


## CASE REPORT

# A case of SARS-CoV-2 pneumonia with successful antiviral therapy in a 77-year-old man with a heart transplant

Daniel Mathies<sup>1</sup> | Dominic Rauschnig<sup>1</sup>  | Ulrike Wagner<sup>1</sup> | Frank Mueller<sup>1</sup> | Maja Maibaum<sup>1</sup> | Christin Binnemann<sup>1</sup> | Stephan Waldeck<sup>2</sup> | Katrin Thinnes<sup>3</sup> | Michael Braun<sup>3</sup> | Willi Schmidbauer<sup>3</sup> | Ralf M. Hagen<sup>4</sup> | Christoph Bickel<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Bundeswehr Central Hospital Koblenz, Koblenz, Germany

<sup>2</sup>Department of Radiology, Bundeswehr Central Hospital Koblenz, Koblenz, Germany

<sup>3</sup>Department of Anaesthesiology, Bundeswehr Central Hospital Koblenz, Koblenz, Germany

<sup>4</sup>Department of Microbiology, Bundeswehr Central Hospital Koblenz, Koblenz, Germany

## Correspondence

Dominic Rauschnig

Email: dominicrauschnig@bundeswehr.org

The SARS-CoV-2 infection can be seen as a single disease, but it also affects patients with relevant comorbidities who may have an increased risk of a severe course of infection. In this report, we present a 77-year-old patient with a heart transplant receiving relevant immunosuppressive therapy who tested positive for SARS-CoV-2 after several days of dyspnea, dry cough, and light general symptoms. Computed tomography confirmed interstitial pneumonia. The patient received antiviral therapy with hydroxychloroquine and showed no further deterioration of the clinical state. After 12 days of hospitalization, the patient was released; he was SARS-CoV-2 negative and completely asymptomatic.

## KEYWORDS

antibiotic: antiviral, clinical research/practice, heart transplantation/cardiology, immunosuppressant – calcineurin inhibitor: tacrolimus, immunosuppression/immune modulation, infection and infectious agents – viral, infectious disease, lung disease: infectious, off-label drug use

## 1 | INTRODUCTION

A 77-year-old male heart transplant recipient presented to our emergency department complaining about shortness of breath, pain on inspiration, and dry cough as well as body aches, fatigue, and decline in body weight for 3 days. Fever and angina pectoris were denied. He was unaware of a contact with a SARS-CoV-2-positive patient and had not been on trip to a high-risk area at that time.

The patient had undergone heart transplant surgery after ischemic cardiomyopathy in 2003. In 2019, he received percutaneous transluminal coronary angiography and drug-eluting stent of the left circumflex and ramus marginalis due to a tandem stenosis. Further past medical history included cytomegalovirus (CMV) colitis in 2005 and septicemia after CMV pneumonia, chronic kidney disease (G3b

KDIGO classification), hypertension, and diabetes mellitus type 2 treated with oral medication.

Medications included sirolimus 0.5 mg daily, mycophenolate 250 mg twice daily, acetylsalicylic acid 100 mg daily, clopidogrel 75 mg daily, bisoprolol 2.5 mg twice daily, telmisartan 80 mg daily, torasemide 5 mg daily, atorvastatin 40 mg daily, ezetimibe 10 mg daily, sitagliptin 25 mg twice daily, allopurinol 100 mg daily, pantoprazole 20 mg daily, and vitamin D 20 000 IE weekly.

## 2 | CASE PRESENTATION

Clinical examination showed a patient with stable cardiopulmonary status and a pulse of 86/min and blood pressure of 140/85 mm Hg. Body temperature was 36.7°C. Respiratory frequency was 16 per minute with an oxygen saturation of 96% without supplementary

**Abbreviations:** bat-CoV, bat-borne coronavirus; COVID-19, coronavirus disease 2019.

Daniel Mathies and Dominic Rauschnig contributed equally.

oxygen. Auscultation of the lung found dry rales in the basal compartments. Examination of the heart and abdomen was unremarkable.

In the initial arterial blood gas analysis,  $P_{O_2}$  was 88 mm Hg with a saturation of 97.2%;  $P_{CO_2}$  was 20.7 with pH 7.35. Laboratory findings showed a procalcitonin of 0.12 ng/mL (<0.05 ng/mL) and a C-reactive protein level of 4.19 mg/dL (<0.5 mg/dL) with normal leukocytes and a blood sedimentation rate of 56 mm/h (<46 mm/h). The differential blood count showed monocytosis, and lymphocytes were normal. There was a normocytic and normochromic anemia. Other values were lactate dehydrogenase, 271 U/L (135-255 U/L); D-dimer, 2.04 mg/L (<0.8 mg/L); hs-troponin T, 19 pg/mL (<14 pg/mL) without further increase after 3 hours; myoglobin, 122  $\mu$ g/mL (28-72  $\mu$ g/mL); elevated creatinine, 2.13 mg/dL (0.67-1.17 mg/dL); blood urea nitrogen, 77.6 mg/dL (16.6-48.5 mg/dL); and glomerular filtration rate calculated for cystatin C, 22 mL/min. Hemoglobin A1c was 6.5%.

An initial electrocardiographic study had no pathological findings. Computed tomography (CT) scan of the thorax showed distinct atypical opaque infiltration of the left lower lobe consistent with viral pneumonia (Figure 1). Swabs from throat and nose as well as sputum tested positive for SARS-CoV-2 on real-time polymerase chain reaction (PCR) on the day of admission.

The patient with heart transplant due to coronary artery disease with ischemic cardiomyopathy was diagnosed with SARS-CoV-2 infection with viral pneumonia.

### 3 | TREATMENT

After establishing the diagnosis, we started a therapeutic trial with hydroxychloroquine with an initial dose of 400 mg twice daily for the first day followed by 200 mg twice daily. We refrained from therapy with lopinavir/ritonavir because of possible interactions due to the shared metabolism path via CYP3A4 with sirolimus. The patient preemptively received piperacillin/tazobactam and cotrimoxazole and ganciclovir because he had a history of CMV infections including colitis and pneumonia. In close cooperation with the transplant center (Ludwig-Maximilians-Universität), we modified immunosuppressive medication, replacing sirolimus with tacrolimus due to its potential lung toxicity.<sup>1</sup> Once a steady serum level was reached, we withdrew mycophenolate.

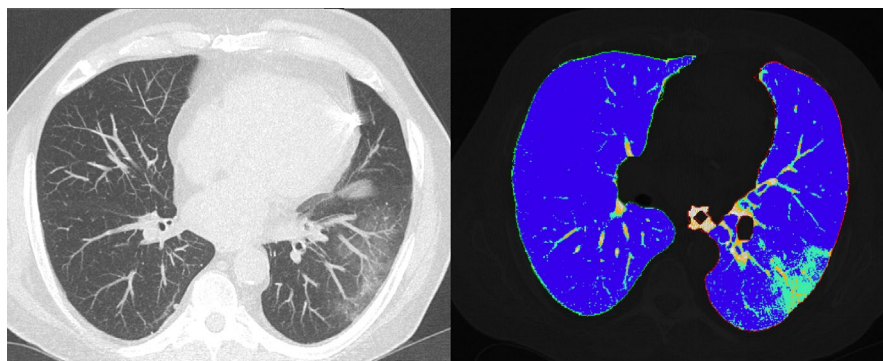
The patient was monitored in an intensive care unit for 3 days and received 4 L oxygen supplementation via nasal cannula. Arterial oxygen saturation dropped as low as 89% with a Horowitz index of 169 mm Hg and an alveolar-arterial gradient of 162 mm Hg (age corrected <23 mm Hg) indicating a potential severe case with a moderate acute respiratory distress syndrome (ARDS) and a consecutive V/Q mismatch. As there were no signs of further relevant deterioration, the patient was transferred to our normal ward. CT was repeated 4 and 9 days after admission, showing fluctuation of the opaque infiltrations on the first and a general decline on the second scan. The patient additionally presented with diarrhea, but stool samples showed a negative culture and multiplex PCR for pathological bacteria or viruses.

After 7 days, the patient started to show relevant improvement in the respiratory situation and required no further oxygen supplementation. There was no increase in procalcitonin or a left shift in granulocytes; thus, antibiotic treatment was discontinued. Respiratory symptoms declined after 9 days so we tested sputum as well as throat and nose swabs for SARS-CoV-2 on the following 2 days. PCR was negative in all specimens. A multiplex PCR in another sputum as well as serological results showed no clues for CMV reactivation or other viral or bacterial agents. The patient received hydroxychloroquine a total of 9 days. We were able to discharge the patient 12 days after admission. An overview of the course is provided in Figure 2.

### 4 | DISCUSSION

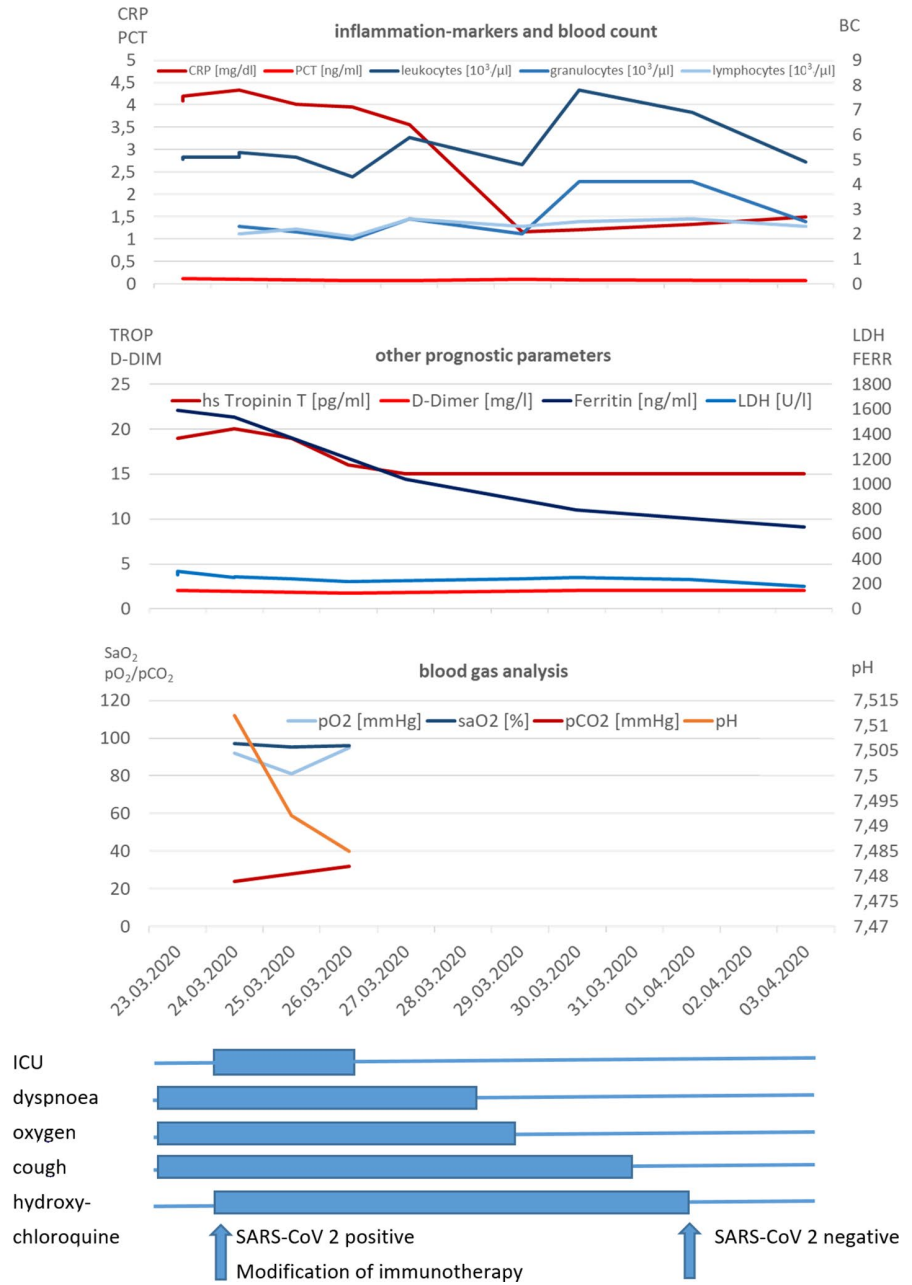
SARS-CoV-2, initially named 2019-nCoV, emerged in December 2019 in the People's Republic of China in the Hubei region, especially in the city of Wuhan. Probably deriving from bat-borne coronaviruses (bat-CoVs), it initially caused a local outbreak of an influenza-like disease with potentially severe pulmonary complications similar to related coronaviruses like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>2,3</sup>

The disease itself was named coronavirus disease 2019 (COVID-19) and ranges from mild and unspecific upper respiratory symptoms with cough and fever to septic courses and ARDS with fatal multiorgan failure. Bacterial superinfection and other viral coinfection, for example with an influenza virus during the current season took place simultaneously, may increase the risk of



**FIGURE 1** Cross-sectional view of the thorax computed tomography scan (maximum intensity projection) with diffuse opaque infiltration and a color-coded analysis of the segmental perfusion mismatch [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**FIGURE 2** Schematic summary of the course of disease [Color figure can be viewed at wileyonlinelibrary.com]



a fatal outcome.<sup>4</sup> Elderly patients and patients with comorbidities, in particular of the lungs or the cardiovascular system, show an increased death rate.<sup>5</sup> Droplet infection is seen as the main method of human-to-human transmission, although smear infection must also be taken into consideration. It is supposed that transmission is possible during the asymptomatic period of incubation about 2 days after virus inoculation.<sup>6</sup>

Due to our globalized society, the virus easily spread around the globe in the beginning of 2020, causing a pandemia with new epicenters in southern Europe and the United States. The first confirmed patient in Germany was registered on January 27, 2020, in Bavaria.<sup>7</sup> On April 4, 2020, there were more than 96 000 reported cases, of which 1444 were fatal. Worldwide, more than 1 200 000 confirmed cases with about 64 800 deaths, especially in Italy and Spain, are registered this day.<sup>8</sup>

Only a fistful of cases of a SARS-CoV-2 infection in patients who received a solid organ transplant have been published so far.<sup>9,10</sup> The known patients have all been receiving different forms of immunosuppression; one might deduce that this would lead to more severe infections. Interestingly, the clinical manifestations range from mild cases with symptoms of a common cold to oxygen dependency to severe respiratory failure that requires intubation and mechanical ventilation. Here, we present the case of a patient who endured a rather mild course of SARS-CoV-2 pneumonia.

Currently, antiviral therapy of COVID-19 makes up part of extended scientific efforts because an evidence-based regimen has not been found yet and the treatment of COVID-19 has been experimental so far. With the knowledge of the recent viral outbreaks of SARS and MERS, several existing agents have been supposed to also have an effect against SARS-CoV-2.<sup>11</sup> Early Chinese reports and

recommendations included lopinavir/ritonavir and (hydroxy-)chloroquine, among others. Because these drugs have national approvals for other indications, there is a broad experience in use, and they were available on the market for prompt delivery, we decided to take them as first-line therapy for COVID-19 cases in our house guideline.

In addition to the therapeutic agents, the moment of starting antiviral therapy is discussed extensively.<sup>12</sup> We prefer an early start of antiviral medication in order to prevent viral shedding with the potential risk of a progress to a severe course of COVID-19. In this case, the combination of radiologic signs of viral pneumonia and the supposed high-risk state of severe immunosuppression led to the decision to start an antiviral therapy immediately after receiving the positive real-time PCR results, although the patient presented with only mild symptoms.

Interactions between medications pose a great challenge. Cyclosporine, tacrolimus, and sirolimus are hepatically metabolized via CYP3A4 enzymes. Lopinavir is combined with ritonavir in order to block this pathway and to increase serum levels of lopinavir. In combination, this will lead to an increase of the immunosuppressive medication as well, which necessitates dose adjustments and measurements of serum levels to avoid toxic levels. Hydroxychloroquine and chloroquine are metabolized via CYP3A4 as well as CYP2C8, thus theoretically also possessing a potential, albeit smaller, for interaction. Due to the medication with sirolimus and later tacrolimus, we decided to treat the patient with hydroxychloroquine rather than lopinavir/ritonavir, which resulted in no relevant increases in serum levels for the immunosuppressive medications. In this complicated situation, Internet-based databases of drug-drug interactions help to reach a decision quickly but responsibly.<sup>13</sup>

A second question is whether patients with a solid organ transplant who receive immunosuppressive medication are at greater risk for a severe manifestation of a SARS-CoV-2 infection or might even benefit from a reduced immunologic reaction. The answer remains uncertain due to the paucity of data considering relevant cases.

For SARS-CoV-2, we found 2 cases of patients with a heart transplant; 1 patient had only mild manifestations and 1 patient required mechanical ventilation but survived.<sup>9</sup> The first patient was a 43-year-old man who had undergone transplant surgery in 2017 and had received tacrolimus and mycophenolate. Therapy included valganciclovir and arbidol as well as several antibiotics. Immunosuppressants were not cancelled. The other patient was a 51-year-old man with a transplant from 2003 who was also receiving therapy with tacrolimus and mycophenolate. Therapeutic trials included ribavirin, human  $\gamma$ -globulins, and methylprednisolone, as well as ganciclovir, arbidol, and antibiotics. Immunosuppressive medication was paused for 13 days.

A patient with a renal transplant and medication that included tacrolimus, everolimus, and prednisone, was on ventilation when the case was published despite omitting tacrolimus and everolimus and a therapeutic trial with lopinavir/ritonavir, hydroxychloroquine, and interferon- $\beta$ .<sup>10</sup> From a cohort of 200 pediatric patients with transplants, 100 patients receiving immunosuppression and 3 patients receiving chemotherapy, 3 mild cases of SARS-CoV-2 without

pneumonia are reported, but it remains unclear whether these are patients with a solid organ transplant.<sup>14</sup>

For infection with SARS-CoV and MERS-CoV, the data are comparable.<sup>15,16</sup> There are few cases of manifestations in patients with renal or liver transplant receiving cyclosporine, azathioprine, tacrolimus, mycophenolate, or prednisone. Some of the patients died although immunosuppressive medication was halted; others survived with reduced therapy.

It is difficult to determine whether immunosuppressive medication should be continued or reduced. The published guidelines from expert associations like ISHLT offer first guidance and recommendations.<sup>17</sup> Considering withdrawal of mycophenolate or azathioprine is recommended. On the other hand, corticosteroids like methylprednisolone are a medication that has been widely used in patients with SARS-CoV-2-mediated ARDS ranging from 1 to 2 mg/kg/d for 3-5 days to mitigate the cytokine storm.<sup>18</sup> The effects of hydroxychloroquine in SARS-CoV 2 might also be related to its immunomodulatory effects.<sup>19</sup>

In conclusion, it remains unclear whether immunosuppressive medication leads to a more serious progression or might even have a positive effect. Further investigation is required. However, a certain degree of medication must be maintained to avoid transplant rejection. Considering antiviral therapy latest reports seem to confirm the in vitro efficiency of hydroxychloroquine in vivo.<sup>20</sup> To the best of our knowledge, this is the first case report of successful antiviral monotherapy with hydroxychloroquine in a patient after heart transplant while continuing a modified immunosuppressive therapy.

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

## ORCID

Dominic Rauschnig  <https://orcid.org/0000-0001-9284-8778>

## REFERENCES

1. Pham PT, Pham PC, Danovitch GM, et al. Sirolimus-associated pulmonary toxicity. *Transplantation*. 2004;77:1215-1220.
2. Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. *Emerg Microbes Infect*. 2020;9:275-277.
3. Wu Y-C, Chen C-S, Chan Y-J. The outbreak of COVID-19: an overview. *J Chin Med Assoc*. 2020;83:217-220.
4. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;NEJMoa2002032.
5. Wu C, Chen X, Cai Y, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online ahead of print 2020]. *JAMA Intern Med*. <https://doi.org/10.1001/jamainternmed.2020.0994>

6. Linton NM, Kobayashi T, Yang Y, et al. Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly available case data. *J Clin Med*. 2020;9:538.
7. Konrad R, Eberle U, Dangel A, et al. Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany, February 2020. *Eurosurveillance*. 2020;25. <https://doi.org/10.2807/1560-7917.ES.2020.25.9.2000173>
8. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time [published online ahead of print 2020]. *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1)
9. Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China [published online ahead of print 2020]. *J Heart Lung Transplant*. <https://doi.org/10.1016/j.healun.2020.03.006>
10. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation [published online ahead of print 2020]? *Am J Transplant*. 2020;1-4. <https://doi.org/10.1111/ajt.15874>
11. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269-271.
12. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19 [published online ahead of print 2020]. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2001282>
13. Liverpool Drug Interactions Group. COVID-19 Drug Interactions. 03. 04. 2020. <https://www.covid19-druginteractions.org/>. Accessed May 5, 2020.
14. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic [published online ahead of print 2020]. *Liver Transpl*. <https://doi.org/10.1002/lt.25756>
15. AlGhamdi M, Mushtaq F, Awn N, Shalhoub S. MERS CoV infection in two renal transplant recipients: case report: MERS CoV in renal transplant recipients. *Am J Transplant*. 2015;15:1101-1104.
16. Kumar D, Tellier R, Draker R, et al. Severe acute respiratory syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening. *Am J Transplant*. 2003;3:977-981.
17. Aslam S, Grossi P, Teuteberg J, et al. *Guidance for Cardiothoracic Transplant and Ventricular Assist Device Centers Regarding the SARS CoV-2 Pandemic*. Addison, TX: The International Society for Heart and Lung Transplantation; 2020.
18. The General Office of National Health Commission Office of State TCM Administration. Diagnosis and treatment protocol for novel coronavirus pneumonia. *Chinese Med J* 2020;133(9):1087-1095.
19. Zhou D, Dai S-M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*. 2020;pii:dkaa114. <https://doi.org/10.1093/jac/dkaa114>
20. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.03.22.20040758>

**How to cite this article:** Mathies D, Rauschnig D, Wagner U, et al. A case of SARS-CoV-2 pneumonia with successful antiviral therapy in a 77-year-old man with heart transplant. *Am J Transplant*. 2020;20:1925-1929. <https://doi.org/10.1111/ajt.15932>