COVID-19 in Kidney Transplantation

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ABSTRACT

Increased mortality of COVID-19 has been reported in older patients with diabetes, high blood pressure, lung disease and immunocompromised people such as kidney transplant recipients. Both the behavior of the viral infection and the treatments proposed so far interact with the state of immunosuppression and immunosuppressants. Herein, we report two cases of kidney transplant recipients with COVID-19 infection. The first patient presented with gastrointestinal symptoms and progressively advanced to multilobar pneumonia. The second case presented with fever accompanied by gastrointestinal and urinary symptoms and dry cough. Both patients responded appropriately to treatment.

KEY WORDS: Coronavirus; COVID-19; Pneumonitis; Kidney transplant

INTRODUCTION

Those with high comorbidities such as diabetes, hypertension, obesity, smoking or lung disease have reported the highest mortality rates from COVID-19 [1]. As a result, most of the focus has been on evaluating medical treatments for these patients in small series [2]. Kidney transplant recipients generally belong to this high-risk group. Both the behavior of the virus and the treatments proposed so far, interact with the state of the immunosuppression and immunosuppressants used, thus, it deserves a parallel discussion [3]. Evidence is built on the experience published around the world. Herein, we describe COVID-19 in two kidney transplant recipients.

CASE 1

The first patient was a 47-year man with a history of chronic kidney disease secondary to primary membranous nephropathy, recipient of a deceased-donor kidney transplant two months before the onset of symptoms, with serum creatinine of 1.71 mg/dL and an estimated filtration rate of 46.6 mL/min/1.73 m^2. He had a history of hypertension receiving carvedilol, nonvalvular atrial fibrillation, and pulmonary thromboembolism anticoagulated with warfarin. He received induction therapy with basiliximab and maintenance therapy with tacrolimus, mycophenolate, and steroids. Prophylaxis with valganciclovir, trimethoprim/sulfamethoxazole and nystatin. He was admitted to the emergency room with a 5-day history of gastrointestinal symptoms—dyspepsia, epigastralgia, and dry cough. Two days prior to consultation, he began experiencing dyspnea with deterioration of the functional class, odynophagia, and diarrhea. He received a dose of ivermectin the day before admission. He reported no other symptoms, no fever, no history of travel or exposure to infected or suspected COVID-19 patients.

Upon admission, he presented with a peripheral oxygen saturation of 88% and crackling rales in both lung bases; other vital signs were within normal limits. Blood work reported a white blood cell count of 7.1×10^3/μL with an absolute lymphocyte count of 0.8×10^3/μL, creatinine of 1.74 mg/dL, elevated C-reactive

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protein of 9.96 mg/dL (reference range: <0.5 mg/dL), ferritin level of 588 ng/mL (<274 ng/mL), and LDH of 292 U/L (<271 U/L). Other labs like D-Dimer and coproscopy were normal. Chest radiography showed opacities of bilateral alveolar occupation and right basal consolidation (Fig 1). Chest CT revealed extensive ground-glass opacities dispersed in both lung fields, predominantly peripheral and with a tendency to consolidation in the lower lobes, characteristics compatible with a viral pneumonia. These findings suggest COVID-19 without discarding multilobar pneumonia of bacterial origin.

He was treated according to the local protocol for COVID-19 therapy with azithromycin for 5 days, hydroxychloroquine (400 mg bid for 24 hours, afterwards 200 mg bid, orally) for 10 days, and lopinavir/ritonavir 400/100 mg bid for 14 days. Additionally, considering that the patient received a kidney transplant two months before, we empirically started piperacillin/tazobactam and maintained that prescription for 7 days. QTc interval was normal and did not change during the treatment course. A molecular panel identification of multiple respiratory pathogens (Filmarray™) that includes the detection of respiratory syncytial virus, influenza A and B, and parainfluenza, resulted negative; viral load for cytomegalovirus was also negative. Nasopharyngeal swab with real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) for COVID-19 reported positive.

Initially, tacrolimus and mycophenolate doses were decreased. Due to the persistence of high oxygen requirement with 40% F_IO_2, mycophenolate was withdrawn on the 6th day. Tacrolimus levels remained high at 25.9 ng/mL despite receiving 1 mg/day of the drug, due to the interaction between ritonavir and hydroxychloroquine, and therefore, it was stopped. Prednisolone was adjusted to 20 mg/day. Although the patient did not require mechanical ventilation, he was treated with intermittent pronation. The patient improved, tolerating oxygen reduction. During hospitalization, he developed diarrhea, probably secondary to administration of lopinavir/ritonavir and tacrolimus.

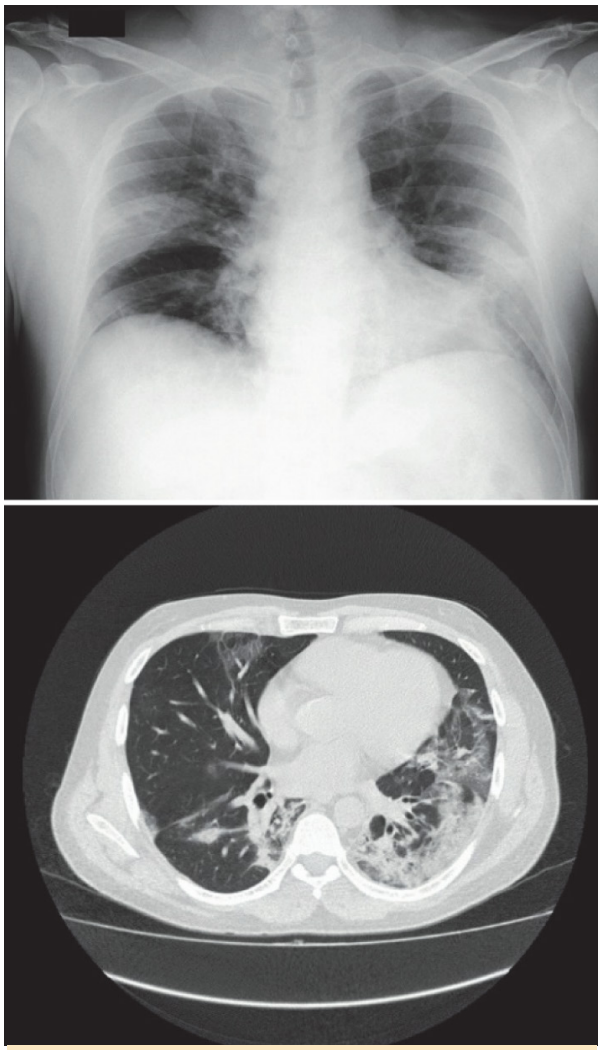

Figure 1: Chest x ray and high-resolution chest CT in case 1

He had a serum creatinine of 1.85 mg/dL at discharge. Ferritin, Dimero D and LDH were normal. Seven days after suspension of tacrolimus, levels remained high at 19 ng/mL. In the last follow up, the patient was at home asymptomatic without oxygen. At 30 days, the rRT-PCR was negative. Tacrolimus and mycophenolate mofetil were restarted. The last creatinine was 1.4 mg/dL.

CASE 2

The second patient was a 41-year-old woman with a history of chronic kidney disease due to lupus nephritis, recipient of a deceased donor-kidney transplant in 2008 with serum creatinine of 1.1 mg/dL and an estimated fil-

tration rate of 62.3 mL/min/1.73m^2. She was admitted to the emergency room due to 5 days of fever (39 °C) and chills, diarrhea in the last three days, dry cough, and mild pain in the renal graft. She exhibited no urinary symptoms and had no travel history or exposure to infected or suspected COVID-19 patients. The patient had a history of recurrent urinary tract infections and asthma. She was under treatment with sirolimus, mycophenolate, prednisolone, inhaled β_2 agonist, montelukast, spironolactone, and statin.

Upon admission, she was hemodynamically stable, did not need oxygen supplementation, showed no significant findings on cardiopulmonary auscultation, and experienced mild pain at palpation in renal graft. Her blood workup showered white blood cells count of 13×10^3/μL, absolute lymphocyte count of 1.1×10^3/μL, serum creatinine of 1.04 mg/dL, normal LDH, PCR 15.9 mg/dL, and urinalysis suggestive of urinary infection. She was empirically started on ertapenem and later, after a positive culture report for Escherichia coli, she was also treated with extended spectrum β-lactamase. The chest radiogram was normal and no oxygenation disorder was reported. Due to pandemic COVID-19 era, rRT-PCR was performed and returned positive after 48 hours. We considered it a mild case of COVID-19, so she did not receive any specific treatments.

The patient was discharged with oral cefuroxime, without need for oxygen supplementation, no positive respiratory symptoms. Sirolimus doses were adjusted according to its levels. The patient fulfills isolation at home in good general condition.

DISCUSSION

We described two cases of kidney transplant recipients with different clinical manifestations, both with good clinical evolution. The first presented with a moderate signs and symptoms, probably due to a higher level of immunosuppression, for a recent transplantation (2 months prior). The second case was a patient who had received their kidney transplant 12 years ago and presented with mild symptoms and an atypical presentation of COVID-19, who did not require any specific treatments.

The condition of a kidney transplant recipient involves changes in the clinical context of COVID-19 infection. The immune response against a viral infection is different compared to that of a non-transplant patient. This consists of two phases—the first innate response dependent on interferon I and the action of natural killer (NK) lymphocytes after recognition of the infected cell, which generally occurs within the first 5 days. Then, a second adaptive phase that depends on the production of antibodies by B-lymphocytes and the cytotoxic action of CD8 T lymphocytes through the presentation of major histocompatibility complex class I (MHC I) [3]. Treatment with calcineurin inhibitors (CNI), rapamycin pathway inhibitors (iMTOR), antiproliferative drugs such as mycophenolate or azathioprine, and the regular use of steroids, directly affect both phases of viral recognition, leaving the host at a theoretical disadvantage more prone to complications.

On the other hand, cytokine storm with hyperinflammation syndrome, which is the pathophysiological basis for multi-organ involvement in severe cases [4], could benefit from the presence of immunosuppressive drugs, although this has not yet been proven. We could even expect atypical presentations of COVID-19 infection, in which respiratory symptoms do not predominate, but rather symptoms of fever, diarrhea or fatigue prevail, as reported by Diekmann [5]. Lymphopenia is a poor prognostic factor and is related to respiratory distress syndrome (ARDS) [6]. The chronic use of immunosuppressive drugs in the transplant recipient induces lymphopenia [7], and it is not yet known if this factor behaves the same way in these patients, so it should be studied over time.

The diagnostic process of COVID-19 in transplant recipient patients can be confusing. Because of the state of immunosuppression

and the probability of unusual presentations, the clinician should guide the diagnosis in the detection of opportunistic, common or atypical infections as a differential diagnosis of COVID-19. In the first case, the patient empirically received management for pneumonia due to common and atypical germs. In the second case, the patient received treatment for acute pyelonephritis. The diagnosis of COVID-19 infection was suspected due to the epidemiological situation and not because of the clinical presentation.

The interaction of the medications used to treat moderate to severe cases of COVID-19 is a determining factor in the management of these patients. Treatment with mycophenolate has been associated with increased viral load, tissue damage to the lung, and higher mortality in a murine model of MERS-CoV infection [2].

Protease inhibitors (lopinavir/ritonavir) are potent inhibitors of cytochrome CYP3A4/5. They dramatically increase the levels of CNI, iMTOR and the bioavailability of mycophenolate. Antimalarials block CYP2D6 cytochrome, which increases CNI levels, with little or no interaction with iMTOR or mycophenolate. On the contrary, interleukin 6 (IL6) blockers such as tocilizumab, seem to decrease both CNI and iMTOR levels [2]. In case 1, the levels of tacrolimus remained high despite completing 7 days of discontinuation of the drug due to the interaction between the protease inhibitor and the antimalarial drug. Similar behaviors were reported by Diekmann [5] and Gandolfini [8].

The management of immunosuppressants in the kidney transplant recipient patient with COVID-19 is not entirely clear. It depends on the disease severity and the treatment used. High levels of CNI and iMTOR are deleterious, not only for high risk of onset adverse effects, but also for progression of viral infection. It is suggested to suspend them in moderate-to-severe cases, in which it is recommended to initiate protease and antimalarial inhibitors. In mild cases of COVID-19, as was our second case, only symptomatic treatment is required; immunosuppression can be continued with monitoring the levels [9]. Different scientific associations such as the Spanish, Colombian and Italian, among others, have agreed on these recommendations [10-12].

The clinical context of each patient must be evaluated in detail to carry out an individualized therapeutic strategy based on the best available evidence. We highlighted the importance of close medical follow-up to identify early signs or symptoms that suggest clinical deterioration in order to adjust the established therapies in a timely manner.

Reports in the literature indicated that transplant recipients with COVID-19 have presented a variable evolution, from mild cases treated ambulatory to severe cases with high mortality. None of our cases presented with acute kidney injury, required mechanical ventilation, or died.

Alberici in Italy reported 20 cases of COVID-19 in kidney transplant recipients with relatively benign disease; all of them presented with fever and only one presented with respiratory distress. Immunosuppressive medication was discontinued in all 20 patients and methylprednisolone equivalent doses of 16 mg were given. Nineteen patients received antiretroviral therapy and six were managed with tocilizumab. The authors highlight the unfavorable evolution in most cases, with an increase in oxygen requirements and radiological progression. Six patients presented with acute kidney injury, four required admission to the Intensive Care Unit, and five died [13]. Regarding treatment, the controversial role of lopinavir/ritonavir in SARS-CoV-2 stands out, with some data supporting its early onset and recognizing the importance of pharmacological interaction with CNIs. The use of tocilizumab favors decreasing oxygen requirements by 50% and radiological compromise by 33%; however, they report two deaths. It is impossible to make recommendations due to the small size of the sample.

In a series of cases from Columbia University in New York, of 15 transplant recipients [14]

with mild and severe symptoms, 13 presented with fever, 9 had cough, 5 had normal chest radiogram, 6 developed acute kidney injury, 4 required invasive mechanical ventilation and 1 died. Nine patients received treatment with hydroxychloroquine and azithromycin; none received antiretroviral therapy. With regard to immunosuppression, the most frequent medical treatment (10 patients) was to withdraw the antiproliferative medication (mycophenolate, azathioprine or leflunomide). Only two patients suspended immunosuppression completely.

The 12 de Octubre Hospital in Spain [15] describes a series of 18 patients with a solid organ transplant with COVID-19; eight kidney transplant recipients, six liver recipients, and four heart recipients. Regarding kidney transplant recipients, the usual symptoms were fever and cough; four patients discontinued their antiproliferative drug; six decreased tacrolimus dose and one stopped all immunosuppression. Five patients received lopinavir/ritonavir and seven hydroxychloroquine. Of the eight patients, three required mechanical ventilation and two died.

With the report of these two cases, we want to increase the descriptions of kidney transplant recipients with COVID-19 and contribute to the construction of better scientific evidence to guide doctors and scientists worldwide to make decisions that favor optimal outcomes for patients.

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