (d)	7	44	37	13

ACEI, angiotensin converting enzyme inhibitor; ARA, angiotensin receptor antagonist; AF, atrial fibrillation; CHD, coronary heart disease; CsA, ciclosporine A; d, days; f, female; FVL, factor V Leiden mutation; HCQ, hydroxychloroquine; HFNC, high flow nasal canula; HT, hypertension; ICU, intensive care unit; IS, immunosuppression; m, male; MMF, mycophenolate mofetil; mo, months; Pip/taz, piperacilline/tazobactam; P, prednisolone; SCr, serum creatinine

Table 2

Outcome of transplanted COVID-19 patients

Patient	1	2	3	4
ARDS	-	+	+	-
Mechanical ventilation	-	-	+	-
Infectious complications	+	+	+	+
Sepsis	-	+	+	-
Pneumonia	-	+	+	+
CMV infection	-	-	+	-
UTI	+	+	-	-
Acute kidney injury stage	1	2	3	1
Baseline SCr (mg/dl)	0.7	2.1	2.5	1.4

Highest SCr (mg/dl)	1.1	2.9	5.7	2.1
Required dialysis	-	-	+	-
Graft loss	-	-	-	-
Cardiac involvement	+	+	+	+
Highest TNT	13	41	85	31
Highest nt-pro BNP	379	9249	61761	296
ECG alterations	QTc	QTc	QTc	QTc
Brugada syndrome				
QTc before HCQ (ms)	397	393	401	362
QTc after HCQ (ms)	430	415	429	401

ARDS, acute respiratory distress syndrome; ECG, electrocardiogram; d, days; HCQ, hydroxychloroquine; SCr, serum creatinine;

UTI, urinary tract infection

Figures

Figure 1

Distinct time courses of SARS-CoV-2 shedding, anti-SARS-CoV-2 antibodies and anti-SARS-CoV-2 neutralizing antibodies in 4 infected kidney transplant recipients.

Supplementary Files

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