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CASE REPORT

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COVID-19 in lung transplant patients: A case series

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Several case reports and small case series have been published on coronavirus disease 2019 infection after solid organ transplantation; however, thus far there are limited data on coronavirus disease 2019 infections in lung transplant patients. In the present single-center case series we discuss 10 lung transplant patients with a documented severe acute respiratory syndrome coronavirus 2 infection, diagnosed with nasopharyngeal swab in 8 and bronchoalveolar lavage in 2. Eight of 10 patients needed hospital admission, of whom 1 was in the intensive care unit. He died after 2 weeks from multiple organ failure. The remaining nine patients recovered. Cell cycle inhibitors were withheld in all patients, whereas the calcineurin inhibitor and corticosteroids were continued at the same dose, with an acceptable outcome.

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

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started by the end of December in Wuhan (China), and was declared a pandemic a couple of months later. Belgium went into lockdown on March 18th, after the first case was diagnosed on February 4th. Meanwhile, in Belgium, 57 342 people tested positive, and there were so far 9312 deaths (until May 24th).

Patients with solid organ transplants (SOTs) may be more susceptible to infecion with the virus because of their immunosuppressive drug treatment. Indeed several case reports and small case series of COVID-19 infection after SOT have been published,[1-6] but data after lung transplantation are still limited. Aigner et al[7] reported a single case report of COVID-19 in a lung transplant patient, who was discharged on day 21. Pereira et al[8] included 17 lung transplant patients in their series of 90 SOT patients with COVID-19. However, they made no separate analysis of this particular patient group. In a Swiss SOT cohort, 1 of 21 patients was a lung transplant patient[9] and the authors concluded that overall the clinical manifestations in SOT patients are similar to those in the general population.[9] In the present article, we report our experience with 10 consecutive lung transplant patients with a PCR-proven, symptomatic COVID-19 infection.

2 | CASE SERIES

Between March 18 and May 24, a total of 10 symptomatic lung transplant patients (1.5% of our total cohort of 680 lung transplant patients in follow-up) were diagnosed with SARS-CoV-2. In 8 of 10 patients the nasopharyngeal swab was real-time PCRPCR positive, whereas in the remaining 2 patients a bronchoalveolar lavage (BAL) confirmed the diagnosis, after a negative nasopharyngeal swab. In 6 of 10 patients, a low-dose computed tomography (CT) scan of the chest was performed and demonstrated typical COVID-19 alterations (bilateral ground glass opacities); in 4 patients only a chest X-ray was done, which showed no abnormalities. Eight patients had to be admitted to the hospital, whereas two remained ambulatory. In the two patients with a negative nasopharyngeal swab, a bronchoscopy

with BAL was performed to exclude other causes for the bilateral ground glass opacities on CT scan.

Characteristics of the patients, who all underwent a double lung transplantation at a median of 26 months before diagnosis (range 6-190 months), are shown in Tables 1 and 2. They were all admitted for monitoring because of their symptoms and fear of progression of the disease.

All patients were at least on a double immunosuppressive regimen with a calcineurin inhibitor (CNI) and corticosteroids (CS), six took an additional cell cycle inhibitor (four mycophenolate mofetil [MMF], and two azathioprine); one patient was taking additional everolimus. All patients received azithromycine, 250-500 mg, 3 times a week, as standard of care in our center.

Median C-reactive protein (CRP) level decreased from 92.2 mg/L at initial presentation to 5.3 mg/L at discharge. D-dimers and interleukin-6 levels were not routinely measured. In four patients, ferritin was available (patients 6, 7, 9, and 10) and it was increased in three patients (range 96-1360 μg/mL), with the highest value (1360 μg/mL) in Patient 6. Three patients were treated for diabetes (two with insulin and one with oral treatment), and five for arterial hypertension. In all patients, respiratory cultures (bacterial, fungal) and other viral PCRs at time of diagnosis were negative.

One of the patients (no. 6) was immediately admitted to the intensive care unit (ICU), initially treated with high flow 100% oxygen, but needed intubation and ventilation 2 days later because of a very low oxygen saturation. Intermittent prone ventilation was used. His CT scan showed very prominent ground glass opacities, covering 50%-70% of both lungs. He received empiric meropenem, hydroxychloroquine, azithromycine (500 mg every day for 5 days), full-dose anticoagulation, and tocilizumab. Remdesivir was not used as it is not available in Belgium. He developed multiple organ failure and died after 13 days. The other seven patients were all admitted to a regular COVID-19 unit and treated with supplemental oxygen, empiric intravenous broad spectrum antibiotics, and hydroxychloroquine (400 mg every 12 hours for the first day, then two times 200 mg per day for 5 days), and we continued azithromycine (500 mg for 5 days), with daily QTc monitoring. They all gradually improved and were discharged home after 8.5 days (range 3-15 days).

One of the ambulatory patients (no. 8), was admitted to the hospital 6 weeks after her first positive nasopharygeal swab, because of recurrence of high fever since 48 hours, dyspnea, tachypnea, cough, and desaturation (88%). Her nasopharyngeal swab remained positive (cycle threshold initially 16.2, at admission 16.9), a CT scan demonstrated extensive bilateral ground glass opacities (>50%), and the BAL (to exclude other causes) was also positive for SARS-CoV-2 (with a cycle threshold of 20.3), without any other positive viral PCR or bacterial/fungal cultures, despite the presence of 84% neutrophils in the BAL cell differential count. She was treated as described above with hydroxychloroquine, an increased dose of azithromycin, and empiric Rocephin, and she was discharged after 18 days. At that time, her nasopharyngeal swab remained positive, with a cycle threshold of 24.1.

In all patients, CNI and CS were continued at the same dose to maintain their normal calcineurin blocker trough level, whereas cell cycle inhibitors were stopped. No steroid bolus was administered.

3 | DISCUSSION

Although several case reports and small case series have been published of COVID-19 infection after SOT,[1-6] there are only limited data on lung transplant patients.[7-9] We report on our

TABLE 1 Clinical characteristic of the 10 patients

Patient number	Age (y), M/F	Disease	POM	IS regimen	Symptoms	O_2 saturation	Outcome, LOS (d)
1	44, F	Non-CF Brect	28	FK/CS	Fever, cough, pain	99%	Recovered, 3 d
2	61, F	COPD	70	FK/AZA/CS	Dyspnea	89%	Recovered, 7 d
3	66, F	COPD	36	FK.EVE/CS	Dyspnea, fever	97%	Recovered, 13 d
4	62, F	COPD	24	FK/CS	Fever	96%	Ambulatory, recovered
5	23, M	OB	6	FK/MMF/CS	Fever, cough	96%	Recovered, 6 d
6	58, M	Non-CF Brect	190	FK/MMF/CS	Fever, cough, dyspnea	72%	ICU, died, 13 d
7	64, F	COPD	19	FK/CS	Nausea, vomitus	95%	Recovered, 9 d
8	20, F	CF	13	CSA/CS	Fever, Cough	99%	Ambulatory, recovered[a]
9	67, F	COPD	150	FK/MMF/CS	Fever, diarrhea	95%	Recovered, 8 d
10	60, M	COPD	14	FK/AZA/CS	Fever, dyspnea	96%	Recovered, 15 d

Abbreviations: AZA, azathioprine; Brect, bronchiectasis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CS, corticosteriods; CSA, cyclosporine; EVE, everolimus; FK, tacrolimus; LOS, length of stay; MMF, mycophenolate mofetil; OB, obliterative bronchiolitis; POM, postoperative month.

[a]This patient was later hospitalized because of recurrent and more severe disease and was discharged after 18 d.

TABLE 2 Risk factors and laboratory data of the 10 patients

Patient	Diagnostic PCR	BMI (kg/m^2)	AHT	Diabetes	eGFR (mL/min/1.73 m^2)	CRP (mg/L)	White cell count/LC 10^9/L	CNI trough level (μg/L)
1	NPS	29.3	No	NO	65	6.3	3.45/0.5	8.3
2	BAL	30.5	No	NO	61	138.3	10.28/1.0	14
3	NPS	21.8	Yes	NO	20	159.6	5.01/0.6	9.2
4	NPS	20.5	Yes	NO	48	—	—	4.8
5	BAL	23.7	No	YES	110	78.6	10.05/0.9	20.9
6	NPS	34.2	Yes	YES	41	156	4.5/0.3	9.4
7	NPS	27.2	yes	NO	47	112.8	4.76/0.3	25.6
8	NPS	23.1	yes	YES	77	5.5	4.23/1.1	89[a]
9	NPS	20.7	no	NO	31	92.2	1.89/0.3	7.4
10	NPS	20.5	no	NO	62	24.2	3.85/0.4	12.8
Median (range)		23.4 (20.5-34.2)			54.5 (20-110)	92.2 (5.5-159.6)	4.5 (1.89-10.28)/0.5 (0.3-1.1)	FK: 9.4 (4.8-25.5)

Abbreviations: AHT, arterial hypertension; BAL, bronchoalveolar lavage; CNI, calcineurin inhibitor; CRP, C-reactive protein; eGFR, estimated GFR; LC, absolute lymphocytosis; NPS, nasopharyngeal swab.

[a]Cyclosporine trough level (all others are tacrolimus).

initial experience with 10 lung transplant patients with COVID-19, among a total cohort of 680 patients in follow-up at our center (1.5%). During the same time period, 23 lung transplant patients who had to undergo an elective bronchoscopy, either as surveillance or because of a decline in Forced expiratory volume in 1 second, and who were otherwise asymptomatic, underwent a nasopharyngeal swab before bronchoscopy, and all tested negative for SARS-CoV-2.

Symptomatology in our 10 SARS-CoV-2 positive patients was comparable to a nontransplanted population and in general was rather mild to moderate, except for one patient who had very severe disease and finally died after 2 weeks. In fact, although most patients had several risk factors for COVID-19 infection (Table 2), this specific patient had most of the accepted risk factors for severe disease and mortality, as mentioned in the literature[10]: male sex, obesity (BMI 34.2), arterial hypertension for which he was treated with an angiotensin-converting enzyme (ACE) inhibitor, diabetes, and immunosuppressive treatment with tacrolimus, MMF, and CS. He also received the highest cumulative dose of immunosuppression, as he had been transplanted 190 months before the COVID-19 infection.

One patient, initially ambulatory when diagnosed, had late new onset of symptoms and needed hospitalization at a low care COVID-19 unit 6 weeks later. Remarkably, her nasopharyngeal swab was still positive after 6 weeks (with a comparable cycle threshold), and also the BAL fluid at admission was positive for SARS-CoV-2, whilst she developed ground glass opacities on CT scan. Despite this, the course of the disease flair up was favorable and she was discharged without oxygen supplement after 18 days.

All patients were at least on dual immunosuppressive treatment with a CNI and CS, whereas 60% were also taking a cell cycle inhibitor. Only these last drugs were stopped temporarily, whereas we did not change the CNI and CS dose. There has been a lot of debate so far about whether immunosuppressive treatment needs to be continued, lowered in dose, or even temporarily stopped in case of a COVID-19 infection. This question is still not resolved, although there is some evidence, specifically in a case series of liver transplant patients, that a higher trough level of CNI may result in a better outcome compared to very low levels. Indeed, in this series, three patients with a very low tacrolimus trough level died, whereas three others, who were more recently transplanted and hence had higher trough levels, survived.[6] In addition, in the experience of the Columbia University kidney transplant group, the immunosuppressive medication was reduced in 15 COVID-19 kidney transplant cases, and 27% needed mechanical ventilation, but over half were discharged home by the end of follow-up.[1] In another two kidney transplant patients, immunosuppressive treatment was left unchanged and both patients fully recovered.[4] In 10 confirmed COVID-19 kidney transplant patients in Wuhan, the immunosuppressive treatment was reduced and the authors found that the severity of pneumonia was greater in the transplanted patients compared to the general population. Indeed five patients became severely ill and three critically ill, but finally 90% of their patients recovered, and only one died of progressive respiratory failure.[11] In their series of 90 SOT patients with COVID-19, Pereira et al also maintained CNI and CS, but tapered/stopped cell cycle inhibitors.[8] Based on these case series and our own results, it is difficult to decide whether immunosuppressive treatment has to be reduced upfront or can be continued at the same level (at least for CNI and CS) when COVID-19 is diagnosed. From our initial experience, it seems fair to say that the outcome without reduction of CNI and CS (but with temporarily arresting MMF and azathioprine) is acceptable. This is also in line with recommendations from the

COVID-19 task force from the International Society for Heart and Lung Transplantation.[12]

For the time being, it can be concluded that we do not know yet whether classical immunosuppression may alter the predisposition to acquiring infection with SARS-CoV-2. This may well be the case as 1.5% of our lung transplant cohort tested positive for SARS-CoV-2, whereas this was only 0.5% in the general Belgian population. However, it must be argued that lung transplant patients come to see us with minor symptoms and will thus be swabbed, whereas this does not hold true for the general population. Whether the disease may become worse or not after lung transplantation[13] is not clear, and in our small series the mortality rate was 10% (1/10), whereas this was 16.2% in the Belgian SARS-CoV-2 positive population, suggesting that COVID-19 may be somewhat more frequent after lung transplantation, but without a worse outcome, although these data should be interpreted with caution.

There is also some evidence that tacrolimus strongly inhibits the growth of human coronaviruses SARS-CoV, HcoV-NL63, and HcoV-229E at low, noncytotoxic concentrations, at least in cell cultures in vitro,[14] which may again support the strategy to continue the CNI at the same dose. Furthermore, azithromycin has been suggested to be beneficial in the treatment of COVID-19 patients, at least when combined with hydroxychloroquine,[15] which has been set as the standard treatment option in our center. Potential side effects when using this drug combination, especially QTc prolongation, need careful monitoring.[15,16] Although hydroxychloroquine has been used widely in the treatment of COVID-19, it remains to be proven whether it is really beneficial in these patients. Several trials are running but convincing data are still lacking.[16,17]

Remdesivir was recently shown to be superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection and may become the treatment of choice.[18] We were not able to use this drug as it is not yet available in Belgium.

In conclusion: this is a single-center report of COVID-19 infection in a series of 10 lung transplant patients. Besides a single patient with severe disease who died, disease presentation was mild/moderate in the other nine patients. One patient had a remarkable course as she was initially ambulatory and needed hospitalization 6 weeks later for recurrent and more severe COVID-19 disease, whereas she remained/became SARS-CoV-2 positive as well in the nasopharynx as in the BAL fluid.

We adapted the policy to temporarily arrest the cell cycle inhibitors, but not to reduce the CNI and CS treatment, which, according to our initial results, seems acceptable.

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CONFLICT OF INTEREST

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 available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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