



CASE REPORT

COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine

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Coronavirus disease 2019 (COVID-19) pneumonia has been poorly reported in solid organ transplanted patients; prognosis is uncertain and best management unclear. We describe the case of a 61-year-old kidney transplant recipient with several comorbidities who was hospitalized and later received a diagnosis of COVID-19 pneumonia; the infection was successfully managed with the use of hydroxychloroquine and a single administration of tocilizumab, after immunosuppression reduction; the patient did not require mechanical ventilation. During the rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, transplant clinicians should be readily informed about new cases of COVID-19 pneumonia in solid organ transplant recipients, with focus on therapeutic strategies employed and their outcome.

KEYWORDS

clinical research/practice, immunosuppressant – fusion proteins and monoclonal antibodies, infection and infectious agents – viral, infectious disease, kidney transplantation/nephrology

1 | BACKGROUND

In late December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a novel pathogen causing severe pneumonia cases, lately named coronavirus disease 2019 (COVID-19), in Wuhan, China.¹ Since then, the infection has been demonstrating a rapid global spread, with a devastating evolution in northern Italy; there, several simultaneous clusters developed with a substantial number of critically ill patients and a very high case fatality rate, especially among the elderly and those with comorbidities.² COVID-19 is considered as potentially having a more severe course in solid organ transplant recipients, due to the chronic immunosuppression these patients are exposed to for preventing rejection. Only a few reports of COVID-19 in kidney transplanted patients are currently available in the literature,³⁻⁷ and prognosis and recommended

management for these patients are unclear. Moreover, the impact of treatments other than best supportive care is unknown.

2 | CASE REPORT

A 61-year-old man, who underwent kidney transplantation from a deceased donor in 2005 for end-stage renal disease due to chronic interstitial nephritis, was admitted to the nephrology unit for persistent fever and shivering over the last 48 hours. He reported no cough or dyspnea, he had not traveled outside town in the past 15 days, and had no history of contact with people positive or suspected for SARS-Cov-2 infection.

The patient had chronic kidney disease stage IIIa (serum creatinine 1.5 mg/dL, estimated glomerular filtration rate of 50 mL/min); maintenance immunosuppression consisted of cyclosporine A (CyA) plus steroid. Past medical history included nodal marginal zone

Abbreviations: COVID-19, coronavirus disease 2019; CyA, cyclosporine A; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

lymphoma in active hematological surveillance; previous unprovoked pulmonary embolism treated with warfarin in secondary prevention; and idiopathic Parkinson disease with motor complications treated with subthalamic neurostimulation, with neurogenic bladder managed with intermittent bladder catheterization and complicated by frequent urinary tract infections.

At first evaluation, physical examination was unremarkable (apart from tremor related to chronic neurological condition); blood pressure was 136/72 mm Hg, and body temperature was 38°C; peripheral capillary oxygen saturation was 97% breathing ambient air. Laboratory blood tests were normal with blood cell count (5460 cells/mm³ with 79% neutrophils), mild acute kidney injury (serum creatinine 1.9 mg/L), and minimally elevated C-reactive protein (4.1 mg/dL); CyA levels were 90 ng/mL (basal) and 136 ng/mL (after 2 hours). Chest radiography showed minimal left pleural effusion. Specimens for urinary and blood cultures were collected; urinary tract infection was suspected and antibiotic treatment with meropenem was initiated, based on a previous isolate.

On day 3 after admission, considering persistence of fever, negativity of urinary cultures and serum procalcitonin, SARS-CoV-2 infection was suspected and the patient isolated in a single room. Antibiotic treatment was stopped, oropharyngeal/nasal swab for SARS-CoV-2 research in reverse transcription polymerase chain reaction (RT-PCR) was performed; a repeated chest radiograph showed bilateral basal interstitial pneumonia; arterial blood gases were unremarkable (pO₂ 91 mm Hg breathing ambient air). In the following days, the patient remained stable with undulating fever and no dyspnea. Search for viral and bacterial pathogens in PCR from upper respiratory tract material resulted negative, as were cytomegalovirus DNA on blood and blood cultures collected at admission. Diagnostic oropharyngeal/nasal swabs for SARS-CoV-2 were repeated and, only at the third attempt on day 9 after admission, the test was positive. In the same week 3 other hospitalized patients and, the week after, 2 healthcare workers resulted positive for SARS-CoV-2 infection in our service; nevertheless, even if cases were probably related, it was not possible to track a clear chronological order.

On the day of diagnosis, arterial pO₂ dropped to 57 mm Hg, and low-flow oxygen through nasal cannula was initiated; the patient was hemodynamically stable. Hydroxychloroquine was started at the dose of 200 mg bid; CyA dose was reduced by a half; intravenous fluids were initiated. Laboratory exams showed leukopenia with lymphopenia (see Figure 1); serum lactate dehydrogenase, hemoglobin, platelets, and D-dimer levels were normal. Two days after, considering the lack of improvement in clinical conditions, CyA was withdrawn and oral steroid dose increased (methylprednisolone 16 mg per day); after discussion with infectious disease specialist and signature of informed consent by the patient, tocilizumab was administered off label at the dose of 324 mg via subcutaneous route. Interleukin-6 (IL-6) levels in blood proved to be high (280.86 pg/mL).

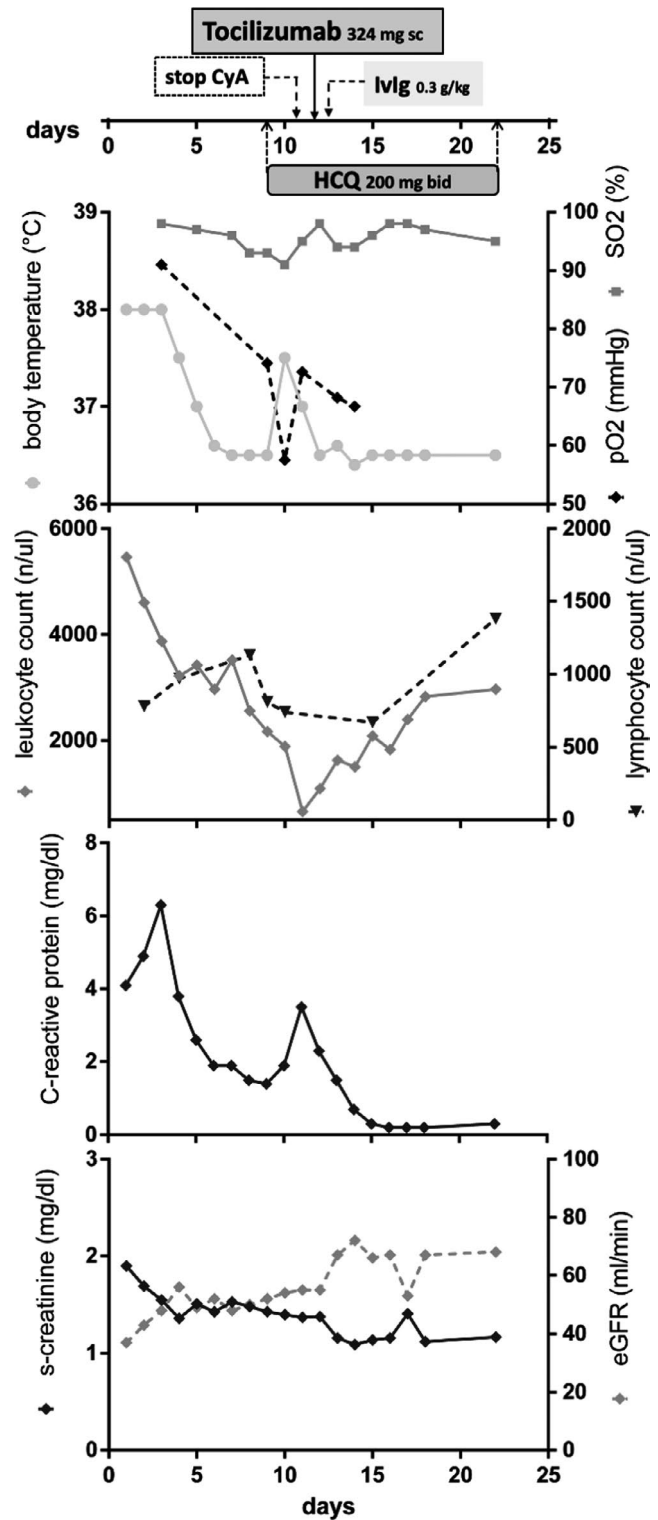


FIGURE 1 Trends of body temperature (°C), arterial pO₂ (mm Hg), and peripheral oxygen saturation (SO₂, %); leukocytes and lymphocyte counts (absolute number/μL); C-reactive protein (mg/dL); serum creatinine (mg/dL) and estimated glomerular filtration rate (eGFR) according to Chronic Kidney Disease Epidemiology Collaboration (mL/min). Timing of administration of tocilizumab, hydroxychloroquine (HCQ), and intravenous immunoglobulins (IVIg) and withdrawal of cyclosporin (CyA) are reported in the top part of the figure

The patient developed progressive leukopenia (with leukocyte nadir at 660/ μ L, neutrophils 400/ μ L). Suspecting that leukopenia with neutropenia could be an immune-mediated process related to tocilizumab, and in order to enhance anti-inflammatory and immunomodulatory response, we administered intravenous immunoglobulins (IVIg) at the dose of 0.3 g/kg. Leukocyte count rose to 2090/ μ L (neutrophils 1180/ μ L, lymphocytes 670/ μ L), with CD4 count 518/ μ L.

On day 14 after admission, urinary culture was positive for multiresistant *Pseudomonas aeruginosa*, and, considering the risk for bacterial disseminated infection after tocilizumab, antibiotic treatment with meropenem was reinitiated. On day 14, chest radiograph showed multiple nonhomogeneous bilateral consolidations, and azithromycin was administered orally for 3 days to prevent bacterial superinfection. The radiographic picture was interpreted as imaging evolution of COVID-19 pneumonia.

Since tocilizumab administration, the patient remained afebrile. Arterial pO_2 showed progressive improvement with values always above 60 mm Hg, and oxygen treatment was stopped. IL-6 levels increased, as expected, 6 days after administration of tocilizumab (619.11 pg/mL).

Kidney function remained substantially stable over the course of hospitalization (Figure 1).

The patient was discharged home on day 22 after admission without fever and with peripheral oxygen saturation of 95% breathing ambient air; respiratory frequency was 14 acts per minute, blood pressure was 140/80 mm Hg; white blood cell count was 2970/ μ L. Oropharyngeal/nasal swab for SARS-CoV-2 was still positive 13 days after diagnosis, and appropriate isolation measures were recommended at home. Hydroxychloroquine was stopped, and CyA is presently still withheld.

3 | DISCUSSION

The world is now facing a pandemic of SARS-CoV-2 infection causing COVID-19, which is unique in terms of rapidity of growth and global involvement; no proven specific therapies are available, other than supportive care. Emerging infectious diseases represent an enormous threat of contagion to transplant recipients; these patients, in turn, are subjected to frequent ambulatory checks and hospitalizations and they can substantially contribute to the spreading of the infection if not promptly identified.

Clinical presentation of COVID-19 is nonspecific, most of the time manifesting as a febrile illness with often mild upper respiratory manifestations. Symptoms and signs can be very subtle especially in the early phases of the infection, requiring a high degree of suspicion by clinicians and imposing logistic challenges in order to isolate suspected cases.

Our report shows potential limitations in the diagnosis of SARS-CoV-2 infection with a single oropharyngeal/nasal swab. Although RT-PCR diagnostic for SARS-CoV-2 infection has been described to be extremely sensitive,⁸ false negative results on oropharyngeal/nasal swab have been reported.⁹ It is postulated that several mechanisms can be responsible for this phenomenon, among them

sampling techniques, timing of viral positivity after initial infection, and lack of expression of angiotensin-converting enzyme 2 (functional receptor of SARS-CoV-2) in nasal and pharyngeal mucosa.^{10,11} It appears then important to perform repeated oropharyngeal/nasal swabs, or consider obtaining bronchoalveolar lavage material if initial testing is negative, in patients with a consistent clinical suspicion for SARS-CoV-2 infection. Moreover, even in the absence of positive RT-PCR positivity, clinical indicators (especially suggestive radiological imaging) should guide clinical diagnosis indicating need for isolation of the patient.¹²

The optimal management of a solid organ transplant recipient with SARS-CoV-2 infection is not clearly determined. It seems rational to reduce the immunosuppressive load, as it is common practice in most severe infections in transplanted patients; in general, our protocol is to withdraw mycophenolate mofetil and, as a second step, reduce and consider stopping calcineurin inhibitor. Nevertheless, because a great part of the pulmonary damage in COVID-19 pneumonia appears to be related to excessive inflammatory response of the host,¹³ it could be argued that antirejection drugs could contribute to reducing this process.

In our patient, we decided to reduce cyclosporine dose by half and later stop it, also considering the high risk for bacterial infection, maintaining low-dose steroid.

Several drugs are being administered off label and are currently under investigation in clinical trials for COVID-19.

There is mounting enthusiasm regarding the use of chloroquine and its analog hydroxychloroquine against SARS-CoV-2. Rationale for its use derived from in vitro studies from China demonstrating that chloroquine was able to block virus infection at low-micromolar concentration in vitro and possessed high selectivity index.¹⁴ Recently, a small nonrandomized clinical trial from France showed that infected patients treated with hydroxychloroquine were more likely to achieve virologic clearance at day 6;¹⁵ nevertheless, this study has received extensive criticism about its methodology and its results have been described as overstating.¹⁶ Despite poor quality evidence, given the lack of alternative effective treatments, the relatively safe toxicity profile and its wide availability, many centers in Italy have adopted hydroxychloroquine as a first-line strategy in patients with confirmed SARS-CoV-2 infection. In our patient, hydroxychloroquine was continued for a total of 13 days.

It is believed that the severity of pulmonary involvement in SARS-CoV-2 infection is mainly driven by an excessive inflammatory response mounted by the host immune system in response to pathogen. Indeed, inflammation-related indices have been reported to be higher in patients with COVID-19 pneumonia who develop acute respiratory distress syndrome compared to those who do not; interestingly, IL-6 was significantly more elevated in these patients.¹³ IL-6 is a multifunctional proinflammatory cytokine which stimulates T cell proliferation/differentiation to T helper cells and differentiation of B-lymphocytes to antibody-secreting plasma cells.¹⁷ Tocilizumab is a humanized monoclonal antibody that competitively inhibits IL-6 by binding to both its soluble and membrane receptors;¹⁷ its use in COVID-19 pneumonia is

currently being investigated in a multicenter, single-arm, open-label, phase 2 study in Italy.¹⁸

In order to reduce pulmonary inflammatory response, we decided to administer tocilizumab in our patient in an early phase, before overt lung damage ensued; our strategy was also supported by demonstrating high levels of IL-6 in blood. The subcutaneous route of administration was chosen according to local stock availability, because intravenous formulation was rapidly exhausted. Administered dose was double that recommended for rheumatoid arthritis and was chosen in the attempt to mimic pharmacodynamics of the intravenous administration. There is no clear consensus regarding a definite schedule of tocilizumab administration in COVID-19; main contraindications to tocilizumab are untreated active infection, aspartate transaminase/alanine transaminase elevation, neutrophil count $<500/\mu\text{L}$, and platelets $<50\,000/\mu\text{L}$. Considering the good clinical response in our patient, we decided not to proceed with additional doses. It must be clarified that an increase in serum IL-6 levels was expected after tocilizumab administration; because IL-6 receptor is fully inhibited, the produced ligand will remain in the circulation until degradation. This phenomenon does not correspond to a lack in tocilizumab efficacy, because the IL-6 signaling pathway is expected to be completely blocked; IL-6 levels are expected to gradually decrease over time.

In addition to that, the patient was also treated with IVIG for leukopenia with neutropenia possibly related to tocilizumab and to counteract aberrant inflammation related to COVID-19. Indeed, tocilizumab have been reported to induce neutropenia, considered to be immune mediated.¹⁹ Moreover, IVIG possess anti-inflammatory and immunomodulatory effects; several are the postulated mechanisms, among them the decrease in the production of proinflammatory cytokines,²⁰ which could have been of benefit in our case, considering the pathogenesis of pulmonary damage in COVID-19.

Because oropharyngeal/nasal swab was still positive for SARS-CoV-2 at discharge, CyA treatment was not resumed; the patient is currently monitored and CyA will be reinstated after demonstrating absence of viral shedding.

In conclusion, we report a case of COVID-19 pneumonia in a kidney transplant recipient with several comorbidities, which was successfully managed with the use of multiple pharmacological treatments (hydroxychloroquine, IVIG, and a single dose of tocilizumab) and reduction of immunosuppression. The patient had no need for mechanical ventilation. We acknowledge that results obtained in a single case are difficult to generalize, considering the multiple drugs involved and the unclear natural course of COVID-19 in transplanted patients. Nevertheless, we consider that transplant clinicians should be aware of potentially useful pharmacological treatments for COVID-19 pneumonia in solid organ transplant recipients. Given the extremely fast growth of the epidemic of SARS-CoV-2 worldwide, we believe it is of paramount importance to report management of cases in special populations, before results of large clinical trials become available.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding author.

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