SARS-CoV-2 infection in the immediate post-transplant period: A report of five kidney transplant recipients

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- LLS: manuscript writing.
- LL, AS, AL: article design.
- CN, CJ, MB, TA, AW: article review.

ABSTRACT

Introduction: The severe acute respiratory syndrome coronavirus 2 pandemic caused a negative impact on transplantation worldwide. One of the complexities is the management of the immunosuppression and anti-viral medication in transplant recipients. Herein we describe our experience managing five patients with coronavirus disease 2019 (COVID-19) immediately after kidney transplant. Description: we describe a series of five transplant recipients. Two were submitted to a low immunological risk induction immunosuppression: one developed severe disease, the other developed critical disease. The remaining three were submitted to a high immunologic risk immunosuppression: one developed mild disease, but approximately two months after diagnosis developed moderate COVID-19; another developed severe COVID-19; the remaining patient developed critical illness and perished. Both patients with critical COVID-19 developed bacterial and fungal superinfections in the Intensive Care Unit. All eligible patients were submitted to remdesivir and dexamethasone. The anti-metabolite was reduced or suspended. Despite worsening kidney function during the acute phase, kidney replacement therapy was only needed in one patient and the average serum creatinine at the time of discharge was lower than the pre-COVID-19 nadir. Discussion: There is still no definitive answer on whether solid organ transplant recipients carry a higher risk for morbimortality. Risk factors for the general population can also affect their outcome. The prolonged viral shedding in recipients may explain the irregular evolution of the patient who developed COVID-19 months after the initial diagnosis. The reduction of immunosuppression can be problematic in early post-transplant, but no apparent signs of rejection were noted. Literature addressing this specific context is scarce and studies are needed to clarify the optimal management of these patients.

Keywords: COVID-19, dexamethasone, immunosuppression, kidney transplantation, remdesivir, SARS-CoV-2

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic caused a profound negative impact in healthcare systems, and consequently on the transplantation activity worldwide¹,². The coronavirus disease 2019 (COVID-19) is predominantly associated with respiratory symptoms, but can have devastating repercussions in multiple organs³. In Portugal, due to fear of outbreaks in transplant centers during the initial stages, transplantation was restricted, but still performed when a high quality organ was available, and after selecting minor risk recipients. However, due to a stabilization in numbers of infections and casualties, kidney transplantation activity returned to near basal levels after August 2020. Unfortunately, Portugal was heavily affected by the pandemic during the third wave, with an abrupt peak of new cases in January 2021, resulting in outbreaks occurring in many hospitals, including transplant centers, such as ours, despite all the efforts put in place to prevent them. There is an increasing amount of data regarding transplant recipients and COVID-19⁴, but still no evidence on the optimal management of these patients, especially regarding the adjustment of their immunosuppressive regimen. In our center, we experienced an outbreak in a period when there were five patients in their first month post-cadaveric donor kidney transplantation, all of them becoming infected. The aforementioned patients had a negative SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test using a nasopharyngeal specimen at admission. Herein, we describe our experience in the management of five cases of SARS-CoV-2 infection in the immediate post-transplant period.

CASE SERIES DESCRIPTION

Patient 1

A 55-year-old caucasian male with end-stage kidney disease (ESKD) of unknown etiology on regular hemodialysis since 2017, was admitted
for deceased donor kidney transplant (KTx) on 31st December 2020. Prior medical history included arterial hypertension with hypertensive cardiopathy and benign prostatic hyperplasia. The immunologic profile identified only 1 mismatch in HLA-A and, according to our protocol, the patient was submitted to an induction immunosuppression (IS) regimen consisting of basiliximab, tacrolimus, mycophenolate mofetil (MMF) and methylprednisolone. Despite immediate kidney function after KTx, the patient presented with acute urinary retention two days after removal of urinary catheter, and was re-catheterized. The patient was maintained on tacrolimus, MMF and prednisolone, and the nadir serum creatinine (SCr) was 1.7mg/dL. Due to a positive SARS-CoV-2 patient in the same ward, the patient was submitted to another SARS-CoV-2 RT-PCR test, with a positive result on day 14 post-transplant. On day 2 post-diagnosis (day 16 post-KTx), the patient developed fever, without any other symptoms. Since the fever developed early after the diagnosis of SARS-CoV2 infection, an alternative source of infection was suspected. Escherichia coli was isolated in the urine and blood cultures, and the patient was started on meropenem according to the antimicrobial sensitivity test. On the 10th day after diagnosis of SARS-CoV-2 infection (day 24 post-KTx), the patient required supplementary oxygen (O2) for resting hypoxemia. He was prescribed remdesivir (200mg on day 1 and then 100mg the following 4 days) and dexamethasone 6mg/day, following the current evidence at the time(5,6), and MMF dose was reduced to 500mg twice daily. The patient’s condition deteriorated on day 12 post-diagnosis, MMF was withheld, the patient was intubated, initiated invasive mechanical ventilation and transferred to the Intensive Care Unit (ICU). The ICU stay had a duration of 16 days, and was remarkable for bacterial (Pseudomonas aeruginosa) and fungal (Aspergillus fumigatus) pulmonary superinfections, requiring a total of 14 days of orotracheal intubation. The patient was started on ceftazidime/avibactam, according to the sensitivity testing, and voriconazole, with reduction of tacrolimus dose. Despite the multiple infectious complications, we documented a maximum SCr of 2.2mg/dL in the ICU, without need for continuous renal replacement therapy. The patient was discharged on the 57th day after KTx, with SCr 1.36mg/dL.

■ Patient 2

A 71-year-old caucasian woman with ESKD due to diabetic nephropathy, on regular hemodialysis since 2015, was admitted for deceased donor KTx with 5 mismatches (only 1 compatibility in A) on 28th December 2020. She had other comorbidities, namely type 2 diabetes mellitus, paroxysmal atrial fibrillation and arterial hypertension. Due to the immunological risk, and according to our center’s protocol, she was submitted to an induction IS regimen with methylprednisolone, intravenous rabbit anti-thymocyte globulin (ATG) 100mg (1.5mg/Kg) for 3 days, intravenous immunoglobulin (IVig) 120g (2g/Kg) given over the next 2 days and MMF. There were no surgical complications, with immediate graft function, and she was maintained on tacrolimus, MMF and prednisolone. On the 8th day post-transplant, we noted an increase in SCr (1.6 to 2.7mg/dL) associated with reduced urine output and acute rejection was suspected. The patient underwent a kidney biopsy, which revealed findings compatible with mixed acute antibody-mediated and cellular rejection. At the same time, we identified de novo donor-specific antibodies (DSA) against HLA-C4 (MFI 1094) and HLA-DQ2 (MFI 1309). The patient was treated with four pulses of methylprednisolone (2x500mg + 2x250mg) and rituximab 600mg (375g/m²), with improvement of kidney function up to SCr 1.7mg/dL, and was maintained on tacrolimus, MMF and prednisolone. Due to the epidemiological context, the patient was re-tested for SARS-CoV-2 infection, with a positive result on day 15 post-KTx. On the 5th day after diagnosis (day 20 post-KTx), she developed shortness of breath and hypoxemia and initiated O2. Given the available data at the time, she was started on remdesivir and dexamethasone and MMF dose was reduced to 500mg twice daily. During the next day, the patient’s hypoxemia aggravated, despite increasing respiratory support, so we suspended MMF and she was transferred to the ICU. Given the recent administration of rituximab, the patient was prescribed IVIg 120g. The ICU stay was complicated by circulatory, respiratory and kidney failure, with a need for invasive mechanical ventilation and continuous renal replacement therapy 48 hours after admission, in the context of septic shock due to bacterial (Pseudomonas aeruginosa) and fungal (Aspergillus fumigatus) superinfections. Despite optimal supportive therapy, the patient’s clinical situation deteriorated and she died in the ICU.

■ Patient 3

A 55-year-old caucasian male with ESKD due to Autosomal Dominant Polycystic Kidney Disease on hemodialysis since 2013, was admitted for deceased donor KTx on the 1st January 2021, with 3 HLA mismatches identified. He had a medical history of arterial hypertension, dyslipidemia, obesity (BMI 31Kg/m²) and prior smoking. The patient was prescribed an induction regimen based on basiliximab, tacrolimus, MMF and methylprednisolone and maintenance regimen consisting of tacrolimus, MMF and prednisolone. There were no surgical complications of note, and immediate diuresis and improvement in kidney function ensued, reaching a nadir SCr of 1.9mg/dL. Given the pandemic context, the patient was submitted to a routine RT-PCR SARS-CoV-2 test, with a positive result on day 13 post-surgery. On the 8th day after diagnosis (day 21 post-KTx), the patient presented with fever, shortness of breath and resting hypoxemia, and was started on supplemental O2. Given the data available at the time, the patient was started on remdesivir and dexamethasone, and MMF was reduced to 500mg twice daily. He required increasing O2 support, up to a Venturi Mask with FiO2 40% and so we temporarily suspended MMF. Due to the absence of clinical improvement after 23 days of SARS-CoV-2 infection diagnosis, we repeated a CT scan, which identified a consolidation and a nodule in the right lower lobe. Given the clinical picture, the patient was submitted to a new induction IS regimen with methylprednisolone (2x500mg + 2x250mg) and rituximab 600mg (375g/m²), with improvement of kidney function up to SCr 1.7mg/dL, and was maintained on tacrolimus, MMF and prednisolone. Due to the epidemiological context, the patient was re-tested for SARS-CoV-2 infection, with a positive result on day 15 post-KTx. On the 5th day after diagnosis (day 20 post-KTx), she developed shortness of breath and hypoxemia and initiated O2. Given the available data at the time, she was started on remdesivir and dexamethasone and MMF dose was reduced to 500mg twice daily. During the next day, the patient’s hypoxemia aggravated, despite increasing respiratory support, so we suspended MMF and she was transferred to the ICU. Given the recent administration of rituximab, the patient was prescribed IVIg 120g. The ICU stay was complicated by circulatory, respiratory and kidney failure, with a need for invasive mechanical ventilation and continuous renal replacement therapy 48 hours after admission, in the context of septic shock due to bacterial (Pseudomonas aeruginosa) and fungal (Aspergillus fumigatus) superinfections. Despite optimal supportive therapy, the patient’s clinical situation deteriorated and she died in the ICU.

■ Patient 4

A 21-year-old caucasian female with ESKD secondary to genetic focal segmental glomerulosclerosis (FSGS) on hemodialysis since 2018 presented for deceased donor KTx with 5 mismatches (only 1 compatibility in A) on 3rd January 2021. She also had a diagnosis of arterial hypertension. According to our center’s protocol, the patient received an induction IS regimen with ATG 50mg (1.25mg/Kg) for 3 days, MMF and methylprednisolone. We verified immediate graft function, without any surgical complications. Due to the etiology of the kidney...
disease, we monitored for early recurrence of FSGS, and documented a urine protein/creatinine ratio of 1.1 on the 3rd day post-KTx. The patient then was treated with rituximab 500mg (375g/m²) and kept on a maintenance regimen composed by tacrolimus, MMF and prednisolone. We documented a Scr nadir of 1.0mg/dL prior to SARS-CoV-2 infection. At day 16 post-transplant, due to the epidemiologic context, she was submitted to a routine RT-PCR SARS-CoV-2 test, with a positive result. Given the recently administered rituximab, we opted for administration of IVIg 80g (2g/Kg) given over the course of 3 days. Other than the rise in Scr (maximum value 1.8mg/dL), this patient only developed mild disease (anosmia), without fever, cough, dyspnea or hypoxemia, and thus was not eligible for remdesivir or dexamethasone, but the MMF dose was reduced to 250mg twice daily. She was discharged 36 days after admission, with Scr of 1.2mg/dL. Approximately two months after the infection diagnosis, the patient complained of fever, dyspnea after minimal effort, vomiting and diarrhea, and was again submitted to a SARS-CoV-2 test, which revealed a positive result and a low cycle threshold (Ct) value (25 cycles). The patient refused hospital admission and was managed with reduction of MMF dose and supportive therapy, with a successful recovery. After resolution of the infection, she maintained a Scr of 1.2mg/dL.

**Patient 5**

A 65-year-old caucasian female with ESKD of unknown etiology on regular hemodialysis since 2014, was admitted for deceased donor KTx on the 31st December 2020. We identified 4 HLA mismatches and anti-HLA B76 (MFI 7428). Her prior medical history included arterial hypertension with hypertensive cardiopathy. We opted for an induction regimen composed by intravenous ATG 75mg (1.5mg/Kg) for 3 days, IVIg 100g (2g/Kg) given over the next 2 days, MMF and methylprednisolone. She was kept on maintenance IS with tacrolimus, MMF and prednisolone and discharged 14 days post-KTx with a Scr of 1.4mg/dL. Ten days after discharge, the patient complained of fever, diarrhea and shortness of breath after minimal effort. She tested positive for SARS-CoV-2, so we reduced the MMF dose and admitted the patient. On the 6th day after diagnosis (day 30 post-KTx), the patient’s dyspnea worsened, with development of resting hypoxemia. She was started on O₂, remdesivir and dexamethasone, and MMF was temporarily withheld. On the 9th day post-diagnosis (day 33 post-KTx), the patient’s dyspnea worsened, with a marked increase in respiratory labour, despite apparently adequate arterial oxygen pressure. She was started on non-invasive ventilation, remaining with that ventilatory support for 72 hours, with progressive improvement afterwards. Despite a maximum Scr value of 1.5mg/dL, the patient was discharged on the 31st day after admittance (day 57 post-KTx), with Scr of 1.0mg/dL.

Patients’ IS regimen, baseline risk factors for severe COVID-19, clinical and laboratorial characteristics and outcomes are summarized in Table 1.

**DISCUSSION**

Initially, it was thought that the immunodepressed status observed in SOT recipients would result in milder disease, since it would prevent cytokine storm[17]. Recent evidence suggests infected SOT recipients may be at higher risk for the development of COVID-19, mechanical ventilation and death, when compared to the general population[8], which can be hypothesized to be related to their immunocompromised state. This gains even more relevance when considering that the average time between transplant and the diagnosis of SARS-CoV-2 infection in our series was 15.8 days. Nonetheless, other comorbidities associated with increased risk for COVID-19 progression and severity, especially cardiovascular disease and/or risk factors [such as age, diabetes mellitus, arterial hypertension or obesity]9–11, are frequently found concomitantly in this population[8], which can also contribute to the outcome. The patients’ comorbidities are summarized in Table 1. To be noted, the deceased patient was the eldest and the only diabetic in our group, both important factors associated with disease progression and severity, as mentioned before. The other patient who developed critical disease, despite the immunosuppressive induction regimen, had concomitant bacteriemia, which may have hindered the host response to the virus. To clarify, the two patients who developed bacterial and fungal superinfection were admitted to different ICUs, which excluded spreading within the same unit. In contrast, the youngest

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<tbody>
<tr>
<td><strong>Clinical and laboratorial characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55</td>
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<td>55</td>
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<td>Dialysis vintage (months)</td>
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<td>Comorbidities</td>
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<td>yes</td>
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<tr>
<td>CRP (mg/dL)</td>
<td>9</td>
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<td>6.4</td>
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<td>Lymphocytes (cells/mm³)</td>
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<td>130</td>
<td>190</td>
<td>150</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>9612</td>
<td>2117</td>
<td>731</td>
<td>2327</td>
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<tr>
<td>Ferritin (ng/mL)</td>
<td>1616</td>
<td>1090</td>
<td>980</td>
<td>2882</td>
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<tr>
<td>Tacrolimus trough at diagnosis (ng/mL)</td>
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<td>3.6</td>
<td>9.2</td>
<td>6.8</td>
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<td>Superinfection</td>
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<td>yes</td>
<td>yes</td>
<td>no</td>
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<tr>
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<td>IMV</td>
<td>VM</td>
<td>NIV</td>
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<tr>
<td>Nadir Scr pre-COVID-19</td>
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<td>1.6</td>
<td>1.9</td>
<td>1.0</td>
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<tr>
<td>Max Scr</td>
<td>2.2</td>
<td>CKRT</td>
<td>2.2</td>
<td>1.8</td>
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<tr>
<td>Discharge Scr</td>
<td>1.36</td>
<td>–</td>
<td>1.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Risk factors for severe COVID-19**

| Age > 60 years | X | X |
| COPD/smoker | X |
| Cardiopathy | X |
| Type 2 DM | X |
| Obesity | X |
| Non-depleting induction IS | X | X |
| Depleting induction IS | X | X |
| Rituximab | X | X |

**COVID-19 severity**

<table>
<thead>
<tr>
<th>critical</th>
<th>severe</th>
<th>mild</th>
<th>severe</th>
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The elevated tacrolimus trough level verified in patient 5 at the time of diagnosis was assumed to be caused by the diarrhea. The trough levels decreased to the therapeutic range shortly after admission.

According to the available literature, infected patients may have a positive SARS-CoV-2 RT-PCR for a long period after resolution of symptoms, but generally associated with high Ct values (Ct >35) and low viral load. A low Ct value, as seen in our patient, is not only indicative of active viral replication, but also of increased probability of progression and worse outcome. This irregular evolution could perhaps be explained by the prolonged viral shedding verified in immunocompromised patients.

Our report adds to the pool of information already published about the impact of the COVID-19 pandemic, but emphasizing the particular peril of the immediate post-transplant period, wherein the immunosuppressive load is higher and the T-lymphocyte response, important in the control of viral infections, is deliberately impaired. We noted that all surviving patients presented with bacterial infections in the aftermath of this episode, which might be expected, given the degree of immunodepression in the first months after transplant, but can also be speculated if SARS-CoV-2 infection can affect the host’s defense even after its clinical resolution. In our cases, the choice of immunosuppressants, developed only mild disease, which may be related to her age and the absence of significant comorbidities, but she ultimately developed symptoms compatible with COVID-19. In table 1 we summarize data regarding some important factors associated with the prognosis in the general population. We found no association between lymphocyte count, C-reactive protein, ferritin, D-dimer and tacrolimus through levels and the verified outcomes in our kidney transplant receptors. The elevated tacrolimus trough level verified in patient 5 at the time of diagnosis was assumed to be caused by the diarrhea. The trough levels decreased to the therapeutic range shortly after admission.

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References


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