Kidney Transplantation in a Recipient with Positive RT-PCR for SARS-CoV-2

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ABSTRACT

When it is safe to proceed with transplantation after coronavirus disease 2019 (COVID-19) infection is still unknown. We describe the clinical course and management of immunosuppression in a patient with positive real-time polymerase chain reaction (RT-PCR) for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a nasopharyngeal swab at the time of kidney transplantation, and with positive antibodies for SARS-CoV-2. The patient had no complications and was discharged with a functioning graft.

KEYWORDS: SARS-CoV-2; kidney transplantation; Immunosuppression therapy

INTRODUCTION

The ongoing pandemic of SARS-CoV-2 has strongly affected transplantation programs. Depending on the severity of the pandemic, transplantation programs were restricted to urgent life-saving procedures or were directly closed due to the strain posed on the availability of healthcare resources [1].

Pre-transplant evaluation should be based not only on specific RT-PCR results (which may yield false negative results), but also on a careful evaluation of the epidemiologic background and the clinical context. Our protocol includes routine chest computed tomography (CT) scan for the recipient, as this method may detect pulmonary infiltrates in asymptomatic patients with SARS-CoV-2 infection, with better sensitivity than a RT-PCR on a nasopharyngeal swab (NPS) [2]. Our local regulatory agency, the Instituto Nacional de Coordinación Único de Ablación e Implantes (INCUCAI), at the time this case occurred (with low viral circulation in the community), allowed transplantation procedures without requiring the recipient's RT-PCR screening result. The final decision was taken based on the transplantation team's clinical judgment.

Our protocol regarding COVID-19 risk contraindicated transplantation if a potential kidney recipient had epidemiological risk factors, clinical symptoms or CT scan findings consistent with SARS-CoV-2 infection. Otherwise, a NPS was obtained, and if the delay in obtaining the result of SARS-CoV-2 resulted in an unacceptably prolonged ischemia time, the procedure was performed with the result of this determination still pending.

We report the management and outcome of a case of a deceased donor kidney recipient,

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Table 1: Management of immunosuppression in a patient with positive SARS-CoV-2 RT-PCR at the time of kidney transplantation.

Day post-Tx / Treatment	0	+1	+2	+3	+4	+5	+6	+7	+8	+10	+14 Discharge
Basiliximab	20 mg	-	-	-	-	-	-	-	-	-	-
Methyl-prednisolone		125 mg	-	-	-	-	-	-	-	-	-
Prednisone (mg/kg/day)			1	1	1	1	1	1	0.75	0.75	0.25
Myf	1,440 mg	with-drawn	-	-	-	-	-	-	720 mg	1,080 mg	1,080 mg
FK dose (mg/kg/day)	-	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.25
FK dosage (ng/mL)					2.7			3.6		7.3	8.1
IVIG	-	-	20 g	20 g	20 g	-	-	-	-	-	-
Hemodialysis	-	YES	-	YES	-	YES	-	-	-	-	-

Tx: Transplantation; Myf: Mycophenolic acid; FK: tacrolimus; IVIG: Intravenous Immunoglobulin G

for whom the screening test for SARS-CoV-2 was known to be positive a few hours after the transplantation procedure.

CASE PRESENTATION

The recipient was a 53-year-old male, with end-stage chronic kidney disease (ESKD) secondary to a membranous nephropathy, on hemodialysis since 2011. He had a history of asthma, coronary disease (coronary angioplasty in 2018), and transient ischemic neurological events in 2010 and 2018. His Human Leukocyte Antigen (HLA) was: A:1/68, B:61/51, DR:4/4; and class I and II panel reactive antibodies were negative. He had no sensitization events.

The donor was a 56-year old female, who died of a subarachnoid hemorrhage. Her HLA was A: 24/31, B: 27/61, DR: 4/8, DQ: - /8 (HLA Missmatch: 2, 1, 1). She came from a hospital without COVID-19 cases, and lived in an area without SARS-CoV-2 circulation at that time.

The recipient reported full compliance with quarantine and patient-safety protocols when going to hemodialysis sessions. There were no COVID-19 cases at his hemodialysis center. He was admitted on May 22nd, 2020 for kidney transplantation. Infection-control measures for COVID-19 were implemented from the patient's admission to the moment when RT-PCR screening results became available.

Physical examination was normal. Chest CT scan was informed without lesions suspicious of COVID-19. A NPS was obtained for SARS-CoV-2 screening. As waiting for the results would result in prolonging ischemia time (which was already 31 hours), it was decided to proceed with a right kidney transplantation, performed without surgical complications.

The patient received induction immunosuppression with basiliximab 20mg (Day 0), methylprednisolone 500mg and sodium mycophenolate 1,440mg, and was hemodynamically stable after the procedure, without need of ventilatory support, without symptoms or fever, but with anuria.

Ten hours after surgery, laboratory confirmed a positive RT-PCR SARS-CoV-2 result (Real Star ® SARS-CoV-2 RT-PCR Kit 1.0, Altona Diagnostics GmbH, Germany) in the NPS. Cycle threshold level (Ct) was 34. Chest CT scan was reassessed, and small sub-pleural lesions informed as non-specific were considered to be consistent with COVID-19 lung

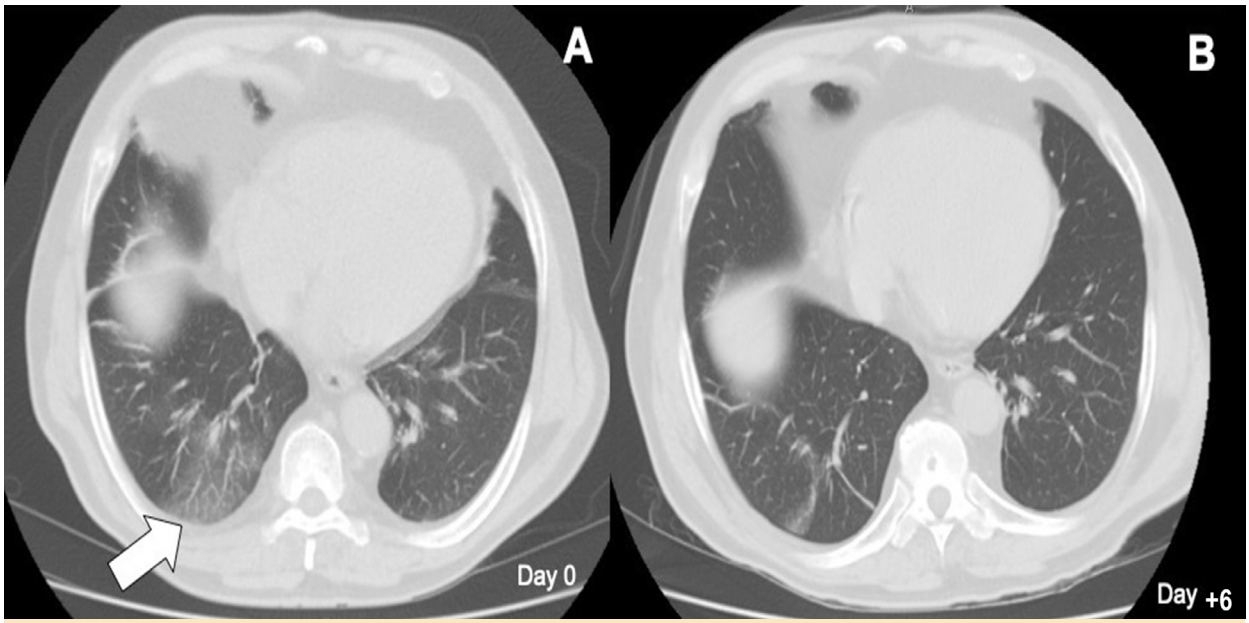

Figure 1: Chest CT findings (Day 0 [A] and Day +6 [B] after transplant) in a patient with positive RT-PCR for SARS-CoV-2 at the time of kidney transplantation.

disease (Fig 1A). On re-interrogation, the patient stated that he failed to report that he had been admitted with gastrointestinal bleeding from April 14th to April 16th to a hospital located in a high COVID-19 circulation area.

With this positive SARS-CoV-2 RT-PCR result, the immunosuppression protocol was modified. (Daily immunosuppression regimen is detailed in Table 1).

IgM and IgG anti-SARS-CoV-2 specific antibodies (day +1) were positive with a cut-off index (COI) of 29.6 and 11.1 respectively. (COI>10 are positive) (COVID-19 ELISA, Vircell SL, Spain). SARS-CoV-2 RT-PCR- NPS on day +3 and +4 after transplantation were negative. Chest CT scan on day +6 showed improvement of the subpleural lesions (Fig 1B). Kidney function progressively improved, (hemodialysis was required on days +1, +3 and +5 post-transplantation). Relevant laboratory values are detailed in Table 2.

The patient was discharged, with normal graft function on day +40 after transplantation.

DISCUSSION

The decision to maintain non-vital organ transplant programs running amidst the COVID-19 pandemic entails carefully weighing the pros/cons of risks that are very difficult to predict due to the lack of strong scientific data.

In our country, graft perfusion machines are not available. Prolonged cold-ischemia time in the absence of kidney graft-perfusion machines is deleterious for graft evolution after transplantation [3]. This was the rationale behind the INCUCAI's clearance to proceed with transplantations based on the clinical team's judgment, even when RT-PCR results were still pending.

Patients with end-stage kidney disease (ESKD) are among the most vulnerable populations due to the immune impairment associated with ESKD and a high comorbidity burden. Epidemiological risk may be also increased due to the need to go to the hemodialysis care centers many times a week.

The pandemic is taking a heavy toll on patients with ESKD, both in terms of a much higher incidence and a higher mortality than that observed in the general population.

Table 2: Laboratory findings in a case of positive SARS-CoV-2 RT-PCR at kidney transplantation.

	May 22nd	May 23rd	May 24th	May 25th	May 26st	May 28th	June 1st	June 5th	June 8th
Day post tx	0	+1	+2	+3	+4	+6	+10	+14	+17
RBC count (x106) (/mm3)	3.28	2.76	3.17	2.92	3.18	3.29	3.04	3.6	3.7
Hematocrit (%)	32	26	29	26	29	29	27	33	36
Hemoglobin (g/dL)	10	8.2	9.1	8.5	9.1	9.7	8.8	10.7	11
WBC count /mm3	7,643	12,990	12,500	8,002	9,695	10,920	5,975	7,904	8,444
Lymphocytes %	29	6	7	10	10	13	11	8	21
Neutrophils %	50	87	84	84	80	73	83	90	75
ERS (mm/1st hour)			58						
D-dimer (ng/ml)			3.37	0.05	>4				
Ferritin (ng/ml)			682	465	487				
Fibrinogen (mg %)			408		395				
Platelet count (/mm3)	235,700	232,000	197,500	154,600	157,100	180,900	229,600	282,100	213,600
Total Bilirubin (mg/dL)	0.6	0.6	0.4	0.5	0.5	0.4	0.3		
ALT (IU/L)	12	13	16	11	12	10	10		
AST (IU/L)	8	10	9	8	10	12	13		
Alk P (IU/L)	75	66	62	58	53	63	54		
LDH (IU/L)									
Albumin (gr/L)	4.3	3.8	3.7	3.6	3.6	3.7			
Urea (mg/dL)	122	136	118	151	154	149	294	182	118
Creatinine (mg/dL)	12.15	13.71	10.98	11.91	11.4	10.93	12.54	3.68	2.38
IgG SARS (COI >10)		11.1						1.03	
IgM SARS (COI >10)		29.6						11.7	
RT-PCR SARS-CoV-2	D				ND	ND			

RBC: Red blood count; WBC: White cells blood count; ERS: Erythrocyte sedimentation rate; ALT: Alanine transaminase; AST: Aspartate transaminase; Alk P: Alkaline Phosphatase; LDH: Lactic Dehydrogenase; COI: Cut-off Index; RT-PCR SARS-CoV-2: real-time Polymerase chain reaction Severe Acute Respiratory Syndrome-Coronavirus-2; D: Detectable; ND: Non -Detectable

Mortality rate in ESKD in one series of patients on peritoneal or hemodialysis was reported to be 31% [4]. One hemodialysis center in Italy reported an incidence of 16% (41/256), an incidence 10-fold higher than that of the general population in the same region [5], with a raw mortality rate of 41% (18/41 patients) [6]. In Spain, in an area heavily impacted by COVID-19, another center reported a 41% infection incidence (37/90 hemodialysis patients), which is also more than 40-fold higher than the incidence observed in the general population in the same area at the same time [7], with a mortality rate of 16%.

The COVID-19 Registry of the Spanish Society of Nephrology found a significantly higher mortality in hemodialysis patients (24.9%) compared to the mortality observed in transplanted patients (18.6%), among 868 patients on renal replacement therapy with COVID-19 infection [8].

The above-mentioned information is consistent with a meta-analysis showing that chronic kidney disease is associated with severe COVID-19 infection [9].

Therefore, the available information suggests that patients on hemodialysis have a signifi-

cant risk of acquiring SARS-CoV-2 infection, with a mortality rate that seems higher than that of kidney transplanted patients experiencing COVID-19 in the same areas. However, this conclusion should be taken with caution, as it may be influenced by many other variables such as age and comorbidities.

Kidney transplanted patients with COVID-19 in the Swiss Transplant Cohort Study had an extrapolated incidence slightly superior (21 cases in a >5,000 solid organ transplant recipients cohort) than the incidence observed in the general population (360/100,000 people) with a mortality rate of 10% (2/21 patients) [10]. The same mortality rate was observed in a small cohort from Wuhan (10%) [11]. A series from the United Kingdom reported a 14% mortality [12]. However, in other series, mortality rate reached 25% [13].

With the information available to date, it is unclear whether the decision to perform transplantation in a patient on chronic hemodialysis is harmful or beneficial, both in terms of the risk of COVID-19 acquisition and mortality. An individualized approach considering the patient's condition and the local epidemiology is needed.

After the start of local circulation of SARS-CoV-2, our institution modified the induction immunosuppression protocol, no longer using thymoglobulin and using basiliximab instead [14].

The management of immunosuppression in this case was initially minimized to tailor it to the possible presence of an active SARS-CoV-2 infection, while trying at the same time to preserve graft function [15]. IVIG was chosen to complete induction immunosuppression, due to its immunomodulatory effect [16] and to its possible positive effects on COVID19 in non-transplanted patients [17,18], also reported in patients with kidney transplantation and SARS-CoV-2 pneumonia [11].

The rapid negativization of RT-PCR after the initial high Ct positive result (consistent with a low viral load), the initial presence of antibodies [19] and the evolution of the subtle pulmonary lesions (not suspected as COVID-19 related initially) were consistent with an already cured subclinical infection. Epidemiological background suggests that the most probable time and place for the initial contagion was his hospitalization one month before transplantation.

All this information allowed for a careful increase in immunosuppression. IgG turned negative and IgM levels drastically decreased on day +14, which may be have been related to the combination of immunosuppression and time elapsed after the initial infection.

Although nowadays we are having access to RT-PCR-screening results at the time of transplantation, false negatives are known to occur. Although these false negative results rarely occur with lower respiratory tract samples as bronchoalveolar lavage [20], obtaining these samples and results in real time in a time-constrained event is a challenge. Chest CT scans are important as part of the initial screening, along with epidemiological history and clinical evaluation, and RT-PCR results.

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