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【 CASE REPORT 】

Persistent SARS-CoV-2 Infection in a Patient with Nephrotic Syndrome under Rituximab Therapy: Successful Treatment with a Combination of Remdesivir and Monoclonal Antibodies

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Abstract:
Rituximab is an effective treatment for frequently relapsing/steroid-dependent nephrotic syndrome, but there is concern about infections caused by humoral immunodeficiency. We herein report a case of prolonged (>7 weeks) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A 24-year-old man with minimal change disease treated with rituximab developed SARS-CoV-2 infection. The clinical response to remdesivir was soon transiently abolished. Treatment with casirivimab and imdevimab (REGEN-COV) monoclonal antibodies in combination with remdesivir resulted in complete clearance of the infection. The REGEN-COV antibody cocktail may improve the outcome of SARS-CoV-2 infection in patients with humoral immunodeficiency.

Key words: minimal change disease, frequently relapsing/steroid-dependent nephrotic syndrome, rituximab, REGEN-COV, monoclonal antibody therapy, COVID-19

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to affect the global population. There have been several reports of immunocompromised patients developing persistent and prolonged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1-16).

A subset of patients with minimal change disease (MCD) develop frequently relapsing/steroid-dependent nephrotic syndrome (FR/SDNS), which responds well to treatment with the anti-CD20 monoclonal antibody rituximab (RTX). However, RTX therapy may result in a state of prolonged humoral immunodeficiency, which can hamper the ability to mount an antibody response to infections. Despite this issue, a standard care regimen for patients who fail to mount an antibody response to COVID-19 has yet to be defined.

We herein report a case of persistent SARS-CoV-2 infection under RTX therapy for FR/SDNS that was treated successfully with a combination of remdesivir and REGEN-COV monoclonal antibodies.

Case Report

A 24-year-old man was admitted to our hospital with a fever and dyspnea. His medical history included an onset of MCD at 17 years old that had been treated with corticosteroids but recurred and been diagnosed as FR/SDNS. One

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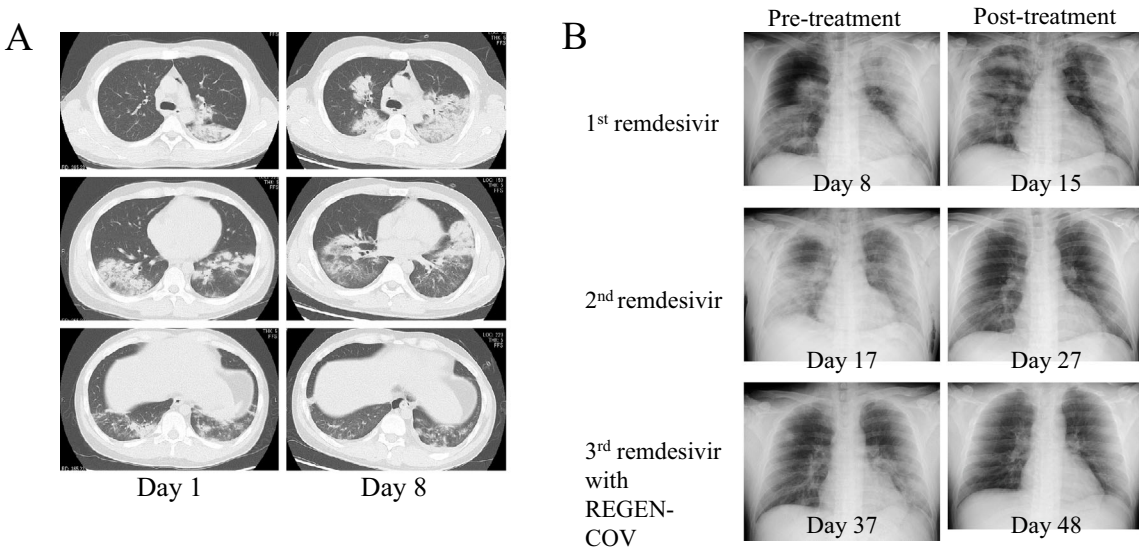

Figure 1. Chest computed tomography (CT) and radiographic findings. (A) Serial chest CT findings. CT on admission showing bilateral multiple consolidations (left panels). CT at day 8 showing progressive consolidations (right panels). (B) Serial chest radiography findings of pulmonary consolidations during the clinical course. Chest radiography findings before and after the first (upper panels), second (middle panels), and third remdesivir therapies combined with REGEN-COV (lower panels).

year after the onset, treatment with RTX was initiated (500 mg) and administered every 6 months thereafter. The dose of prednisolone was gradually tapered to 4 mg/day, and no adverse events or relapse had occurred. The patient received RTX in the second week of July 2021. He received his first dose of the Pfizer BNT162b2 SARS-CoV-2 vaccine in the third week of July 2021 and his second dose in the third week of August 2021.

He developed a fever and systemic fatigue in the first week of September 2021. The SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) (nasal swab) test was positive, and the patient stayed in a recovery facility. In mid-September 2021, his SARS-CoV-2 RT-PCR test was negative, and he was discharged from the facility. Subsequently, he developed a fever and progressive dyspnea on effort and was admitted to our hospital for the treatment of pneumonia in late September 2021. His body temperature was 38.6°C, and percutaneous oxygen saturation (SpO_2) was 92% on room air.

Chest computed tomography (CT) revealed multiple non-segmental consolidations in both lungs (Fig. 1A). Table 1 shows the results of laboratory examinations performed on admission. Blood tests revealed an elevated serum C-reactive protein (CRP) level and hypogammaglobulinemia. The nasopharyngeal SARS-CoV-2 RT-PCR swab was negative on admission.

The patient's clinical course is shown in Fig. 2. He was started on empirical antibiotic therapy with azithromycin and ceftriaxone for community-acquired pneumonia. Pharyngeal mycoplasma antigen, serum cryptococcal antigen, and urine *Streptococcus pneumoniae* antigen tests were all negative. On day 4, his prednisolone dosage was increased to 15 mg/day because of relapse of MCD identified on admission. On day 7, we switched from ceftriaxone to cefazolin for methicillin-sensitive *Staphylococcus aureus* (MSSA) pneumonia because sputum culture detected MSSA. On day 8, the patient developed a fever and progressive dyspnea with hypoxemia. SpO_2 was 95% by mask with an oxygen flow rate of 6 L/min. Laboratory investigations revealed elevated CRP levels, positive SARS-CoV-2 RT-PCR results, and radiographic changes, including bilateral air space consolidation Fig. 1A. He was diagnosed with severe COVID-19 illness according to the National Institutes of Health (NIH) severity classification for SARS-CoV-2 infection. He received all treatments currently recommended for severe COVID-19 (oxygen; dexamethasone, 6 mg/day orally for 10 days; remdesivir, 200 mg on day 1, followed by 100 mg administered daily on days 2-5; and heparin, 10,000 units/day). The antibiotic was changed to meropenem for *Pseudomonas aeruginosa* coverage. His pneumonia and general condition improved rapidly after the 5-day course of remdesivir (Fig. 1B, 2).

On day 15, he developed a fever, and his oxygen requirement increased. On day 17, he was diagnosed with persistent SARS-CoV-2 infection; he was treated again with remdesivir for 10 days and started on 5 g/day intravenous immunoglobulin for hypogammaglobulinemia (5-day course). His treatment response was prompt, and both the fever and consolidation in the lungs disappeared (Fig. 1B). Complete remission of MCD was achieved 22 days after increasing the prednisolone dose. On day 37, his body temperature slightly rose to 37.1°C, and the serum CRP level was elevated (Table 1). He complained of cough and sputum without dyspnea. SpO_2 was 95% on room air. Chest X-ray

Table 1. Laboratory Results at Admission and the Second and Third Dose of Remdesivir.

Laboratory finding	Day 1	Day 17	Day 37	Reference range
Blood count				
WBC count (×10³/μL)	5.0	11.6	7.7	3.3-8.6
Neutro (%)	83.9	87.8	67.5	40.6-76.4
Lympho (%)	12.9	9.1	26.8	16.5-49.5
Mono (%)	2.8	3.0	5.2	2.0-10.0
Eosino (%)	0.2	0.0	0.1	0.0-8.5
Baso (%)	0.2	0.1	0.4	0.0-2.5
Hemoglobin (g/dL)	14.6	14.8	14.9	13.7-16.8
Platelet count (×10³/μL)	121	240	21.8	158-348
Coagulation system				
D-dimer (μg/mL)	3.6	2.7	-	0-1.0
Serum				
Total protein (g/dL)	5.1	4.8	6.1	6.6-8.1
Albumin (g/dL)	2.9	2.2	3.1	4.1-5.1
Creatinine (mg/dL)	0.73	0.45	0.62	0.65-1.07
BUN (mg/dL)	9.0	9.0	9.0	8-20
AST (U/L)	75	76	63	13-30
ALT (U/L)	39	60	61	10-42
LDH (U/L)	481	507	319	124-222
KL-6 (U/mL)	377	-	-	0-499
CRP (mg/dL)	8.79	5.34	6.55	0-0.14
PCT (ng/mL)	0.18	0.13	-	0-0.05
IgG (mg/dL)	433	374	-	861-1,747
IgA (mg/dL)	66	64	-	93-393
IgM (mg/dL)	11	9	-	33-183
Urine				
Protein	2+	±	±	
RBC	0-1/HPF	-	0-1/HPF	
P/CR ratio (g/g Cr)	1.66	0.44	0.10	0-0.15

AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, LDH: lactate dehydrogenase, PCT: procalcitonin, P/CR: protein/creatinine ratio, RBC: red blood cell, WBC: white blood cell

showed exacerbation of infiltrative shadow in the left lower lung field (Fig. 1B). He was diagnosed with relapse of SARS-CoV-2 infection and had moderate illness according to the NIH severity classification. The patient was retreated with remdesivir for 5 days.

His clinical course had raised concerns about long-lasting SARS-CoV-2 infection due to prolonged B cell depletion and impaired adaptive humoral immunity. Therefore, we decided to initiate neutralizing antibody therapy against SARS-CoV-2 to prevent relapse of SARS-CoV-2 infection. An antibody cocktail [REGEN-COV 1,200 mg (600 mg each of casirivimab and imdevimab)] was administered on day 42, and the patient's general condition improved markedly thereafter. The patient was discharged from the hospital on day 49.

The patient presented to our outpatient clinic 31 days after discharge. He did not have any symptoms, and a urinary examination showed complete remission of nephrotic syndrome under maintenance therapy with 20 mg/day of prednisolone.

Discussion

Previous observational studies have shown that RTX is effective in patients with FR/SDNS (17-20). A study investigating the effects of RTX in Japanese patients with refractory nephrotic syndrome showed that 4.9% experienced Grade ≥3 infections/infestations as adverse drug reactions (ADRs) of RTX (21). Yusof et al. reported that low IgG levels at baseline and during treatment predicted severe infections in rheumatic disease patients treated with RTX (22). Our patient also had hypogammaglobulinemia and was therefore considered at an increased risk of infection.

Patients with prior RTX exposure are known to respond poorly to various types of vaccines (23), including the BNT 162b2 vaccine (24). Therefore, the SARS-CoV-2 vaccine should be administered as late as possible after the last RTX dose, and RTX therapy should be avoided for two to four weeks after vaccination (25, 26). However, in our patient, we failed to adequately discuss the vaccination schedule in

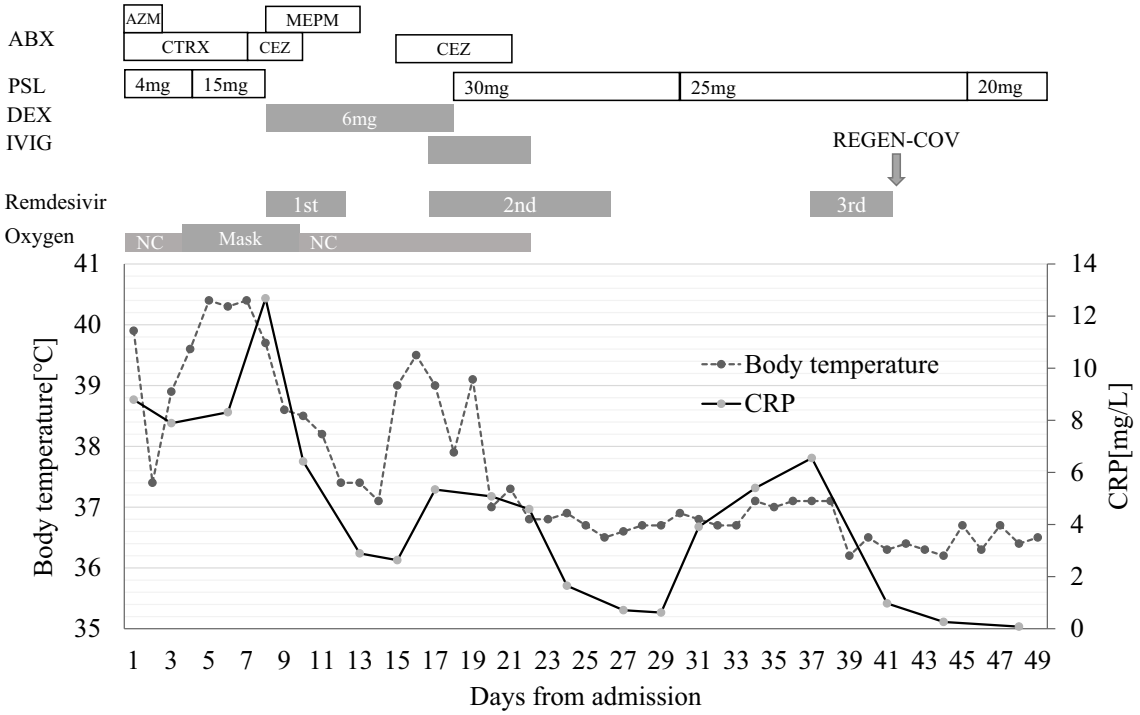

Figure 2. Clinical course during hospital admission. Therapies administered and kinetics of body temperature and CRP during hospitalization are shown. ABX: antibiotics, AZM: azithromycin, CEZ: cefazolin, CRP: C-reactive protein, CTRX: ceftriaxone, DEX: dexamethasone, IVIG: intravenous immunoglobulin, MEPM: meropenem, NC: nasal cannula, PSL: prednisolone

relation to RTX therapy. For this reason, our patient was deemed less likely to develop an antibody response than other recipients.

An analysis by the COVID-19 Global Rheumatology Alliance indicated that 42/192 (21.9%) RTX users died of COVID-19, corresponding to a >4-fold higher odds ratio of death than patients on methotrexate therapy (27). Patients with multiple sclerosis on RTX therapy were at an increased risk of hospitalization for COVID-19, but the risk decreased with increasing time since the last RTX infusion (28). There are concerns that RTX, especially when used with corticosteroids, may lead to more severe disease and an increased risk of death from COVID-19.

Persistent SARS-CoV-2 infection may occur in immunocompromised individuals, and these patients tend to remain infectious for ≥3 weeks. Table 2 lists reported cases of persistent SARS-CoV-2 infection in patients under anti-CD20 therapy, including this case (1-15). Most case reports are of malignant lymphoma or chronic lymphocytic leukemia, and rarely of other diseases. Treatment depends on the time of the onset; in addition to antiviral therapy, intravenous immunoglobulin (IVIG), convalescent plasma, and monoclonal antibodies have been used. No standard treatment has been established. Our patient was a young man with only MCD. This is the first case of persistent SARS-CoV-2 infection in a patient with a non-malignant disorder that improved with REGEN-COV and remdesivir. Their symptoms were found to resolve promptly upon viral clearance, suggesting that the severe manifestations in these patients were predominantly driven by ongoing viral infection.

However, several case reports of persistent COVID-19 have shown that immunocompromised patients did not improve with remdesivir alone (1, 3-6, 8, 12, 15, 16). In a recent report of patients hospitalized with COVID-19, REGEN-COV reduced the 28-day mortality rate (29). In a retrospective analysis of immunodeficient patients, REGEN-COV therapy was associated with rapid viral clearance and improved clinical features in patients with persistent COVID-19 (30). These reports support the validity of a therapeutic approach using an antibody cocktail for immunocompromised patients, even in later stages of infection.

However, the decision to use therapeutic monoclonal antibodies may depend on the variant involved in the infection. Based on the timing of infection, our patient was likely infected with the delta or alpha variant, which was consistent with his good clinical course following REGEN-COV antibody cocktail therapy. Based on previous reports (1, 3-6, 11, 12), we predicted that our patient would relapse after discharge from the hospital. Because further relapse of pneumonia would lead to future deterioration of the lung function, we decided to administer antibody cocktail therapy. We suspect remdesivir had some effect on COVID-19 pneumonia, but REGEN-COV was necessary to achieve a complete cure.

In summary, we reported persistent SARS-CoV-2 infection in a patient with MCD who received RTX. In our case, remdesivir monotherapy was not sufficient, but combination therapy with REGEN-COV resulted in sustained clinical im-

Table 2. Cases of Persistent SARS-CoV-2 Infection in Patients Receiving Anti-CD20 Therapy in the Literature.

Reference	Patient age/ gender	Underlying disease	Anti-CD20 treatment	Treatment for COVID-19				Severity of illness categories (NIH)	Relapse	Time to RT-PCR negative or discharge (day)	Out-come
				Antiviral therapy	Cortico-steroid	Monoclonal antibody	Other				
Lymphoma and CLL											
(1)	50/M	CLL	RTX	RDV ×2	N/A	N/A	CP	Severe	2	65	Alive
(2)	47/M	FL	OBZ	FVP, LPV/ RTV	N/A	N/A	N/A	Moderate	0	65	Alive
(3)	53/F	FL	OBZ	RDV ×2	N/A	N/A	CP	Severe	4	Approx. 110	Alive
(4)	56/F	FL	RTX	RDV	N/A	N/A	CP, infliximb	Clitical	1	>120	Alive
(5)	62/M	FL	OBZ	RDV	DEX	N/A	HP ×2	Severe	1	66	Alive
(6)	55/M	MCL	RTX	RDV	DEX	REGEN-COV	N/A	Severe	1	Approx. 90	Alive
(7)	74/M	CLL	RTX	N/A	N/A	N/A	CP ×4	Moderate	0	111	Alive
(8)	75/M	MCL	RTX	RDV ×2, IVM, IFNβ	DEX, mPSL	N/A	IVIG	Clitical	0	80	Alive
(9)	71/F	FL	OBZ	N/A	DEX	Bamla-nivimab	N/A	Severe	0	32	Alive
(10)	71/M	FL	RTX	RDV	DEX	N/A	N/A	Severe	0	Approx. 70	Alive
(11)	34/F	FL	RTX	FVP	N/A	N/A	IVIG, CP	Severe	2	68	Alive
	66/M	FL	OBZ	Unknown	Unknown	Unknown	IVIG, CP	Severe	2	61	Alive
	45/F	CLL	RTX	FVP ×2	N/A	N/A	IVIG, CP	Severe	1	73	Alive
	62/M	MCL	OBZ	Unknown	Unknown	Unknown	Unknown	Severe	1	51	Alive
(12)	55/M	FL	Glofit-amab	RDV ×4, NTZ	DEX ×3	REGEN-COV	CP	Severe	3	213	Alive
Other disease											
(13)	48/M	MN	RTX	LPV/RTV, HCQ, OST	N/A	N/A	AZM	Severe	0	Approx. 26	Alive
(14)	25/F	NMOSD	RTX	Unknown	Unknown	Unknown	PE	Clitical	1	Approx. 70	Alive
(15)	22/M	GLILD	RTX	RDV	DEX ×3	N/A	SCIG, CP	Severe	3	Approx. 90	Alive
Current case	24/M	MCD	RTX	RDV ×3	DEX, PSL	REGEN-COV	IVIG	Severe	2	49	Alive

AZM: azithromycin, CLL: chronic lymphocytic leukemia, CP: convalescent plasma, DEX: dexamethasone, F: female, FL: follicular lymphoma, FVP: favipiravir, GLILD: granulomatous lymphocytic interstitial lung disease, HP: hyperimmune plasma, IVIG: intravenous immunoglobulin, IVM: ivermectin, LPV/RTV: lopinavir/ritonavir, M: male, MCD: minimal change disease, MCL: mantle cell lymphoma, MN: membranous nephropathy, NMOSD: neuromyelitis optica spectrum disorder, NTZ: nitazoxanide, OBZ: obinutuzumab, OST: oseltamivir, PE: plasma exchange, RDV: remdesivir, RTX: rituximab, SCIG: subcutaneous immunoglobulin, XLA: X-linked agammaglobulinemia

provement. Further discussion is required regarding treatment strategies for COVID-19 in patients receiving maintenance immunosuppressive therapies, including those using RTX.

The patient provided informed consent.

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

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