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CASE REPORT

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SARS-CoV-2 infection in two patients following recent lung transplantation

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has become a global health problem with pandemic character. Lung transplant recipients may be particularly at risk due to the high degree of immunosuppression and the lung being the organ primarily affected by COVID-19. We describe a 16-year-old male and a 64-year-old female recently lung transplanted patients with COVID-19 during inpatient rehabilitation. Both patients were receiving triple immunosuppressive therapy and had no signs of allograft dysfunction. Both patients had close contact with a person who developed COVID-19 and were tested positive for SARS-CoV-2. Subsequently, both patients underwent systematic screening and SARS-CoV-2 was ultimately detected. Although the 16-year-old boy was completely asymptomatic, the 64-year-old woman developed only mild COVID-19. Immunosuppressive therapy was unchanged and no experimental treatment was initiated. No signs of graft involvement or dysfunction were noticed. In conclusion, our report of patients with asymptomatic SARS-CoV-2 infection and mild COVID-19, respectively, may indicate that lung transplant recipients are not per se at risk for severe COVID-19. Further observations and controlled trials are urgently needed to study SARS-CoV-2 infection in lung transplant recipients.

KEYWORDS

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

Abbreviations: BOS, bronchiolitis obliterans syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 second; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMP/SMX, trimethoprim/sulfamethoxazole.

[Correction added on 05 November, 2020, after first online publication: Nikolaus Kneidinger was designated as corresponding author]

1 | INTRODUCTION

Coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has become pandemic. Older people and people with comorbidities are at risk for severe COVID-19.[1] Because patients after solid organ transplantation with multimodal immunosuppression are prone to viral infection,[2] the course of SARS-CoV-2 infection remains unknown. The lung is the main organ affected by COVID-19, leading to mechanical ventilator–dependent respiratory insufficiency in some cases.

Tissue damage in COVID-19 might be mediated by a direct SARS-CoV-2–induced cytopathogenic effect. Therefore, the transplanted lung is likely at particular risk. Impaired mucociliary clearance and the high-degree of immunosuppression might further contribute to disease severity.

On the other hand, tissue damage might be the consequence of an immune-mediated inflammatory response to the SARS-CoV-2. In this case, immunosuppression might at least in part counteract the hyperinflammatory response to SARS-CoV-2 infection, leading to the worst form of COVID-19.

Course and management of COVID-19 in lung transplant recipients remains unknown. Furthermore, differential response to SARS-CoV-2 infection within lung transplant recipients is likely. Time since transplantation and acquired comorbidities might influence the course of disease.

Gathering of clinical information is of urgent need. Therefore, the aim of this report is to contribute to the collection of information on COVID-19 in this vulnerable patient population until large-scale studies are available.

2 | CASE PRESENTATION

2.1 | Case 1

A 16-year-old male patient underwent double lung transplantation due to bronchiolitis obliterans after hematopoietic stem cell transplantation 15 years ago. The postoperative course was without any complications. The patient received triple immunosuppressive therapy with twice daily (b.i.d.) tacrolimus (trough level 12-15 ng/mL), 1000 mg mycophenolate mofetil (MMF) b.i.d., and 15 mg prednisolone once per day (q.d.). Induction therapy was not performed. Trimethoprim/sulfamethoxazole (TMP/SMX) was applied for pneumocystis prophylaxis. Due to low risk CMV serostatus, no prophylaxis with valganciclovir was applied.

The patient was referred to our inpatient rehabilitation unit approximately 6 weeks after lung transplantation. His clinical presentation was subjectively well and without signs of infection or allograft dysfunction. On admission, partial pressure of oxygen (PaO_2) without supplemented oxygen was 90 mm Hg; partial pressure of carbon dioxide ($PaCO_2$) was 33 mm Hg. Lung function on admission demonstrated values above 100% of predicted. Because forced expiratory volume in 1 second (FEV1) was constantly rising, the best postoperative FEV1 was not yet established.

The accompanying mother showed respiratory symptoms in form of coughing already on arrival and developed subsequently fever up to 39°C. Coronavirus disease 2019 (COVID-19) was suspected and consequently a nasopharyngeal smear was taken, which confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by real-time polymerase chain reaction (RT-PCR). Thereupon, both were quarantined in a single room in a separated wing of the hospital. Swabbing of the 16-year-old patient was performed and turned out to be positive. Rehabilitation was performed in the single room. The patient care was provided with the use of personal protective equipment consisting of long-sleeved disposable fluid repellent gown, eye protection, gloves, and particulate-filtering facepiece respirator. Due to immediate containment, no spread of SARS-CoV-2 to health care professionals or patients was anticipated.

Immunosuppressive therapy and drug target levels remained unchanged and no experimental antiviral or anti-inflammatory treatment for COVID-19 was started.

The clinical course was unremarkable, especially commonly reported symptoms of COVID-19, like cough, fever, diarrhea or loss of smell, and taste were not reported. Furthermore, laboratory results were unremarkable in the context of recent lung transplantation. Lymphocyte count were stable (~3000/μL) and did not decrease over the course. Slight eosinopenia (27/μL) was noticed once. Lactate dehydrogenase (LDH) values were not noticeable, so were inflammation parameters as shown in the Table 1. The chest X-ray showed no infiltrates and the patient reported well-being throughout the course of infection; therefore no further imaging was performed. pO_2 values were constantly over 90 mm Hg, FEV1 did not decrease and showed stable values over the infection period. Twenty-six days after confirmation of infection, shortly before preparation of this manuscript, the nasopharyngeal swab SARS-CoV-2 RT-PCR was still positive.

2.2 | Case 2

A 64-year-old female patient was admitted for repeated inpatient rehabilitation following bilateral lung transplantation for chronic obstructive pulmonary disease (COPD) approximately 14 months earlier. Posttransplant course was unremarkable, except for a mild cellular rejection and lymphocytic bronchiolitis (A1/B1) detected upon surveillance bronchoscopy without any intervention. No signs of graft dysfunction were present and current FEV1 was 96% of baseline. Immunosuppressive therapy consisted of tacrolimus q.d. (trough level 6-8 ng/mL), MMF 1000 mg b.i.d., and prednisolone 5 mg q.d. Azithromycin was used for prophylaxis of bronchiolitis obliterans syndrome (BOS) and TMP-SMX for pneumocystis prophylaxis. No antiviral prophylaxis or treatment was applied.

Over the course of rehabilitation the patient had contact with an employee health care professional (HCP) who subsequently developed symptoms of COVID-19 and was tested positive for

TABLE 1 Laboratory results of lung transplant recipients with SARS-CoV-2 infection

		Case 1						Case 2					
Day		**16.03.20**	**21.03.20**	**23.03.20**	**30.03.20**	**06.04.20**	**14.04.20**	**16.03.20**	**23.03.20**	**26.03.20**	**31.03.20**	**06.04.20**	**14.04.20**
Leukocytes	$\times 10e^3/\mu L$	9.12		6.82	7.37	7.87	8.76	6.51	5.58	3.72	5.12	3.96	4.8
Eosinophils	%	0.6		0.4	0.5	0.4	0.5	2.4	2	6.3	7.8	4.2	6
Lymphocytes	%	43		46	40.1	45.7	43.7	37.9	26.2	38.3	49.9	39.9	47.5
Platelets	$\times 10e^3/\mu L$	440		342	347	382	380	309	261	321	463	341	372
Hemoglobin	g/dL	11.3		11.8	11.9	11.4	11.8	9.9	8.6	8.5	9.8	8.4	9.8
C-reactive protein	mg/L	2.1		4.2	0.6	<0.5	<0.5	15.9	54	34.2		35.4	15.6
Creatinine	mg/dL	0.48		0.43	0.42	0.51	0.77	0.93	0.61	0.75		0.93	0.92
Procalcitonin	µg/L								0.14			0.21	
Blood urea nitrogen	mg/dL	36		34	27	41	43	53	22	30		37	36
Alanine transaminase	U/L	17		33	14	17	18	13	11	13		12	17
Aspartate transaminase	U/L	22		22	10	13	12	4	<3	1		0	3
Tacrolimus trough level	ng/mL	14.3		15.5	15.8	13.1	15.9	11.2	4.9	6.7		9.6	9.7
SARS-CoV-2-PCR			(+)			(+)	(+)			(−)	(+)		(−)

SARS-CoV-2. The HCP was quarantined at home for 14 days and until two negative nasopharyngeal smears were present. In addition, 4 patients with chronic lung disease were infected by one or more HCP. Due to immediate measures and systematic testing, a further spread of SARS-CoV-2 could be prevented.

The first nasopharyngeal swab of our patient shortly after the last contact was negative and a second test 5 days later confirmed SARS-CoV-2 by RT-PCR. The patient developed COVID-19 with only mild cold symptoms. Cough, dyspnea, diarrhea, or change of taste and smell were never present. C-reactive protein (CRP) increased up to 54 mg/L without procalcitonin elevation. Once mild lymphopenia (1462/μL), but no eosinopenia was noticed. CRP decreased to normal levels within a few days without antimicrobial therapy as shown in the Table 1. Immunosuppressive therapy was continued unchanged and no experimental antiviral treatment was initiated. No signs of allograft dysfunction were present (PaO_2 71 mm Hg, $PaCO_2$ 39 mm Hg), symptoms resolved completely after a few days and a negative SARS-CoV-2 RT-PCR result was obtained 2 weeks after diagnosis. Lung function remained stable throughout COVID-19.

3 | DISCUSSION

We provide evidence for mild to asymptomatic COVID-19 infection in highly susceptible patients following recent lung transplantation on high dose immunosuppression. This is of interest because immunosuppressed patients are prone to viral infections in general. The severity of such infection may be evoked by the marked immunosuppression of lung transplant recipients alongside impaired respiratory mucociliary clearance.[2]

SARS-CoV-2 may result in asymptomatic and self-limiting upper respiratory tract infection. The occurrence of pneumonia and subsequent development of respiratory failure is of prognostic relevance.[3] None of our patients had evidence of significant pneumonia, which might be a reason for the favorable course. Furthermore, laboratory analysis did not demonstrate signs of systemic disease. Lymphopenia and eosinopenia are common features in patients with COVID-19 and might be a critical factor associated with disease severity and mortality.[4] In the setting of transplantation, cytopenia might be multifactorial and should be interpreted cautiously. Furthermore, high levels of interleukin 6 and CRP are indicators for disease severity.

Recently, two cases of COVID-19 infection in solid organ transplant patients other than lung were reported.[5] In these patients, immunosuppressive agents were discontinued upon diagnosis of COVID-19 and methylprednisolone with prophylactic antibiotics was initiated. Both patients developed lung injury and died despite maximal intensive care treatment with mechanical ventilatory support.[5] In contrast, in our present patients, the intensive immunosuppressive therapy after recent lung transplantation was not altered.

Age is the main contributor to disease severity and outcome[1]; this could be the reason for the asymptomatic course of Case 1. On the other hand, Case 2 was female and women are less affected compared to men. Furthermore, comorbidities were not present, as these had been ruled out prior to transplantation. Together these factors might also explain why our patients experienced an oligosymptomatic course of disease.

Both patients were systematically screened after exposure to an infected family member and HCP, respectively. Without screening both patients would possibly not have been diagnosed. This has to be taken into account when comparing our patients to other patients who are hospitalized because of clear symptomatic disease. On the other hand, high-dose immunosuppression might have lessened symptoms, in particular fever. Therefore asymptomatic presentation might not automatically indicate mild disease.

Recently, Romanelli et al addressed the potential beneficial role of immunosuppressive drugs as a valid "therapeutic" choice, by reducing the activity of the T cell immune system and preventing organ injury.[6] The overactivation of the immune system, especially T cells, manifested by an increase of Th17 and high cytotoxicity of CD8 T cells might account for the severe immune injury in COVID-19.[7] The anti-inflammatory effects of immunosuppression could diminish the clinical expression of disease.[6,8] Calcineurin inhibitors reduce the production of interleukin-2, a regulator of proliferation, survival, and maturation for all T cells. Furthermore, tacrolimus and MMF inhibit interleukin-17 production with a stronger inhibitory effect on Th17.[6,9,10]

Both of our patients underwent lung transplantation recently. Despite being under a high dose of immunosuppression both were not affected by long-term side-effects of immunosuppressive therapy and acquired comorbidities. Chronic myelosuppression, kidney failure, arterial hypertension, and many others are potential COVID-19 modifiers in the setting of posttransplant SARS-CoV-2 infection. Furthermore, none of our patients had signs of early onset chronic allograft dysfunction, which could further aggravate the course of disease.

Our data do no support that transplantation and related immunosuppression per se predispose to the development of severe COVID-19 upon SARS-CoV-2 infection. Our observations may support the continued use of maintenance immunosuppressants. However, whether immunosuppression might protect against severe cytokine storm–induced COVID-19 needs to be carefully assessed in larger cohorts.

DISCLOSURE

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

ETHICAL CONSIDERATIONS

Written informed consent was obtained from both patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this Journal.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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