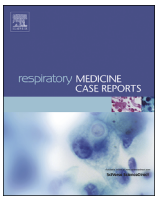
Respiratory Medicine Case Reports 51 (2024) 102104

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Protracted coronavirus disease 2019 after chimeric antigen receptor-T cell therapy successfully treated with sequential multidrug therapy

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ARTICLE INFO

Keywords:
Chimeric antigen receptor-T cell therapy
Coronavirus disease 2019
Multidrug therapy
Organizing pneumonia

ABSTRACT

A 56-year-old woman who received CD19 chimeric antigen receptor-T cell therapy for refractory diffuse large B-cell lymphoma developed severe coronavirus disease 2019 (COVID-19) and was treated with nirmatrelvir/ritonavir in April 2022. However, she experienced persistent fatigue and cough and fever in June. Computed tomography revealed bilateral ground-glass opacities (GGO), and the patient was treated with corticosteroids for organizing pneumonia after COVID-19. Partial improvement was observed, but new GGO appeared despite corticosteroid therapy. Genome analysis of severe acute respiratory syndrome coronavirus 2 detected Omicron variant BA.1.1.2, which was prevalent at the time of initial infection. The patient was diagnosed with protracted COVID-19 and was treated with remdesivir, molnupiravir, nirmatrelvir/ritonavir, and tixagevimab/cilgavimab. These treatments appeared to contribute to the improvement of protracted COVID-19.

1. Introduction

Chimeric antigen receptor-T (CAR-T) cells are T cells obtained from a patient and transfected with receptors that recognize tumors and activate T cells. CAR-T cell therapy has demonstrated substantial clinical efficacy for the treatment of B cell and plasma cell malignancies [1]. However, recipients of CAR-T cell therapy are at risk of severe coronavirus disease 2019 (COVID-19) because of chronic B-cell aplasia and hypogammaglobulinemia [2]. In CAR-T cell therapy, normal B cells and plasma cells expressing the CAR-T cell target antigen, including CD19 or B cell maturation antigen, are damaged, resulting in B-cell aplasia and hypogammaglobulinemia. In addition, conditioning regimens for CAR-T cell therapy can cause lymphopenia and diminish B- and T-cell functions.

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https://doi.org/10.1016/j.rmcr.2024.102104
Received 19 April 2024; Received in revised form 20 August 2024; Accepted 29 August 2024
Available online 2 September 2024

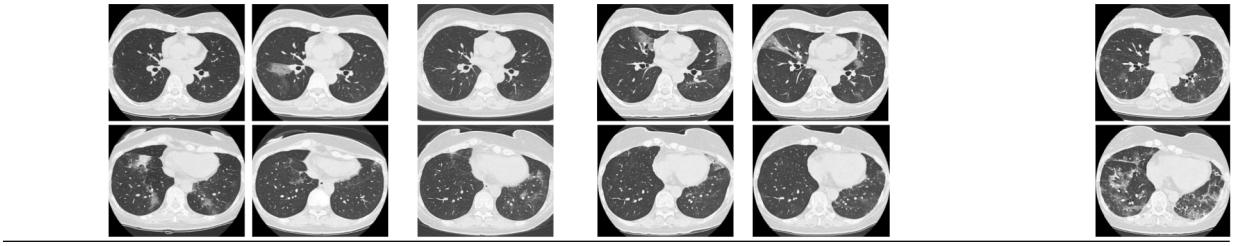
Recently, the concept of "protracted COVID-19" with polymerase chain reaction (PCR) positivity lasting >21 days has been proposed [3]. The risk factors for protracted COVID-19 include B-cell depletion by CAR-T cell therapy, hematopoietic stem cell transplantation, and anti-CD20 monoclonal antibodies.

Herein, we report a case of successful treatment of protracted COVID-19 using multiple antiviral drugs and neutralizing antibodies in a patient who underwent CD19 CAR-T cell therapy. Informed consent was obtained from the patient for publication of the report and associated images.

2. Case presentation

A 56-year-old woman who had been treated with tisagenlecleucel, a CD19 CAR-T cell product for refractory diffuse large B-cell lymphoma, 15 months earlier developed COVID-19 in April 2022. Immunoglobulin G (IgG) levels gradually declined after CAR-T cell therapy, but the patient did not require supplementation because the IgG levels were >500 mg/dL. She had not been vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The patient was treated with nirmatrelvir/ritonavir (300 mg/100 mg twice a day for 5 days); however, fatigue and cough persisted, and she developed fever in June. Computed tomography (CT) revealed bilateral ground-glass opacities (GGO) and consolidations (Fig. 1; images in mid-June); however, SARS-CoV-2 PCR (Cepheid Xpert® Xpress SARS-CoV-2 assay) showed a cycle threshold (Ct) value of E – and N2 41.9. She was diagnosed with organizing pneumonia after COVID-19 because of the high Ct value, and corticosteroid therapy (prednisolone [PSL], 20 mg/day) was initiated. Fig. 1 shows the course of CT images during 3 months of corticosteroid therapy for organizing pneumonia. Corticosteroid therapy resulted in partial improvement, but new GGO were also observed at the beginning of July. SARS-CoV-2 PCR was negative (E, - and N2, -) in mid-July. Because new GGO appeared even with PSL 20 mg/day, the PSL dose was increased to 40 mg/day at the beginning of August. However, new GGO were still observed along with partial improvement in mid-August. In mid-September, she was admitted to our hospital because of worsening pneumonia.

On admission, the patient had a temperature of 37.2 °C, blood pressure of 108/70 mmHg, pulse rate of 96 beats/min, SpO_2 of 92 % (room air), and respiratory rate of 28 breaths/min. Table 1 shows the laboratory data on admission. Pancytopenia, hypogammaglobulinemia, and mildly elevated C-reactive protein levels were observed. Chest CT revealed bilateral GGO (Fig. 1). Bronchoalveolar lavage (BAL) showed increased lymphocyte counts (47.7 %), and SARS-CoV-2 PCR of BAL fluid was positive (BD MAX™ system; Ct values: N1, 16.3 and N2, 16.4) (Table 2). SARS-CoV-2 PCR of nasopharyngeal swab on the day after BAL was also positive (Cepheid Xpert® Xpress SARS-CoV-2 assay; Ct values: E, 24.4 and N2, 21.3). Genomic analysis of SARS-CoV-2 revealed the Omicron variant BA.1.1.2, which was prevalent at the time of initial infection and was no longer detected as of September 2022 according to the genome surveillance data reported by the National Institute of Infectious Diseases [4]. In addition, the Elecsys Anti-SARS-CoV-2 S (S300) assay (Roche Diagnostics, Rotkreuz, Switzerland) did not detect neutralizing antibodies targeting the SARS-CoV-2 spike protein in the patient's serum. The patient was diagnosed with protracted COVID-19 associated with impaired humoral immunity induced by CAR-T cell therapy. Fig. 2 shows the treatment for COVID-19 and viral load. The patient was treated with steroid pulse ther-



WBC (/μL)	3370	4670	3260	2460	3140	3010
CRP (mg/dL)	6.14	1.28	3.02	3.41	1.40	3.24
IgG (mg/dL)	594.7	NA	554.3	491.7	NA	457.5

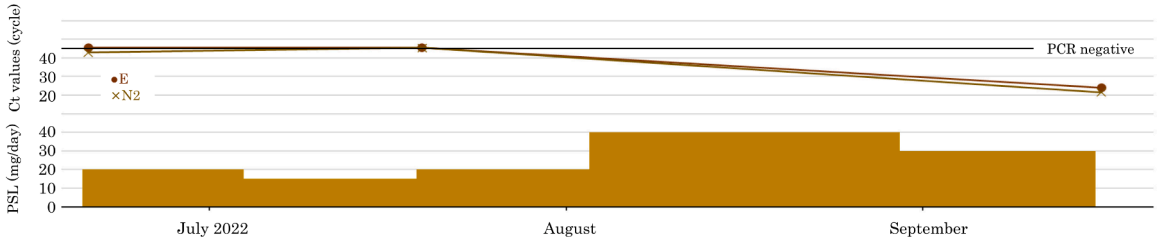


Fig. 1. Course of CT images during 3 months of corticosteroid therapy
CT images obtained in mid-June 2022, when the patient was initiated on corticosteroid therapy for organizing pneumonia after coronavirus disease 2019, show bilateral ground-glass opacities (GGO) and consolidation. Partial improvement has been observed at the beginning of July, but new GGO have appeared in the bilateral lungs. At any point in time, partial improvements and new GGO are observed. CT images in mid-September are at the time of admission. Laboratory data, viral load, and dose of prednisolone at each time point are shown.
Abbreviations: WBC, white blood cell; CRP, C-reactive protein; NA, not available; Ct, cycle threshold; PCR, polymerase chain reaction; PSL, prednisolone; CT, computed tomography.

Table 1
Laboratory data on admission.

WBC	2830	/μL	TP	5.3	g/dL	Ca	7.8	mg/dL
Neu	94.0	%	Alb	2.8	g/dL	CRP	1.77	mg/dL
Lym	2.5	%	AST	28	U/L	KL-6	549	U/mL
T cell	93	%	ALT	37	U/L	SP-D	57.9	ng/mL
B cell	0	%	LDH	399	U/L	SP-A	47.0	ng/mL
NK cell	6	%	ALP	372	U/L	IgG	457.5	mg/dL
Mon	2.5	%	γ-GTP	157	U/L	IgA	26.8	mg/dL
Eos	0.0	%	T-Bil	0.32	mg/dL	IgM	5.7	mg/dL
Bas	0.0	%	BUN	19.5	mg/dL	Ferritin	956	ng/mL
Meta	0.5	%	Cr	0.45	mg/dL	D-dimer	<0.5	μg/mL
Myelo	0.5	%	UA	3.8	mg/dL	β-D-glucan	7	pg/mL
RBC	2.73	$\times 10^6$/μL	Na	141	mmol/L	C7-HRP	negative	
Hb	8.9	g/dL	K	3.5	mmol/L			
Plt	8.7	$\times 10^4$/μL	Cl	107	mmol/L			

Table 2
Findings of bronchoalveolar lavage fluid.

Recovery	53	%
Total cell count	2.24	$\times 10^5$/mL
Mac	48.3	%
Lym	48.7	%
Neu	3.0	%
Eos	0.0	%
CD4/8	0.24	
SARS-CoV-2 PCR (Ct value)	N1: 16.3	N2: 16.4
P. jirovecii PCR	negative	

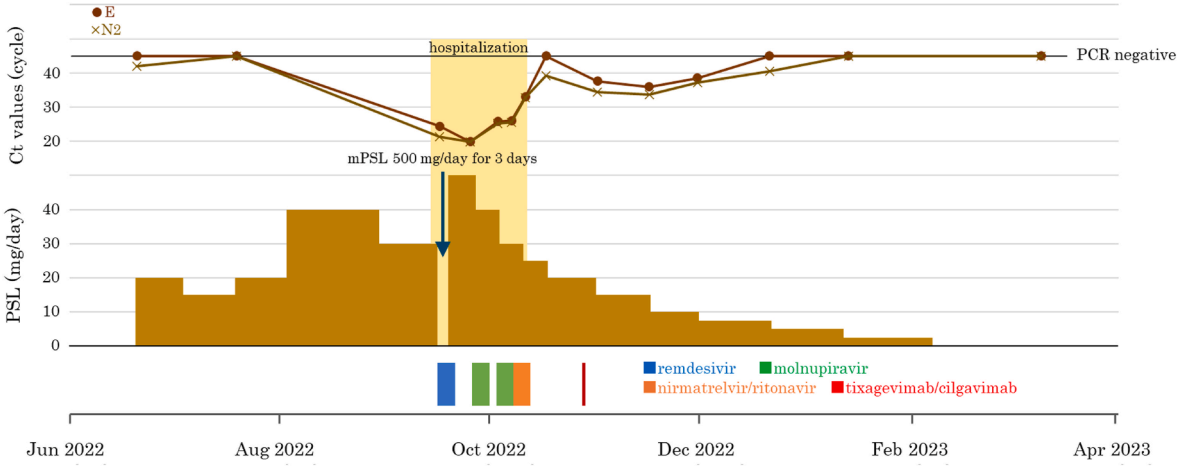


Fig. 2. Treatment against coronavirus disease 2019 and the viral load
The viral load is evaluated using Cepheid Xpert® Xpress SARS-CoV-2 assay (E and N2).
Abbreviations: Ct, cycle threshold; mPSL, methylprednisolone; PCR, polymerase chain reaction; PSL, prednisolone.

apy and remdesivir for 5 days. Remdecivir was used first because it has been shown to be effective in patients with severe COVID-19 and hypoxemia. Despite treatment, Ct values decreased (E, 19.9 and N2, 19.8). She received sequential molnupiravir (800 mg twice a day) for 10 days and nirmatrelvir/ritonavir (300 mg/100 mg twice a day) for 5 days. Moreover, tixagevimab/cilgavimab (150 mg/150 mg as a single dose) was administered (Fig. 2). The corticosteroid dose was tapered off over 5 months duration. SARS-CoV-2 PCR yielded negative results owing to sequential antiviral therapy, and the bilateral GGO on chest CT disappeared (Fig. 3). No SARS-CoV-2 reactivation was observed after the treatment.

3. Discussion

Herein, we present a case of protracted COVID-19 that was initially misdiagnosed as delayed-onset organizing pneumonia after COVID-19. Previous studies have reported that organizing pneumonia can occur >1 month after SARS-CoV-2 infection despite the absence of virus detection [5,6]. However, in our patient, new GGO appeared even while taking PSL 40 mg/day, and the course of

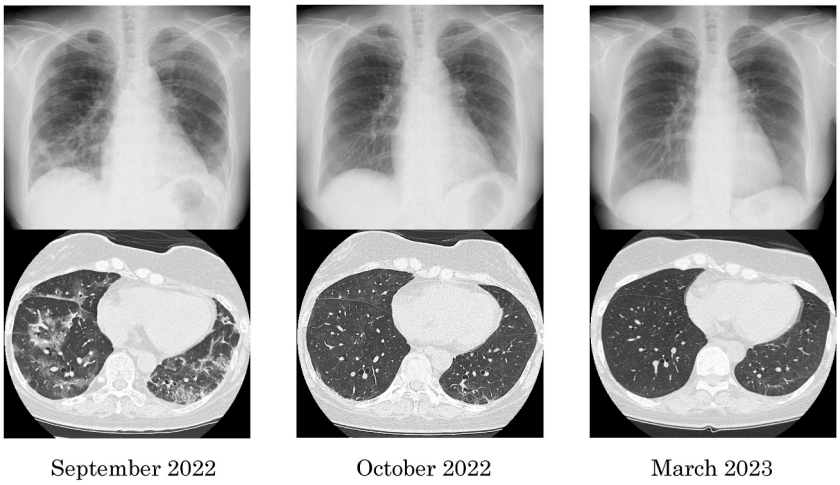


Fig. 3. Chest radiography and computed tomography after hospitalization
Chest images obtained in September 2022 at the time of admission. Remarkable improvement is observed in October 2022, and ground-glass opacities completely disappeared in March 2023.

treatment was not typical for organizing pneumonia. New GGO did not appear after administration of antiviral drugs. In addition, genomic analysis of SARS-CoV-2 revealed the Omicron variant BA.1.1.2, which was prevalent at the time of initial infection and was no longer detected at the time of exacerbation in Japan. No sample remained at the time of initial infection in this case, and genome analysis was not possible; therefore, it was not possible to prove whether the strain was strictly the same at the time of initial infection and exacerbation. However, the diagnosis of protracted COVID-19 is reasonable based on consistently persistent fatigue and cough since the initial infection, the fact that GGO did not disappear with corticosteroid therapy alone but disappeared after administration of antiviral drugs, impaired humoral immunity induced by CAR-T cell therapy, and the results of genomic analysis.

The inability to produce neutralizing antibodies against SARS-CoV-2 due to B-cell depletion is thought to be the main cause of protracted COVID-19, and the main risks are CAR-T cell therapy, hematopoietic stem cell transplantation, and CD20 antibody therapy [3]. Patients with these immunosuppressed conditions should be followed up for the possibility of protracted COVID-19. A case of protracted COVID-19 has been reported, in which SARS-CoV-2 was negative on nasopharyngeal swab PCR even though there was an abnormal shadow in the lung field, similar to the present case [7]. Therefore, if SARS-CoV-2 is negative but persistent symptoms or abnormalities are observed on examination, repeated antigen and PCR testing or specimen collection from the lower respiratory tract should be considered.

Although the optimal treatment for protracted COVID-19 has not been established, a combination of remdesivir and convalescent plasma or neutralizing antibody drugs has been reported to result in viral negativity in 13 of 14 patients [8]. Another study showed that nirmatrelvir/ritonavir combined with remdesivir for 20 days resulted in viral negativity [9]. Successful treatment with remdesivir for 28 days has also been reported [10]. In the present case, remdesivir was used initially because of its demonstrated efficacy in patients with severe COVID-19 and hypoxemia [11]. However, as the Ct values decreased, we determined that additional treatment was necessary and added molnupiravir, although its efficacy has not been established for severe cases [12]. Since the increase in Ct values remained insufficient following molnupiravir treatment, nirmatrelvir/ritonavir was added. In addition, neutralizing antibodies were administered in anticipation of long-term antiviral effects. Although the efficacy of all neutralizing antibodies was considered attenuated against BA.1.1.2, we selected tixagevimab/cilgavimab because Takashita et al. reported that these antibodies had better neutralizing activity for BA 1.1 than other neutralizing antibodies [13]. We cannot rule out the possibility of improvement without using multiple drugs. However, considering the fact that the Ct values, once elevated after administering the three antiviral drugs, decreased after discontinuation of the medication followed by an increase again after tixagevimab/cilgavimab administration (Fig. 2), we believe that each drug contributed to the improvement of protracted COVID-19. Multiple and long-term use of antiviral drugs until the SARS-CoV-2 PCR results are negative is considered a reasonable treatment option.

4. Conclusion

We report a case of protracted COVID-19 after CAR-T cell therapy. Even if the virus is temporarily undetectable, patients who have received treatment that reduces B cells must be followed up for the possibility of protracted COVID-19. There is no established treatment for protracted COVID-19, and future case studies are required to establish optimal treatment, including the combination method, and administration period of antiviral and antibody drugs.

Funding

This study did not receive any funding.

CRediT authorship contribution statement

Masahiro Yamashita: Writing – original draft. **Hisao Higo:** Writing – review & editing. **Nobuharu Fujii:** Writing – original draft. **Chiaki Matsumoto:** Investigation. **Go Makimoto:** Investigation. **Kiichiro Ninomiya:** Investigation. **Masanori Fujii:** Investigation. **Kammei Rai:** Investigation. **Eiki Ichihara:** Investigation. **Kadoaki Ohashi:** Investigation. **Katsuyuki Hotta:** Investigation. **Masahiro Tabata:** Investigation. **Yoshinobu Maeda:** Supervision. **Nobuaki Miyahara:** Supervision.

Declaration of competing interest

The authors declare no conflicts of interest associated with this manuscript.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

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