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【 CASE REPORT 】

Immediate Amelioration of Severe Respiratory Distress in Sjögren's Syndrome with COVID-19 Treated with a Single Dose of Off-label Tocilizumab

Hiroshi Kataoka[1], Fumihiro Kodama[2], Tomoko Tomita[1], Makoto Kondo[1], Atsushi Nagasaka[2], Shuji Nishikawa[3] and Masaya Mukai[1]

Abstract:
The coronavirus disease 2019 (COVID-19) pandemic has become an urgent global health issue. An older age and underlying conditions, such as diabetes, have been reported as risk factors, but whether or not autoimmune diseases increase the risk remains unknown. An 85-year-old man with Sjögren's syndrome developed a severe COVID-19 infection that required oxygen supplementation. After discussing the goals of care with him and his wife, off-label tocilizumab was given concomitantly, resulting in a rapid improvement in his symptoms and respiratory failure. This patient represents a supplementary case confirming the efficacy and safety of tocilizumab for COVID-19 in elderly patients with autoimmune diseases.

Key words: acute respiratory distress syndrome, COVID-19, cytokine storm, tocilizumab, Sjögren's syndrome

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus severe acute respiractory syndrome coronavirus 2 (SARS-CoV-2), which first arose in Wuhan, China, in December 2019, and has since spread worldwide. Eighty percent of patients with COVID-19 develop mild or moderate pneumonia without severe hypoxia. In contrast, severe disease that requires oxygenation occurs in 15%, and 5% suffer from critical disease with respiratory failure and acute respiratory distress syndrome (ARDS) (1). The risk factors for ARDS and death have been determined through retrospective observational studies and include an older age, oxygen therapy requirement, high sequential organ failure assessment (SOFA) score, low lymphocyte count, high serum interleukin-6 (IL-6), and elevated D-dimer level (2, 3). Underlying noncommunicable diseases, such as diabetes, hypertension, and cardiac disease, are also included among risk factors (1). Rheumatic diseases may be associated with a high susceptibility to COVID-19 infection and its severity in terms of immune disorders due to the diseases and the use of immunosuppressants. While rheumatic diseases were not recognized as risk factors for the high incidence and severity of COVID-19 in cohort studies (4-6), glucocorticoid use over 10 mg/day of prednisolone may be a risk factor for severe disease that requires hospitalization (7).

The present COVID-19 case was an elderly Sjögren's syndrome (SS) patient being treated with the low-dose methylprednisolone (mPSL) for salivary gland swelling and arthropathy. He developed severe dyspnea and was admitted to our hospital due to severe respiratory distress. On the day of admission, tocilizumab was administrated intravenously concomitantly with a short-term increase in prednisolone to 20 mg. His respiratory condition improved immediately, and he was discharged three weeks later. This case represents additional evidence of an elderly COVID-19 patient with a severe autoimmune disease being successfully cured after tocilizumab treatment, suggesting the efficacy and safety of tocilizumab in such cases.

[1]Department of Rheumatology and Clinical Immunology, Sapporo City General Hospital, Japan, [2]Department of Infectious Diseases, Sapporo City General Hospital, Japan and [3]Department of Gastroenterology, Sapporo City General Hospital, Japan
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Correspondence to Dr. Hiroshi Kataoka, hiroshi.kataoka@doc.city.sapporo.jp

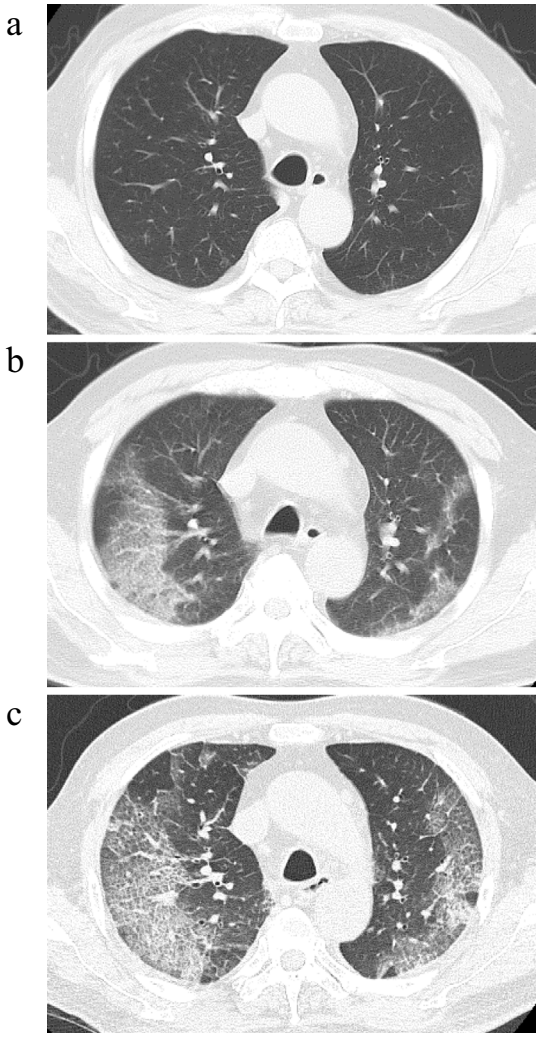

Figure 1. Chest computed tomography images from the onset of COVID-19 to the day of admission. Chest computed tomography (CT) findings are shown. a: Image taken when the patient visited his primary doctor complaining of a fever and cough (day 2), b: image taken when the SARS-CoV-2 PCR test was done (day 8), c: image taken on the day of admission (day 11).

Case Report

An 85-year-old man with SS and no other remarkable medical history was being treated with 2 mg/day mPSL for swollen salivary glands and polyarthropathy at his primary rheumatology clinic. He had never had extraglandular lesions or abnormal blood test findings, including leukopenia, elevated lactate dehydrogenase (LDH) and C-reactive protein (CRP), aside from chronic kidney disease stage 3b due to nephrosclerosis. He had been well until 12 days before he visited his doctor complaining of a fever and cough.

Chest X-ray and computed tomography (CT) findings were normal (Fig. 1a), and he was given an antibiotic agent for five days. However, it did not improve his symptoms. He revisited his doctor for progressive dyspnea six days later. Chest X-ray and CT conducted again showed ground-glass opacities (GGOs) that were located predominantly in the periphery of both lungs (Fig. 1b), and a SARS-CoV-2 polymerase chain reaction (PCR) test was conducted. As the result was positive despite an untraceable transmission pathway, he stayed at home for two days until being admitted to our hospital.

While waiting, he had a sustained fever and a decrease in his urine volume. He lost his appetite and became barely able to go to the restroom. On arrival at the emergency room of our hospital (11th day from the onset), his consciousness was clear (Glasgow Coma Scale; E4V5M6). He complained of shortness of breath, and the oxygen pulse monitor showed 83% on room air. His heart rate was 80/min, respiratory rate was 24-28/min, and blood pressure was 112/71 mmHg. His SpO_2 rose to 90% by 5 L/min oxygen (SpO_2/FiO_2 = 170, rough conversion to PaO_2/FiO_2 = 100), so he was admitted to the infectious disease ward. He still complained of dyspnea and spoke very slowly. He had a dry cough, and his tongue was dry. His body temperature was 38.1℃, his BMI was 27, and he reported that he had received bacille Calmette-Guerin (BCG) vaccination. He had a history of smoking. His salivary glands were not swollen, and he did not report any arthropathy or eye symptoms, such as red eyes, eye pain or dry eye.

CT showed expanding bilateral GGOs mainly in the peripheral lungs displaying a crazy-paving pattern, but the central area was spared (Fig. 1c). There was no massive pleural effusion or obviously enlarged pulmonary veins, although slight cardiomegaly was observed. The mediastinal lymph nodes were mildly swollen. There was no traction bronchiectasis or cystic changes that were likely to be found in SS-related interstitial pneumonia (IP) (8). These CT findings were typical for COVID-19 (9), whereas clinically evident pulmonary edema and SS-related IP were unlikely. Laboratory data showed a normal white blood cell count (8,900/μL), relatively low lymphocyte count (845/μL), mildly elevated LDH (394 IU/L), ferritin (445 μg/L), D-dimer (1.7 μg/dL), high CRP (13.02 mg/dL) and increased serum IL-6 [154 pg/mL (measured by a chemiluminescent enzyme immunoassay at SRL; normal range <4 pg/mL)]. His SOFA score was 2. We judged his COVID-19 to be in a critical state with ARDS according to the COVID-19 disease severity in the clinical management guide of COVID-19 (1).

He was treated with compassionate use of favipiravir and ciclesonide (inhalant corticosteroid) according to the 4th edition of the treatment guideline published by the Japanese Association for Infectious Diseases (10) (6th edition is currently available). As described above, he had been taking 2 mg/day mPSL [roughly equivalent to 2.5 mg/day prednisolone (PSL)] before admission, so we gave him an increased dose of PSL at 20 mg/day to prevent relative adrenal failure due to his severe systemic condition and the deterioration of SS secondary to severe infection.

The goals of care were discussed with him personally and also with his wife on the phone. Both he and his wife expressed their wish to receive all of the care we could pro-

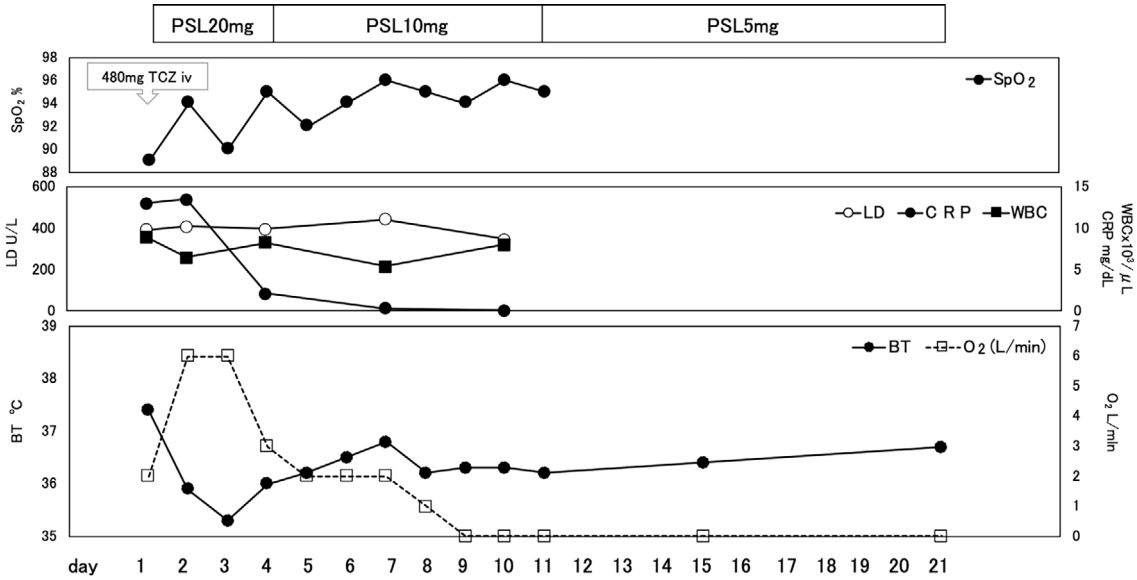

Figure 2. **Oxygenation and blood data during hospitalization. The oxygen saturation (SpO_2), LD, CRP, WBC, BT, and oxygen therapy are described. PSL was initiated at 20 mg/day on the day of admission and then reduced to 10 mg/day on the 4th hospital day and to 5 mg/day on the 11th hospital day, which was continued until discharge. Tocilizumab (480 mg/body) was intravenously introduced on the day of admission. PSL: prednisolone (mg/day), TCZ iv: intravenous administration of tocilizumab, LD: Lactate dehydrogenase (U/L), CRP: C-reactive protein (mg/dL), WBC: white blood cell count ($\times 10^3/\mu L$), BT: body temperature (°C)**

vide, including off-label treatment, but he did not wish to receive mechanical ventilation if his respiratory failure was deemed irreversible.

Given his wish to ameliorate his dyspnea and lethargy, a single dose of 480 mg/body of tocilizumab was administered intravenously to suppress a cytokine storm that was triggered by SARS-CoV-2 infection and caused a high fever, respiratory failure, and elevated levels of ferritin, D-dimer, CRP, and IL-6 (11) after receiving his written consent and his wife's agreement (Fig. 2). Thereafter, his body temperature fell to 35.9℃, and SpO_2 rose to 94% at 6 L/min oxygen supply within a day. On the third hospital day, his SpO_2 was 94% by nasal 2 L/min oxygen. As there seemed to be no risk of secondary adrenal insufficiency or worsening of the salivary gland or joint symptoms, PSL was rapidly tapered by discharge (Fig. 2). Oxygenation was discontinued on the ninth hospital day. The CRP level dropped below the normal limit on the 10th hospital day.

He was finally discharged on the 21st hospital day, and his care was taken over by his primary rheumatologist.

Discussion

This was a critical case of COVID-19 infection presenting ARDS in an elderly man with SS that was cured by the combination of favipiravir and ciclesonide with short-term use of a mildly increased corticosteroid and the additional off-label use of tocilizumab. The patient had risk factors for the rapid deterioration of COVID-19, including an older age (85 years old), corticosteroid use, and hypertension (1, 7). Angiotensin-converting enzyme 2 and specific transmembrane serine proteases, which facilitate SARS-CoV-2 virus entry, are expressed in the salivary glands (12). As the presence of connective tissue diseases is a risk factor of COVID-19 with a poor outcome, SS might have contributed to the severe cases of COVID-19 infection in this patient (13).

In a large US cohort, COVID-19 patients ≥85 years old were shown to have the highest risk of death among all ages (304.9 deaths per 1,000 cases) (14). The crazy-paving pattern was newly observed on CT images of both of the present patient's lungs on the 11th day, resulting in his being categorized as a severe case (Fig. 1a, c). All manifestations of dyspnea, the decreased SpO_2, low lymphocyte count, high LDH, CRP, and ferritin had never been experienced by this patient before in relation to his SS, and the findings were compatible with those shown in severe cases of COVID-19 (15). As this patient developed COVID-19 before the approval of remdesivir or dexamethasone in Japan, we administered favipiravir and ciclesonide, which had been proven to have antiviral effects but were limited to compassionate use. In addition, as he regularly received 2 mg/day mPSL, which was equivalent to 2.5 mg/day of PSL, we increased the dose of PSL to 20 mg/day considering his critical systemic condition, particularly the respiratory failure that carried a risk of inducing secondary adrenal insufficiency and worsening symptoms of SS after admission (16). The immediate improvement of his fever, dyspnea, and SpO_2 after the administration of a single dose of intravenous tocilizumab was an impressive feature in this case.

Typical CT findings in COVID-19 include multiple GGOs with peripheral and subpleural distributions in multiple lobes, particularly the lower lobes, and in severe cases, multifocal consolidation, linear opacity, and a crazy-paving pattern (9). Viral pneumonia due to other viruses, pulmonary edema, alveolar hemorrhaging, and drug-induced pneumonitis are differential diagnoses in cases with these CT abnormalities (9). In patients with SS, nonspecific IP, usual IP, and lymphocytic IP can develop as extraglandular manifestations (8). The distribution of interstitial changes and presence of traction bronchiectasis and cysts might be clues for distinguishing SS-IP and COVID-19 pneumonia, although it is difficult to do so based solely on CT findings without an assessment of the clinical features.

Cytokine storm is also referred to as cytokine release syndrome (CRS) and is a critical condition that occurs due to the massive release of various cytokines, including IL-6 from *in situ* immune cells, resulting in serious tissue damage (17). In COVID-19, this critical condition begins around 7-10 days after the infection of SARS-CoV-2 and results in ARDS a few days later. Almost all non-survivors of COVID-19 develop ARDS, indicating that cytokine storm is a life-threatening event (3).

Risk factors for death include an older age, worse SOFA score, and high D-dimer level (>1 μg/mL). In the current case, his age of 85 years old, SOFA score of 2 (respiratory failure without mechanical ventilation), and D-dimer level of 1.7 μg/mL were all consistent with these risk factors, suggesting that his outcome would likely be fatal. We therefore decided to use off-label tocilizumab concomitantly with PSL cover after he and his family were given sufficient information about the likelihood of adverse events and the expected effect of tocilizumab.

In a report on critically ill patients, the serum levels of IL-6 and IL-8 were markedly elevated from the beginning of the COVID-19 course, and these cytokine levels were inversely correlated with the lymphocyte counts (18). CRS has reportedly developed in more than half of diffuse large B cell lymphoma patients treated with tisagenlecleucel [anticluster of diffrentiation 19 (CD19) chimeric antigen receptor T-cell (CAR-T) therapy], with patients developing a fever, hypoxia, and high serum level of IL-6 and ultimately requiring oxygen supplementation (19-21). Tocilizumab is an IL-6 receptor monoclonal antibody and an approved drug that ameliorates CRS in patients receiving CAR-T therapy (19). In the context of the similarity in patients' conditions, tocilizumab has been used to ameliorate CRS and ARDS in severe COVID-19 cases as an off-label therapy (22, 23). The survival of severe COVID-19 patients treated with tocilizumab was similar to that of non-severe patients in a retrospective study performed in the US where 153 tocilizumab-treated patients were analyzed (23). In an Italian retrospective study in which 91 subcutaneous tocilizumab-treated patients and 88 intravenous tocilizumab-treated patients were enrolled, the risk of mechanical ventilation or death was reduced in tocilizumab-treated patients compared with the standard therapy group treated with hydroxychloroquine and lopinavir-ritonavir/darunavir-cobicistat (22). Given the requirement of oxygen supplementation, the current patient was eligible for tocilizumab treatment according to the inclusion criteria of the two studies. Therefore, this is an elderly case showing additional evidence supporting the promising effect of IL-6 inhibition on severe COVID-19 in patients with autoimmune diseases.

Glucocorticoids were not recommended for COVID-19 treatment due to the risk of infection, except for in cases with the possible exacerbation of asthma or chronic obstructive pulmonary disease, according to the May 2020 WHO management guideline (1). In rheumatic disease patients, the regular use of ≥10 mg/day glucocorticoid may carry a risk of hospitalization (7). However, the WHO ultimately approved the efficacy of dexamethasone in the RECOVERY trial (ClinicalTrials.gov Identifier: NCT04381936) (24). As approximately one-third of severe COVID-19 cases treated with tocilizumab were given glucocorticoid concomitantly, the net effect of tocilizumab could not be easily estimated (22, 23). In the present case, 20 mg/day prednisolone was given for the initial 3 days concomitantly with tocilizumab, and mPSL pulse therapy was not administered. Thus, the glucocorticoid in this case was a relatively low dose administered for a shorter period than the 6 mg/day of dexamethasone (corresponding to approximately 37.5 mg PSL) administered for 10 days in the RECOVERY trial (24-27). As a result, tocilizumab in this case was thought to show a greater effect on respiratory failure than the increased PSL dose.

In terms of the negative effects of tocilizumab therapy, no adverse events occurred in this case. However, sepsis, fungal infection, elevated liver transaminases, neutropenia, and intestinal perforation were observed in previous studies (23, 28-30). Therefore, although our patient did not experience any adverse events, special care should be taken when patients are treated with off-label tocilizumab.

In conclusion, IL-6 inhibition may be an optional treatment in patients with a severe respiratory condition. A recent study of sarilumab, another IL-6 receptor blocker, showed the rapid clinical improvement in patients with less severe lung involvement (31). These findings suggest that determining the appropriate cases and timing for introducing IL-6 inhibition is an urgent issue. Therefore, prospective studies should be carried out to establish how to use IL-6 receptor antibodies effectively with reliable safety.

The patient provided us with a written consent form.

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

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