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【 CASE REPORT 】

Severe Coronavirus Disease 2019 That Recovered from Respiratory Failure by Treatment That Included High-dose Intravenous Immunoglobulin

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Abstract:
We herein report a case of severe coronavirus disease 2019 (COVID-19) in which high-dose intravenous immunoglobulin (IVIg) treatment achieved significant clinical improvement of deterioration of pulmonary inflammation after temporary clinical improvement. In the present case, clinical and radiological deterioration occurred despite a decrease in viral load, suggesting that deterioration was caused by reactivation of proinflammatory factors, such as tumor necrosis factor-α and interleukin-6, rather than direct viral effects. IVIg treatment may provide not only immunosuppressive effects but also inhibition of proinflammatory cytokines, indicating that treatment including IVIg may be effective by inhibiting cytokine storm in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.

Key words: coronavirus disease 2019, COVID-19, intravenous immunoglobulin, severe acute respiratory syndrome-coronavirus-2, acute respiratory distress syndrome, deterioration

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Introduction

Coronavirus disease 2019 (COVID-19) causes fatal clinical manifestations, which lead to acute respiratory distress syndrome (ARDS). Inflammatory cytokine storm is considered to be related to the development of ARDS in COVID-19 (1). Although some reports have described clinical and radiological recurrence during treatment for COVID-19 (2-5), the pathogenesis of the recurrence has not yet been elucidated.

Treatment for COVID-19 can mainly be divided into two types depending on the targets: severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and systemic inflammation induced by the SARS-CoV-2 infection (6). Intravenous immunoglobulin (IVIg) has been used as an adjunctive therapy in patients with severe infection, and high-dose IVIg treatment was attempted in several COVID-19 patients (7-13).

We herein report the efficacy of treatment including high-dose IVIg for deterioration after temporary clinical improvement in the severe COVID-19 patient. While previous reports have shown the efficacy of high-dose IVIg in the early phase, to our knowledge, this is the first report showing the possible efficacy of this treatment even in the late phase, such as in cases of deterioration after clinical improvement

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Table. Laboratory Data on Admission.

Hematology		Blood chemistry		Blood chemistry	
White blood cell	9,100 /μL	Total protein	7.4 g/dL	BNP	7.6 pg/mL
Neutrophils	84 %	Albumin	2.7 g/dL	KL-6	300 U/mL
Lymphocytes	11 %	AST	113 U/L	Glucose	147 mg/dL
Monocytes	4 %	ALT	102 U/L	HbA1c (NGSP)	6.8 %
Eosinophil	0 %	LDH	602 U/L	PCT	0.50 ng/mL
Red blood cell	579 $\times 10^4$/μL	ALP	234 U/L	β-D glucan	<6.0 pg/mL
Hemoglobin	19.6 g/dL	Total bilirubin	0.9 mg/dL	Immunologic test	
Hematocrit	57.2 %	BUN	26 mg/dL	IgG	1,678 mg/dL
Platelet	16.9 $\times 10^4$/μL	Creatinine	1.18 mg/dL	IgA	479 mg/dL
Coagulation test		Na	137 mEq/L	IgM	95 mg/dL
PT	99.2 s	K	4.3 mEq/L	Arterial blood gas (room air)	
PT-INR	1.00	Cl	101 mEq/L	pH	7.47
APTT	40.2 s	AMY	495 U/L	PaO_2	55.6 mmHg
Fibrinogen	804 mg/dL	CK	124 U/L	$PaCO_2$	28.4 mmHg
FDP	4.1 μg/mL	Ferritin	3,390 ng/mL	HCO_3^-	20.3 mEq/L
D-dimer	1.2 μg/mL	CRP	22.1 mg/dL	BE	-1.4 mEq/L

PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation products, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, AMY: amylase, CK: creatine kinase, CRP: C-reactive protein, BNP: brain natriuretic peptide, KL-6: Sialylated carbohydrate antigen Krebs von den Lungen-6, HbA1c (NGSP): hemoglobin A1c (National Glycohemoglobin Standardization Program), PCT: procalcitonin, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, BE: base excess

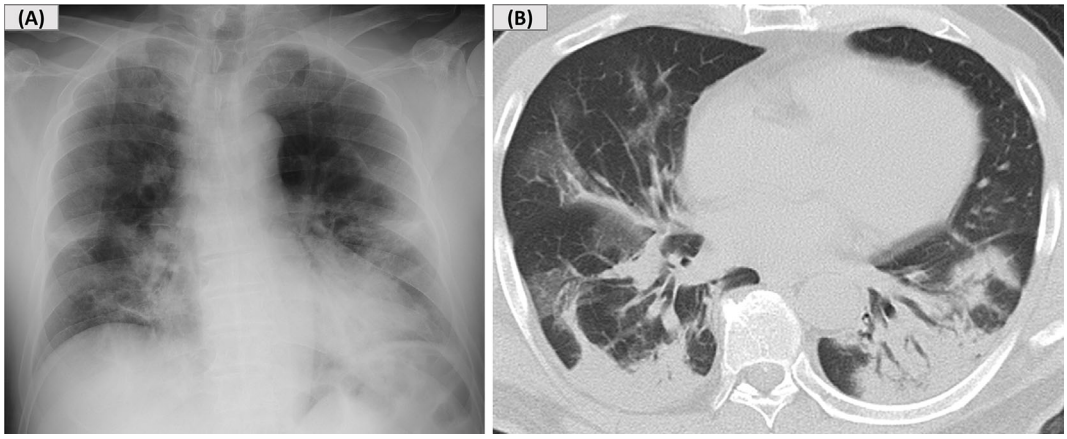


Figure 1. Chest radiological findings on admission. Chest radiograph showed bilateral lower lung predominant consolidation (A). Chest CT demonstrated consolidations and multifocal ground glass opacities with bilateral lower lobe dominance (B). CT: computed tomography

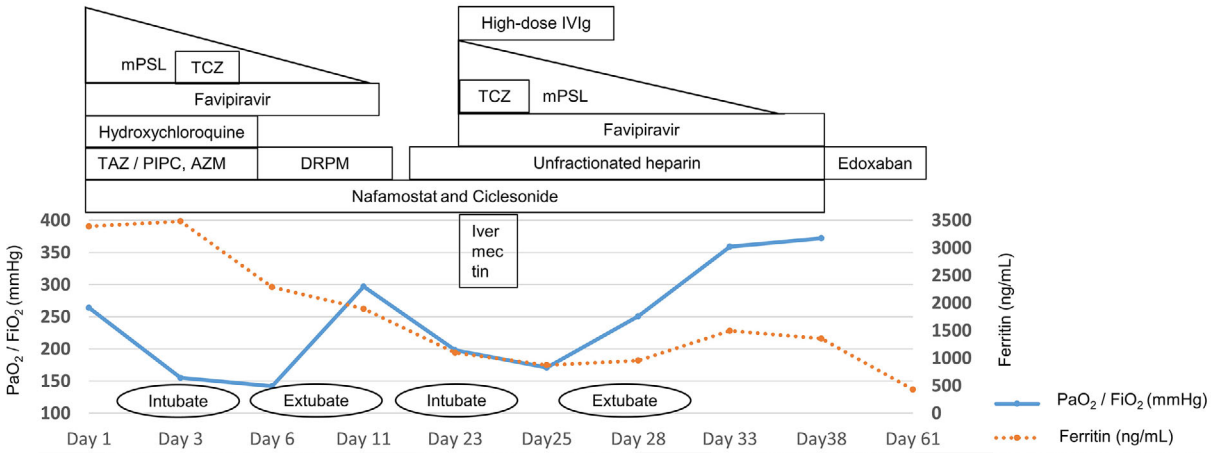
in severe COVID-19 patients.

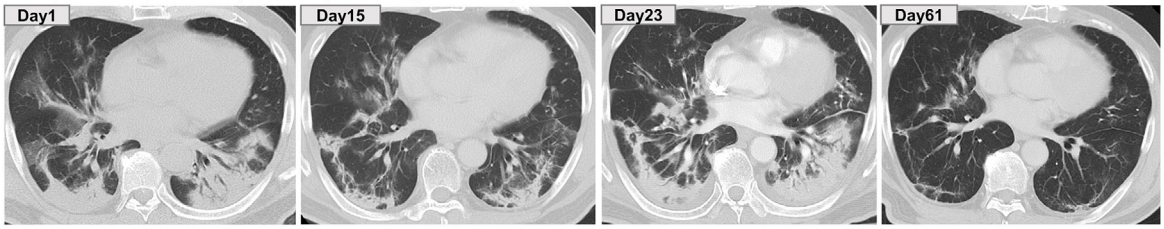
Case Report

A 64-year-old man complaining of a fever, cough, fatigue and dyspnea for over a week visited a local hospital. Nasopharyngeal swabs were positive for SARS-CoV-2 by real-time polymerase chain reaction (rPCR), and the patient was transferred to our hospital for intensive care. He had a history of untreated diabetes and smoking for 35 pack-years. There were coarse crackles in the right lower zone on auscultation with 89% oxygen saturation on ambient air.

As shown in the Table, laboratory findings on admission revealed a slight increase in the white blood cell count (9,100/μL) with lymphopenia (11%), as well as elevated C-reactive protein (22.1 mg/dL) and d-dimer (1.2 μg/mL). In addition, the serum ferritin levels were dramatically increased (3,390 ng/mL). A blood gas analysis showed hypoxemia [arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2): 264 mmHg]. Chest radiography showed bilateral infiltrates (Fig. 1A), and chest computed tomography (CT) demonstrated consolidation and multifocal ground glass opacities with bilateral lower lobe dominance (Fig. 1B).

The patient was treated with favipiravir (3,600 mg/day on Day 1 followed by 1,600 mg/day for 13 additional days),





	Day 1	Day 4	Day 7	Day 15	Day 22	Day 77
Anti-SARS-CoV-2 IgG (S/CO)	2	42	51	60	57	18

Virus loads (copies/5μL)

Samples	Local hospital admission	Day 14	Day 22	Day 33	Day 43
Nasopharyngeal swabs	3,286	4	N/D	N/D	N/D
Sputum	N/A	54	20	39	1

Figure 2. Clinical course after admission. Chest CT demonstrated consolidation and multifocal ground glass opacities with bilateral lower lobe dominance (Day 1). Although these shadows improved temporarily after the initial treatment (Day 15), the bilateral consolidation in the bilateral lower lobes became exacerbated (Day 23). Second treatment including IVIg significantly improved the bilateral consolidation and multifocal ground glass opacities (Day 61). The viral loads in the nasopharyngeal swabs and sputum samples decreased after the initial treatment and were not remarkably increased even after recurrence. Anti-SARS-CoV-2 IgG was measured using the Access SARS-CoV-2 IgG assay (Beckman Coulter, Brea, USA) according to the manufacturer's protocol. Results were reported as signal sample/cut-off (S/CO) with S/CO values ≥ 1.0 interpreted as positive. AZM: azithromycin, CT: computed tomography, DRPM: doripenem, IgG: immunoglobulin G, IVIg: intravenous immunoglobulin, mPSL: methylprednisolone, N/A: not applicable, N/D: not detectable, PaO_2/FiO_2: the arterial partial pressure of oxygen/fraction of inspired oxygen ratio, SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2, TAZ/PIPC: tazobactam/piperacillin, TCZ: tocilizumab

400 mg/day of hydroxychloroquine, 100 mg/day of nafamostat and 1,200 μg/day of ciclesonide. Although no bacteria were detected in a sputum culture obtained on admission, tazobactam/piperacillin (13.5 mg/day) and azithromycin (500 mg/day) were also started due to the possibility of complication with bacterial pneumonia. Furthermore, 80 mg/day of methylprednisolone was initiated on the day of admission because of his aggravated respiratory condition. Since his respiratory condition had deteriorated, he was intubated on Day 3 and maintained on mechanical ventilation. Tocilizumab was administrated at a dose of 400 mg every 12 hours (total 1,200 mg) for the treatment of cytokine storm induced by the SARS-CoV-2 infection. His respiratory status gradually improved with the treatment, with methylprednisolone being tapered over several days by 20 mg/day. The patient was extubated on Day 8.

On Day 15, CT showed improvement in the radiological findings in the lung fields (Fig. 2). However, unfractionated heparin was started because thrombus of the right pulmonary artery was found. On Day 23, his respiratory status suddenly worsened, and CT revealed deterioration of the consolidation in the bilateral lower lobes (Fig. 2). As no new thrombus of the pulmonary artery was found and clinical findings, such as negative sputum cultures, did not suggest bacterial pneumonia, we judged the condition to reflect deterioration of COVID-19. Mechanical ventilation was restarted along with favipiravir, methylprednisolone, tocilizumab and 200 μg/kg/day of ivermectin. Furthermore, high-

dose IVIg treatment was started at 25 g/day for 5 days.

His general status subsequently improved, and he was extubated on Day 28. On Day 46, rPCR showed negative results for SARS-CoV-2 in both nasopharyngeal swabs and sputum. On Day 61, CT revealed the significant improvement of the consolidation in both lung fields (Fig. 2) and the disappearance of the pulmonary artery thrombus. The direct oral anticoagulant, edoxaban (60 mg/day) was started, and he was discharged from our hospital on Day 64.

Discussion

To date, there have only been a few reports describing high-dose IVIg treatment for COVID-19. Xie et al. reported that the administration of high-dose IVIg (20 g/day for 5 days) as adjuvant treatment within 48 hours after admission significantly improved the survival rate of COVID-19 patients (7), and other studies have also demonstrated the efficacy of such treatment for severe COVID-19 patients (8-13). However, in those previous reports, high-dose IVIg was administered in the early phase after the onset of COVID-19. To our knowledge, this is the first report describing the efficacy of high-dose IVIg in the late phase of severe COVID-19, such as following deterioration after temporary improvement. Our case showed additional evidence supporting the efficacy of high-dose IVIg treatment for COVID-19.

Interestingly, deterioration occurred after temporary improvement during the course of COVID-19 in the present case. Although there are few reports describing the clinical course of COVID-19 in detail, some have mentioned recurrence of COVID-19 (2-5). In those reports, negative results of rPCR before recurrence turned positive when recurrence was observed, suggesting that the reactivation of SARS-CoV-2 induced recurrence. However, in the present case, the results of sputum samples were still positive according to rPCR at the time of deterioration, although the viral loads had decreased.

The mechanisms underlying the deterioration in the present case are unclear. However, Liu et al. reported the possible involvement of anti-SARS-CoV-2 antibody in the pathogenesis of deterioration (14). They demonstrated using SARS-CoV/macaque models that viral surface antigen S and host antibody complex (anti-spike-IgG) facilitate the activation of proinflammatory signals in macrophages through interaction with membrane receptors for the Fc portion of the immunoglobulin (FcR), leading to severe lung injury. In addition, the injection of purified anti-spike-IgG-neutralizing antibody to infected macaques led to acute diffuse alveolar damage despite a reduction in SARS-CoV loads (14). Furthermore, the peak levels of serum anti-spike-IgG-neutralizing antibody in non-survivors had been reached at 14.7 days from the onset of their symptoms, a shorter duration than in survivors (20 days) (15). These studies indicate that even if the viral loads decrease, anti-spike-IgG antibodies, which persist until the late stages of SARS-CoV infection, may induce severe lung injury. These results suggest that SARS-CoV-2 infection causes lung damage via similar mechanisms.

Furthermore, it is well-known that sub-optimal antibodies that cannot completely clear the virus induce inflammation [antibody-dependent enhancement (ADE)]. ADE is a phenomenon induced by the interaction of infectious viral antibody complexes with FcR and is reported in infectious cases of some viruses, such as dengue and influenza (16). Although the role of ADE in SARS-CoV-2 infection has not yet been clarified, it may be involved in deterioration. In fact, in the present case, seroconversion had occurred and IgG for SARS-CoV-2 was already positive before deterioration.

Because these results showed the importance of inflammatory responses via FcR, the anti-inflammatory effects of IVIg treatment may be induced by blocking the activation of Fcγ receptors (FcγR) on innate immune effector cells (17). In addition, IVIg treatment shows not only these immunosuppressive effects but also the inhibition of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 (13, 18). These results suggest that IVIg treatment may be useful by inhibiting cytokine storm in SARS-CoV-2 infection. Furthermore, IVIg treatment has been available for decades with limited side effects (19), and in fact, we did not note any significant side effects in our case. Taken together, these findings suggest that IVIg is an ideal treatment for COVID-19 patients.

In the present case, ivermectin was also administered when deterioration was observed. Therefore, ivermectin, a potent inhibitor against SARS-CoV-2 replication (20), might have played some role in the improvement of the patient. However, because viral loads were low and remained almost the same during the deteriorating phase (Fig. 2), the improvement by the treatment after deterioration was thought to be largely due to the suppression of pro-inflammatory signals through the treatment, which included high-dose IVIg.

Several limitations associated with the present study warrant mention. First, it may be difficult to assess the efficacy of IVIg treatment because IVIg, methylprednisolone and tocilizumab were all started simultaneously at the time of deterioration. However, after the onset of deterioration, the effects of methylprednisolone and tocilizumab were inadequate to suppress the inflammation, and additional IVIg treatment significantly improved the clinical condition, suggesting the anti-inflammatory effect of IVIg treatment. Second, our report concerns only one patient.

In conclusion, we described a case of severe COVID-19 administered treatment including high-dose IVIg, resulting in significant clinical improvement. Our present case suggests that high-dose IVIg is effective against severe COVID-19 not only in the early phase but also in the late phase, such as after deterioration. Although accumulating more cases is necessary to confirm the precise role of IVIg treatment in severe COVID-19 patients, it will be worthwhile to conduct this treatment until effective treatments are estab-

lished.

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

References

1. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **395**: 1033-1034, 2020.
2. Ye G, Pan Z, Pan Y, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. J Infect **80**: e14-e17, 2020.
3. Hoang VT, Dao TL, Gautret P. Recurrence of positive SARS-CoV-2 in patients recovered from COVID-19. J Med Virol **25**: 10.1002, 2020.
4. Hu R, Jiang Z, Gao H, et al. Recurrent positive reverse transcriptase-polymerase chain reaction results for coronavirus disease 2019 in patients discharged from a hospital in China. JAMA Netw Open **3**: e2010475, 2020.
5. Loconsole D, Passerini F, Palmieri VO, et al. Recurrence of COVID-19 after recovery: a case report from Italy. Infection **16**: 1-3, 2020.
6. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B **10**: 766-788, 2020.
7. Xie Y, Cao S, Dong H, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect **81**: 318-356, 2020.
8. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis **7**: 21, 2020.
9. Ikuyama Y, Wada Y, Tateishi K, et al. Successful recovery from critical COVID-19 pneumonia with extracorporeal membrane oxygenation: a case report. Respir Med Case Rep **30**: 101113, 2020.
10. Sheianov MV, Udalov YD, Ochkin SS, Bashkov AN, Samoilov AS. Pulse therapy with corticosteroids and intravenous immunoglobulin in the management of severe tocilizumab-resistant COVID-19: a report of three clinical cases. Cureus. Forthcoming.
11. Mohtadi N, Ghaysouri A, Shirazi S, et al. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: a case series. Virology **548**: 1-5, 2020.
12. Lanza M, Polistina GE, Imitazione P, et al. Successful intravenous immunoglobulin treatment in severe COVID-19 pneumonia. IDCases **16**: 21, 2020.
13. Nguyen AA, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: proceed with caution! Clin Immunol **216**: 108459, 2020.
14. Liu L, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight. Forthcoming.
15. Zhang L, Zhang F, Yu W, et al. Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals. J Med Viro **78**: 1-8, 2006.
16. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin **35**: 266-271, 2020.
17. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol **13**: 176-189, 2013.
18. Lau AC, Duong TT, Ito S, Yeung RS. Intravenous immunoglobulin and salicylate differentially modulate pathogenic processes leading to vascular damage in a model of Kawasaki disease. Arthritis Rheum **60**: 2131-2141, 2009.
19. Bonilla FA. Intravenous and subcutaneous immunoglobulin G replacement therapy. Allergy Asthma Proc **37**: 426-431, 2016.
20. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot (Tokyo) **73**: 593-602, 2020.