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CASE REPORT

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COVID-19 pneumonia in lung transplant recipients: Report of 2 cases

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Coronavirus disease 2019 (COVID-19) has been declared pandemic since March 2020. In Europe, Italy was the first nation affected by this infection. We report anamnestic data, clinical features, and therapeutic management of 2 lung transplant recipients with confirmed COVID-19 pneumonia. Both patients were in good clinical condition before the infection and were receiving immunosuppression with calcineurin inhibitors (CNI), mycophenolate mofetil, and corticosteroids. Whereas mycophenolate mofetil was withdrawn in both cases, CNI were suspended only in the second patient. The first patient always maintained excellent oxygen saturation throughout hospitalization with no need for additional oxygen therapy. He was discharged with a satisfactory pulmonary function and a complete resolution of radiological and clinical findings. However, at discharge SARS-CoV-2 RNA could still be detected in the nasopharyngeal swab and in the stools. The second patient required mechanical ventilation, had a progressive deterioration of his clinical conditions, and had a fatal outcome. Further insight into SARS-CoV-2 infection is eagerly awaited to improve the outcome of transplant recipients affected by COVID-19 pneumonia.

KEYWORDS

clinical research/practice, immunosuppressant, immunosuppression/immune modulation, infection and infectious agents – viral, lung disease: infectious, lung transplantation/pulmonology

1 | INTRODUCTION

A pneumonia of unknown origin, detected in Wuhan (China), was first reported to the World Health Organization (WHO) on December 31, 2019. On January 9, 2020, a new strain of coronavirus (SARS-CoV-2) was identified as the etiologic agent of this novel respiratory disease called COVID-19. Since then, the infection has spread in more than 200 countries, becoming pandemic in March 2020 with a total of 2 078 605 confirmed cases and 139 515 deaths according to the latest WHO report (April 17, 2020).[1]

Italy was the first European country confronted with the COVID-19 infection, with the first 2 cases reported on January 31, 2020. To date (April 17, 2020), according to latest report of the Italian Ministry of Health, a total of 168 941 cases and 22 170 deaths have been

Abbreviations: BAL, bronchoalveolar lavage; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; C-PAP, continuous positive airway pressure; CRP, C-reactive protein; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; MERS, Middle East respiratory syndrome; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

confirmed.[2] In the past 2 months, the country has faced a dramatic crisis that has heavily affected the National Health Care System (which collapsed in some regions), the national economy, and personal relationships.

SARS-CoV-2 causes illnesses with different degrees of severity.[3] COVID-19 infection is commonly characterized by fever and upper airway manifestations such as dry cough and dyspnea. Other symptoms reported include headache, myalgia, hyposmia, hypogeusia, and gastrointestinal disorders.[4] The virus has been isolated in nasopharyngeal and oropharyngeal swabs as well as in stool samples, saliva, and cerebrospinal fluid. The virus is predominantly transmitted through respiratory droplets or via direct contact.

In the case of COVID-19 infection, transplanted patients are particularly at risk of severe complications due to their immunosuppression and the frequent coexistence of comorbidities. Indeed, the management of COVID-19 infections in transplant recipients remains unclear.

Here, we report the first 2 cases of COVID-19 pneumonia in 2 lung transplant recipients in Veneto, a region in the northeastern part of Italy with a total of 15 374 confirmed cases of SARS-CoV-2 infections as of April 17, 2020.[2]

2 | CASE REPORT

2.1 | Case 1

The first case is a 46-year-old man who underwent bilateral lung transplant for cystic fibrosis in April 2011. Lung transplant was performed according to standard surgical technique. No intraoperative complications were reported, and the patient was discharged with an immunosuppressive therapy based on cyclosporine, mycophenolate mofetil, and corticosteroids. In 2015, the patient developed progressive renal failure that ultimately lead to dialysis in 2019. In March 2017, the patient was switched to tacrolimus.

On March 14, 2020 (D0), the patient developed hyperpyrexia (39.3°C) with no other symptoms. At that time, he was on a 3-week antibiotic course (teicoplanin) and on low-molecular-weight heparin (enoxaparin, 4000 IU/d), started the last week in February due to the presence of fever and thrombosis associated with possible infection of the arteriovenous fistula. As a precautionary measure, mycophenolate mofetil was discontinued. Two days later (D2), a nasopharyngeal swab was performed that was positive for SARS-CoV-2 RNA. The patient was immediately hospitalized at the Infectious Disease Unit of the Padua University Hospital where an area dedicated to COVID-19 patients has been established recently. On admission, the patient was alert and well oriented. He was breathing normally, with O_2 saturation of 99% in ambient air, and pathological noises could be appreciated; the clinical examination was otherwise normal. A Quinton catheter was present in his right jugular vein.

Chest radiography showed the presence of ground-glass opacities in the bases of both lungs, with apparent left pulmonary thickening. Furthermore, several laboratory abnormalities could be observed. In particular, inflammation markers were moderately elevated (CRP, 17 mg/L; procalcitonin, 2.55 μg/L); there was a thrombocytopenia (56×10^9 cells/L); and the patient had elevated D-dimer levels (301 μg/L) and normal fibrinogen levels (2.20 g/L).

On D4, high-resolution computed tomography (CT) showed the presence of many ground-glass opacities in the peripheral site of all lung lobes except for the apical ones, as well as many peribronchovasal consolidations with confluent aspect to basal segments of left lower lobe, with notes of air bronchogram (Figure S1). In the light of his overall clinical conditions, the risk of potential drug interactions with ongoing treatments, and the lack of specific recommendations for COVID-19 patients on dialysis, no antiviral therapies or hydroxychloroquine was administered. Blood cultures were negative for both bacteria and fungi. In addition, the following precautionary measures were put in place: first, the Quinton catheter was removed; second, due to its possible contribution to the fever and pancytopenia, teicoplanin was stopped. Moreover, as CT scanning could not rule out the presence of a concurrent bacterial superinfection, the patient received meropenem for 9 days associated with tigecycline for 7 days. During his hospital stay, the patient continued enoxaparin and his dialysis treatment. The clinical conditions did not deteriorate, and the patient maintained good O_2 saturation (Sao_2 > 95%) with no need for additional oxygen therapy. The patient was discharged on D15 in good general condition with no fever, no cough, or other symptoms and a clear chest radiograph. Immunosuppression at that time was based on tacrolimus (0.5 mg × 2/d) and corticosteroids (7.5 mg/d). At discharge and 72 hours later, the nasopharyngeal swabs were still positive for SARS-CoV-2 RNA although the CT scan was clear and showed no particular alterations (Figure S2). Furthermore, at that time the patient also had mild diarrhea, and SARS-CoV-2 could be isolated from the stools. On D33, a nasopharyngeal swab was still positive, whereas on D37 both nasopharyngeal and rectal swabs were found to be negative.

2.2 | Case 2

The second case is a 71-year-old man who underwent bilateral lung transplant due to chronic obstructive pulmonary disease (COPD) in June 2011. No intraoperative complications were reported, and the patient was discharged with an immunosuppressive therapy based on cyclosporine, mycophenolate mofetil, and corticosteroids.

In the following years, the patient developed diabetes (treated with insulin), progressive chronic renal failure, hypertension (treated with verapamil and furosemide), acute pancreatitis, osteoporosis, and an increase in body weight (body mass index: 29 kg/m^2) but he maintained a stable and satisfactory respiratory function.

On March 7, 2020 (D0), he developed an episode of hyperpyrexia (37.6°C), dyspnea associated with cough, and diffuse arthralgia. He was initially treated at home with azithromycin for 4 days with no resolution of the symptoms. On D6, a nasopharyngeal swab was negative for SARS-CoV-2 RNA, whereas analysis of the sputum

showed the presence of SARS-CoV-2 infection. A chest radiograph performed on the same day showed bilateral interstitial pneumonia with no pleural effusion (Figure S3). Because of a progressive decline in O_2 saturation, the patient was admitted to the Treviso Hospital with a diagnosis of acute respiratory distress in COVID-19 pneumonia. On admission, clinical laboratory results showed normal white blood cell and lymphocyte counts (5.96×10^9 cells/L and 3.66×10^9 cells/L, respectively), a substantial reduction of neutrophils (0.54×10^9 cells/L), and a considerable elevation of both CRP (16.32 mg/L) and D-dimer (1.254 μg/L). A CT scan showed diffuse interstitial involvement in all the lobes (although mainly in the upper ones) and diffuse ground-glass opacity areas with multiple consolidations, especially in the right lung (Figure S4). Cyclosporine and mycophenolate mofetil were discontinued, whereas corticosteroids were maintained (methylprednisolone, 40 mg twice daily, with gradual tapering of the dose). Furthermore, an anticoagulation regimen was initiated (enoxaparin 4000 UI/d), in accordance with the prone positioning protocol in place at the Treviso Hospital. The patient was ventilated with C-PAP (PEEP 10 cm H_2O, FIO_2 60%) and treated with lopinavir/ritonavir, hydroxychloroquine, and piperacillin/tazobactam. After the first week of treatment, acyclovir was added. The subsequent clinical course was characterized by gradual deterioration of gas exchanges, associated with progressive worsening of lymphocyte counts (0.17×10^9 cells/L) and neutrophilia (16.05×10^9 cells/L). Notwithstanding the medical support provided, the clinical conditions irremediably deteriorated and the patient died on D27.

The demographic and clinical characteristics of the 2 patients together with the laboratory results are shown in Tables 1 and 2, respectively.

3 | DISCUSSION

Transplant recipients have been only minimally affected by earlier infections mediated by coronaviruses, such as SARS and MERS epidemics.[5] In contrast, since its initial detection in Wuhan at the end of last year,

TABLE 1 Demographic and Clinical Characteristics

	Patient 1	Patient 2
Sex	Male	Male
Age at transplant, y	37	62
Date of transplant	April 2011	June 2011
Comorbidities	Chronic renal failure; patient on hemodialysis	Chronic renal failure Diabetes mellitus Arterial hypertension Osteoporosis
Age at time of infection, y	46	71
Immunosuppression at time of infection	Tacrolimus Mycophenolate mofetil Corticosteroids	Cyclosporine Mycophenolate mofetil Corticosteroids
Immunosuppression after confirmation of COVID-19	Tacrolimus + corticosteroids (mycophenolate mofetil stopped)	Only corticosteroids (tacrolimus and mycophenolate mofetil stopped)
Symptoms at onset	Fever	Fever Diffuse arthralgia Cough Dyspnea
Antiviral therapy	No	Lopinavir/ritonavir
Hydroxychloroquine	No	Yes
Antibiotic therapy	Meropenem Tigecycline	Piperacillin/tazobactam
Mechanical ventilation	No	C-PAP

TABLE 2 Laboratory Findings

Patient 1	Reference Range	On Admission (March 16, 2020)	Day 7 From Admission (March 23, 2020)	At Discharge (March 26, 2020)
Hb (g/L)	140-175	98	99	105
WBC ($\times 10^9$ cells/L)	4.40-11.00	5.30	6.16	6.05
Neut ($\times 10^9$ cells/L)	1.80-7.80	2.87	2.46	2.37
Lym ($\times 10^9$ cells/L)	1.10-4.80	1.93	3.02	2.73
PLT ($\times 10^9$ cells/L)	150-450	56	115	83
CRP (mg/L)	0-6	17	4.30	2.90
D-dimer (μg/L)	0-250	301	217	389

Patient 2	Reference Range	On Admission (March 13, 2020)	Day 7 From Admission (March 20, 2020)	Day 12 From Admission (March 25, 2020)	Day 17 From Admission (March 30, 2020)	At Time of Death (April 3, 2020)
Hb (g/L)	140-175	127	117	121	96	87
WBC ($\times 10^9$ cells/L)	4.40-11.00	5.96	4.75	11.87	16.01	16.55
Neut ($\times 10^9$ cells/L)	1.80-7.80	0.54		11.04	14.89	16.05
Lym ($\times 10^9$ cells/L)	1.10-4.80	3.66		0.24	0.32	0.17
PLT ($\times 10^9$ cells/L)	150-450	223	311	237	159	117
CRP (mg/L)	0-6	16.32	21.49	3.04	7.82	11.63
D-dimer (μg/L)	0-250	1254			1094	1341

Abbreviations: CRP, C-reactive protein; Hb, hemoglobin; Lym, lymphocytes; Neut, neutrophils; PLT, platelets; WBC, white blood cells.

at least 21 cases of COVID-19 disease in transplant patients have been reported.[6-17] To date, these cases have primarily involved kidney, liver, bone marrow, and cardiac allograft recipients, whereas this case report describes 2 lung transplant recipients affected by COVID-19 pneumonia.

Unquestionably, it is far too premature to draw any meaningful conclusion from these 2 cases. Nevertheless, these 2 patients allow us to make at least 5 important considerations regarding the COVID-19 disease in lung transplant recipients. First, it is yet unclear whether, when, and to what extent the immune response should be turned off in transplant recipients with COVID-19 pneumonia. On the one hand, withdrawal of immunosuppression should enable a more timely and efficient immune response that should neutralize the virus, prevent the development of the viral pneumonia, and, ultimately, allow patient recovery. On the other hand, some would argue that COVID-19 pneumonia and the systemic hyperinflammatory syndrome suggest a vigorously dysregulated immune response that needs to be switched off.[18] Second, it may well be that the most appropriate immunomodulatory strategy may vary according to the type of transplanted organ. For instance, it is of interest that the first patient who had a successful outcome did not discontinue the treatment with calcineurin inhibitors as suggested in the recently proposed guidelines for the management of kidney transplant recipients with COVID-19 infection.[19] Third, our 2 cases and the 21 patients reported to date suggest that, as in the general population, the presence of comorbidities in COVID-19–infected transplant recipients is associated with increased risk of fatal outcome. On the other hand, the strikingly elevated case-fatality rate observed in the transplant population with COVID-19 pneumonia (26% of the cases we are aware of) far exceeds that reported in the general population by the Chinese Center for Disease Control.[3] Fourth, viral shedding and infectivity in transplanted patients may not be substantially different from those observed in the general population.[20] Finally, it is yet unknown whether recovery from COVID-19 pneumonia will be associated with a faster progression to chronic lung allograft dysfunction.

In conclusion, our data suggest that the outcome of COVID-19 pneumonia in lung transplant recipients is not invariably associated with fatal outcome. Furthermore, our case report also suggests that complete withdrawal of immunosuppression is not mandatory to enable the clinical recovery of lung transplant recipients affected by COVID-19 pneumonia.

DISCLOSURE

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available. Please see the list of references cited.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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