Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7089-21
Intern Med 60: 2297-2300, 2021
http://internmed.jp

【 CASE REPORT 】

A Kidney Transplant Patient Who Died of COVID-19-associated Severe Acute Respiratory Distress Syndrome

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Abstract:
We herein report a 67-year-old kidney transplant patient who died of COVID-19. He was treated with hydroxychloroquine and azithromycin and received mechanical ventilation that temporarily improved his respiratory status. Despite our efforts, however, he later developed respiratory failure and died 43 days after the disease onset. The autopsy revealed prominent organization of alveoli and alveolar ducts, with a massive accumulation of macrophages in the lungs. A few severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen-positive cells were detected in the lung, suggesting delayed virus clearance owing to his long-term immunosuppressed state, leading to constant lung damage and ultimately respiratory failure.

Key words: COVID-19, SARS-CoV-2, kidney transplant, immunosuppressed, Coronavirus disease 2019

(Intern Med 60: 2297-2300, 2021)
(DOI: 10.2169/internalmedicine.7089-21)

Introduction

Coronavirus disease 2019 (COVID-19) has become a global pandemic, with more than 30 million people infected worldwide and 1,000,000 deaths reported as of October 20, 2020 (1).

Patients COVID-19 and a clinical history of other conditions, including cardiovascular and chronic respiratory diseases, reportedly demonstrate a greater need for mechanical assistance and present a higher mortality risk than those without such a history (2). While the prognosis of kidney transplant patients with COVID-19 and how best to efficaciously adjust their immunosuppressants remain unclear, a small case series has reported that 5 out of 20 kidney transplant patients died from COVID-19 (3) and that kidney transplant patients were more likely to develop severe disease than their family members, experiencing a prolonged infection course (4).

We herein report the clinical course and autopsy findings of a kidney transplant patient who used immunosuppressants for a prolonged period and died from COVID-19-associated severe acute respiratory distress syndrome after receiving treatment that included mechanical ventilation.

Case Report

The patient was a 67-year-old man who developed chronic kidney failure owing to immunoglobulin A nephropathy, resulting in his undergoing living-donor kidney transplantation in 1993 and 2005. Thereafter, he received continuous treatment with oral methylprednisolone (2 mg/day), tacrolimus (2.5 mg/day), and mycophenolate mofetil (500 mg/day). In 2005, he underwent coronary artery bypass surgery for acute myocardial infarction.

He was a mariner and had traveled to the Philippines 17 days before admission. He developed a cough 15 days before admission and a fever 7 days before admission, and 4 days later, he was taken by ambulance to his general practitioner. Three days later, on subjecting a nasal swab sample to a polymerase chain reaction (PCR) test, he was found to be positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was transferred to our hospital.

On an examination, he had an oxygen saturation of 91%

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Received: January 14, 2021; Accepted: April 12, 2021; Advance Publication by J-STAGE: May 29, 2021
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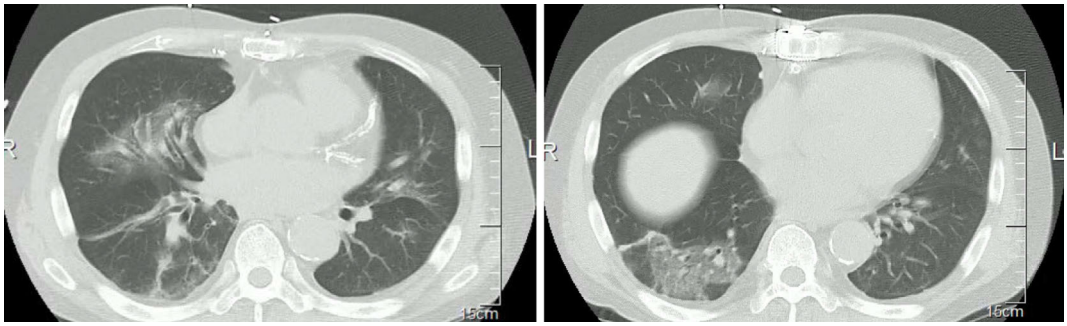

Figure 1. Chest computed tomography performed on disease day 13 shows ground-glass opacities in the right middle and lower lobes.

at 2 L via cannula, and his body temperature was 37.6 °C. Computed tomography showed ground-glass opacities and air space consolidation along the bronchi, consistent with COVID-19-induced pneumonia (Fig. 1). A blood test revealed an elevated C-reactive protein level (21 mg/dL) and reduced lymphocyte count (257/μL). His D-dimer level was low (0.9 μg/mL) on the day of admission.

We decided to maintain treatment with tacrolimus and suspend mycophenolate mofetil. We initiated treatment with hydroxychloroquine (400 mg/day) and azithromycin (500 mg/day) for 3 days, with a corticosteroid (hydrocortisone 240 mg/day as severe community-acquired pneumonia) also initiated owing to the increased oxygen demand.

Despite this treatment strategy, his respiratory status worsened on the fourth hospital day, resulting in the need for intubation and mechanical ventilation because of a deteriorated respiratory condition due to COVID-19-associated severe acute respiratory syndrome coronavirus (SARS). On the 5th hospital day, the D-dimer level was elevated to 2.1 μg/mL, so heparinization was started. Later, his P/F ratio seemed to improve, staying in the 300 range, and hydrocortisone treatment was discontinued on the 7th hospital day. Three days later, air space consolidation had worsened in the lung field, which was considered evidence of inflammatory relapse, and he was managed with hydrocortisone 100 mg/day. However, his P/F ratio deteriorated, and the air space consolidation expanded. On the 18th hospital day, we performed bronchoscopy, and the obtained sputum was negative for SARS-CoV-2 according to PCR. Piperacillin tazobactam was administered owing to the possibility of ventilation-associated pneumonia, but his blood culture was negative, and only candida was detected in his sputum culture. His anti-COVID-19 spike IgG titer was low on the 22 nd hospital day. After that, his respiratory status continued to gradually worsen. He developed multiple organ failure and died on the 28th hospital day, 43 days after the symptom onset.

Macroscopically, the lung cut surface showed extensive and ill-defined pale consolidations, with only sporadic air spaces. The rest of the lungs were highly congested, leaving little space for ventilation (Fig. 2A, B). Microscopically, spiculated and branching fibrosis was seen throughout the alveolar ducts and alveoli over a wide area of the bilateral lungs, with abundant macrophages occupying the rest of the alveoli. In addition, alveolar pneumocyte hyperplasia and squamous metaplasia were observed. Hyaline membrane formation was limited, and the organization was often detached from the alveolar wall. In contrast with this drastic fibrosis in the airspaces and epithelial hyperplasia, the interstitium showed mild inflammation and fibrosis. Thrombotic microangiopathy was not evident (Fig. 2C, D). The old kidney graft exhibited clear cortical atrophy, while the new kidney graft showed maintained glomerular, vascular, and tubular functions.

Total ribonucleic acid (RNA) was extracted from formalin-fixed paraffin-embedded (FFPE) tissue specimens using the PureLink® FFPE RNA Isolation Kit (Thermo Fisher, Waltham, USA) according to the manufacturer's instructions. The copy numbers of SARS-CoV-2-RNA were determined by real-time reverse transcription (RT)-PCR with QuantiTect Multiplex RT-PCR Kits (Qiagen, Hilden, Germany). To amplify a segment within the nucleoprotein (NP) region of SARS-CoV-2 RNA (GenBank accession MN 908947, 29191-29251), forward (5'-GGCCGCAAATTGCACAAT-3') and reverse (5'-CCAATGCGCGACATTCC-3') primers were used with a labeled probe 5'-(FAM)CCCCCAGCGCTTCAGCGTTCT (TAMRA)-3', as described previously (5). For normalization, we used the human glyceraldehyde-3-phosphate dehydrogenase messenger RNA (GAPDH mRNA) as an internal reference for each extracted RNA. SARS-CoV-2-RNA was detected in the lung, small intestine, and mediastinal lymph nodes. The ratios of SARS-CoV-2 copy numbers to GAPDH mRNA copy numbers were 9.11×10^{-3} in the lung, 9.21×10^{-3} in the small intestine, and 1.23×10^{-3} in the lymph node. No viral RNA was detected in the heart, kidney, liver, or spleen.

Immunohistochemistry was performed using a mouse monoclonal antibody against a SARS-CoV-2 spike protein (1:1000, clone1A9, GTX632604; GeneTex, Irvine, USA) using a catalyzed signal amplification (CSA) II method (Agilent DAKO, Santa Clara, USA). SARS-CoV-2 spike-positive cells were detected in a few lung tissue specimens (Fig. 2E).

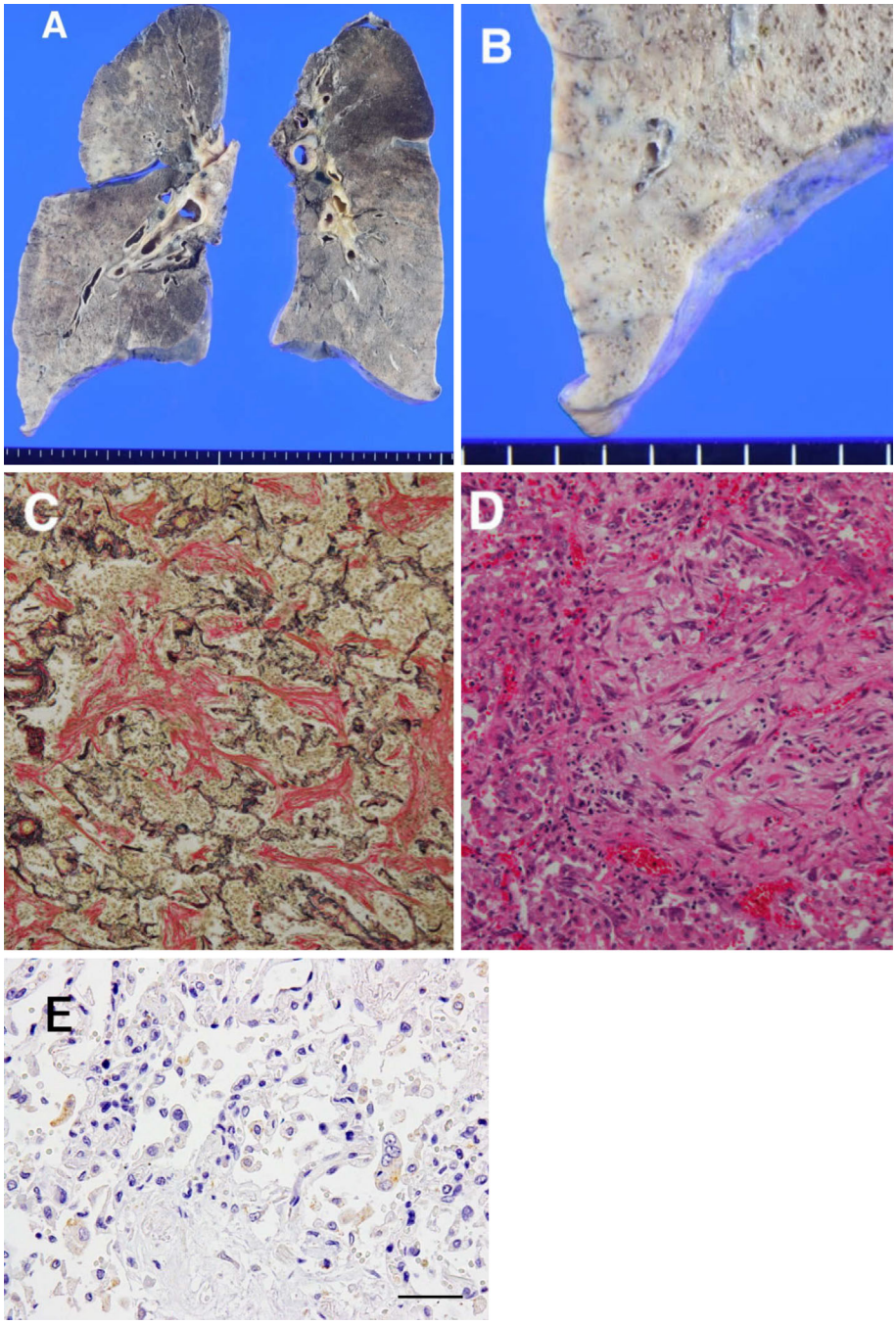

Figure 2. **(A, B) Lungs showing extensive consolidation and congestion. (C, D) Spiculated organizing lesions are seen throughout the alveolar ducts and alveoli. Fibrosis is detached from the alveolar wall. Fibroblasts in this lesion have enlarged nuclei and are highly active. The remaining air spaces are filled with macrophages (C: Elastica van Gieson staining, D: Hematoxylin and Eosin staining). (E) Immunohistochemistry shows SARS-CoV-2 spike protein (brown) in the cytoplasm of a few cells in the alveolar airspace. Scale=50 μm.**

Discussion

We encountered a kidney transplant patient for whom persistent viral infection associated with an immunocompromised state resulted in continuous lung damage and death due to respiratory failure.

A previous report revealed that 58-80% of kidney transplant recipients with COVID-19 presented more commonly with a fever as an initial symptom, lower lymphocyte counts, and more rapid clinical progression than those in the general population with COVID-19 (6,7). In that report, most recipients had received immunosuppressive agents, such as tacrolimus, and lymphocyte counts lower than 1,000 per mm^3 were observed in nearly 80% of patients. The mortality rate of kidney transplant patients using immunosuppressants was estimated to be 25-28% (3,6). In our patient, the lymphocyte count was 257 per mm^3 at the time of hospi-

talization, and despite azithromycin and hydroxychloroquine treatment, the patient died 43 days after the symptom onset.

Severe pneumonia in COVID-19 is considered an overreaction of the immune system with an excessive release of cytokines, contributing to the development of acute respiratory distress syndrome (8). Among healthy patients, SARS-CoV-2 was detected in lung tissue in patients who died one to two weeks after the symptom onset but not in those who died three to four weeks after the symptom onset (9). Patients who undergo organ transplantation require lifelong immunosuppressant therapy. Although these immunosuppressants may help suppress the cytokine storm, the histopathological examination of our case showed extensive organization in the lungs. Real-time RT-PCR and immunohistochemistry revealed protracted viral infection 43 days after the symptom onset, which implies the long-standing toxicity of SARS-CoV-2.

At present, the ideal method of adjusting immunosuppressive drugs in COVID-19 patients who have undergone renal transplant remains unclear, and the discontinuation of antiproliferative drugs, such as azathioprine and mycophenolate, is considered in response to severe infections (10). Calcineurin inhibitors can be expected to suppress inflammation caused by COVID-19, and since there was a report showing that tacrolimus suppressed the replication of a coronavirus in an *in vitro* experiment conducted before the COVID-19 pandemic, it is believed that the dose should be either maintained or reduced (11).

Several other COVID-19 autopsies have revealed endothelial damage and microemboli in pulmonary capillaries (12). In the current patient, thrombotic microangiopathy was not observed, possibly due to the heparinization treatments performed after hospitalization.

In our case, we used low-dose corticosteroids (hydrocortisone 240 mg/day) for severe COVID-19 lung injury, and the condition improved. However, after corticosteroid withdrawal, the respiratory status worsened and led to multiple organ dysfunction. Although we continued treatment with tacrolimus, it was insufficient to suppress the cytokine storm or progression of pulmonary fibrosis in this case.

It may be possible to delay the eradication of SARS-CoV-2 from the body in immunosuppressed patients, such as transplant recipients receiving immunosuppressants (4), as this immunosuppressed state might be associated with the disease severity observed in transplant patients with COVID-19.

At present, based on the results of the RECOVERY trial (13), it is recommended that COVID-19 patients with oxygen demand receive dexamethasone for 10 days. However, in some patients, the disease may worsen during dexamethasone administration or after corticosteroid therapy. While increasing the corticosteroid dose may be helpful for suppressing the cytokine storm, this approach might be harmful in immunosuppressed patients, such as the present case, because of delayed virus clearance.

In conclusion, we described a case of a kidney transplant patient who died of COVID-19 and had a delayed virus clearance due to long-term immunosuppression, which might be a trigger for constant lung damage. There is no solid evidence suggesting the appropriate amount or duration of corticosteroid therapy for transplant patients with COVID-19, but clinicians should assess the validity of corticosteroid therapy independent of the respiratory status and laboratory data.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We would like to thank Teruaki Oka for offering advice on the pathological diagnosis. We would also like to thank the members of the National Center for Global Health and Medicine Research Institute for the virological advice provided.

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