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Case report

Secondary organizing pneumonia after coronavirus disease 2019: Two cases

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has been reported to induce persistent symptoms even after an acute phase. However, the pathophysiology and treatment of this condition have been unclear. We report two patients who recovered from COVID-19, but presented persistent respiratory symptoms. Their respiratory conditions deteriorated, and computed tomography showed remaining ground glass opacities and consolidations. The pathological findings of transbronchial lung biopsy corresponded to organizing pneumonia. We diagnosed them with secondary organizing pneumonia after COVID-19. Subsequently, we administered systemic corticosteroids. Their symptoms, oxygenations, radiologic findings, and pulmonary functions rapidly improved after the treatment of corticosteroids. The two cases showed that secondary organizing pneumonia may be a cause of persistent respiratory failure after COVID-19. In this condition, corticosteroids may be effective.

1. Introduction

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has spread worldwide and resulted in a pandemic [1]. The overall fatality rate of patients diagnosed with COVID-19 was reported to be 2.3% [2]. Even if patients with COVID-19 survived and were discharged, some of them experienced persistent symptoms [3]. Two months after the symptom onset, 66% and 30% of non-critical COVID-19 patients who needed admission experienced one or more symptoms and dyspnea, respectively [4]. With respect to objective findings, 52.6% of patients showed less than 80% of predicted values of diffusing capacity of the lungs for carbon monoxide (DLCO) 1 month after discharge [5]. Moreover, 47% of patients showed a persistent abnormality in computed tomography (CT) findings 3 weeks after discharge [6]. As to how long these dysfunctions persist remain unclear. Although many COVID-19 survivors suffered from a so-called "sequelae," the pathophysiology of this condition and efficient treatments has not been established yet [7].

Secondary organizing pneumonia can develop after various infectious pneumonias, including viruses [8]. The typical clinical findings of organizing pneumonia include fever and elevation of inflammation reaction, consolidation and bilateral distribution in CT, restrictive ventilatory defect and dysfunction in diffusion capacity, and elevation of lymphocytes in bronchoalveolar lavage (BAL) fluid [8,9]. However, because these findings are not specific, a histopathological diagnosis is required [8].

Herein, we present two cases of secondary organizing pneumonia after COVID-19, in which corticosteroids had been effective.

2. Case reports

2.1. Case 1

A 56-year-old man with no remarkable medical history presented with a 7-day history of fever and body malaise and a 1-day history of cough and dyspnea. On admission, his body temperature, heart rate, blood pressure, respiratory rate, and percutaneous oxygen saturation (SpO_2) on room air was 37.9 °C, 100 beats/min, 113/79 mmHg, 28 breaths/min, and 83%, respectively. He tested positive for polymerase chain reaction (PCR) of SARS-CoV2 ribonucleic acid (RNA) on his nasopharyngeal sample. Chest CT showed posterior ground glass opacities (GGOs) in both lungs (Fig. 1A). Laboratory blood tests exhibited an increase in the level of C-reactive protein (CRP) (11.55 mg/dL). Despite

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Abbreviations

BAL	bronchoalveolar lavage
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CT	computed tomography
DLCO	diffusing capacity of the lungs for carbon monoxide
GGOs	ground glass opacities
PCR	polymerase chain reaction
RNA	ribonucleic acid
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SpO_2	percutaneous oxygen saturation
TBLB	transbronchial lung biopsy

the initiation of favipiravir and dexamethasone, his SpO_2 rapidly deteriorated to 88% with supplemental oxygen of 5 L/min within a day. We introduced invasive mechanical ventilation, and transferred him to another hospital exclusively for critical COVID-19 patients. He was extubated on illness day 13 because of respiratory condition improvement. Concurrently, favipiravir and dexamethasone were stopped. He tested negative for PCR of SARS-CoV2 RNA twice, on illness days 14 and 15, and returned to our hospital on illness day 16. However, upon re-hospitalization to our hospital, his respiratory failure persisted, and a nasal oxygen supplementation of 4 L/min was required to maintain a SpO_2 of 97%. On illness day 26, he no longer had fever, and the serum CRP level declined to the normal range. However, he still needed a nasal oxygen supplementation of 3 L/min. Chest CT showed that GGOs remained and partially became consolidations in both lobes (Fig. 1B). We performed BAL and transbronchial lung biopsy (TBLB) on illness day 29. The BAL fluid from the left B^4 (recovery rate 35%, 53/150 mL) showed a cell count of 9.6×10^5 cells/mL with 94% macrophages, 5% lymphocytes, and 1% neutrophils. The PCR of SARS-CoV2 RNA from the BAL fluid was negative. A microscopic examination of the TBLB from left B^4 and B^5 revealed intra-alveolar granulation, interstitial lymphocytes infiltration, and fibroblastic tissue proliferation in the interstitium (Fig. 2). Considering his clinical course and pathological findings, we diagnosed secondary organizing pneumonia after COVID-19. We initiated an oral administration of prednisolone 60 mg/day (1 mg/kg/day)

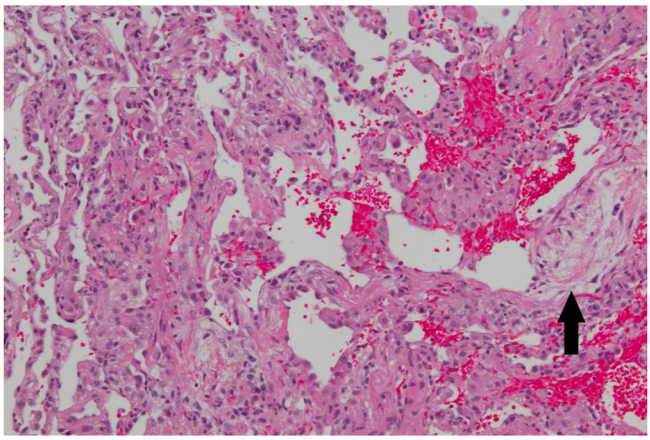

Fig. 2. Histopathological findings of TBLB in case 1 (hematoxylin and eosin stain; × 10). Arrow indicates an intra-alveolar granulation. There were interstitial lymphocyte infiltrations and fibroblastic tissue proliferation in the interstitium.

on illness day 35. After, his respiratory condition rapidly improved, and maintained a SpO_2 of 95% on room air on illness day 42. Furthermore, the CT on illness day 41 showed a remarkable improvement of consolidations (Fig. 1C). We decreased the prednisolone dose to 30 mg/day (0.5 mg/kg/day) on illness day 42. On illness day 56, he was discharged without oxygen supplementation. Spirometry on illness day 61 was within the normal range, and the DLCO was 82.8% of predicted values. We tapered the prednisolone dose to 15 mg/day on illness day 84 without recurrence.

2.2. Case 2

An 84-year-old woman with a medical history of hypertension, hypercholesterolemia and hypothyroidism presented with a 9-day history of body malaise. She did not complain of dyspnea. On admission, her body temperature, heart rate, blood pressure, respiratory rate, and SpO_2 on room air was 36.7 °C, 78 beats/min, 148/87 mm Hg, 24 breaths/min, and 90%, respectively. She tested positive for the PCR of SARS-CoV2 RNA on her nasopharyngeal sample. Chest CT showed patchy GGOs dominantly in the periphery of the right lung lobe (Fig. 3A). Laboratory

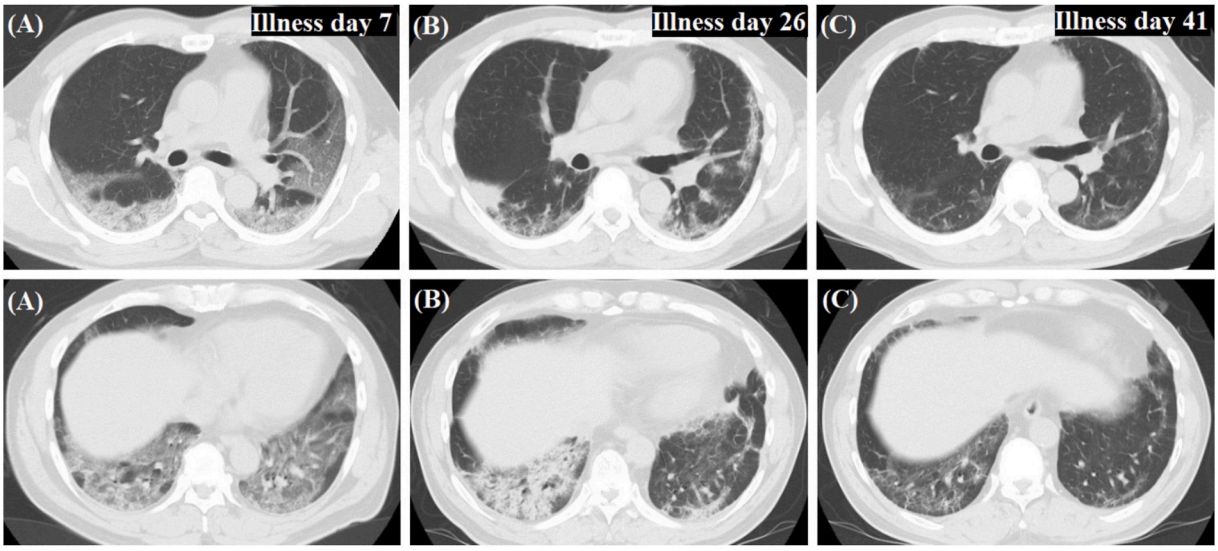

Fig. 1. Chest CT images of case 1 on illness day 7, on the first admission to our hospital (A), on illness day 26, before prednisolone introduction (B), and on illness day 41, 6 days after the introduction of prednisolone (C). Peripheral ground glass opacities in the bilateral posterior lobes progressed to consolidation, and improved after the treatment of prednisolone.

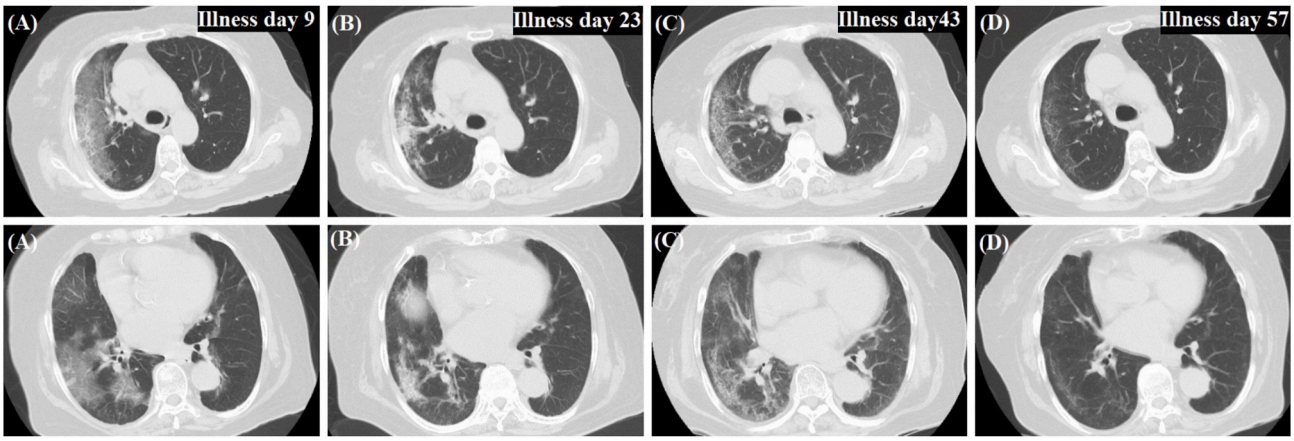

Fig. 3. Chest CT images of case 2 on illness day 9, on the admission to our hospital (A), on illness day 23, soon after the discontinuation of dexamethasone (B), on 43 days after the onset, before prednisolone introduction (C), and illness day 57, 6 days after the introduction of prednisolone (D). Bilateral ground glass opacities partially turned to consolidations and improved after the treatment of prednisolone.

blood tests exhibited a slight increase in CRP (2.62 mg/dL). We initiated favipiravir and dexamethasone after the admission. She temporarily needed a nasal oxygen supplementation of 4 L/min on the next day of admission, but then, her symptom and oxygenation gradually improved. We discontinued dexamethasone and favipiravir on illness days 20 and 24, respectively. She tested negative for the PCR of SARS-CoV2 RNA twice, on illness days 30 and 31. However, she remained in the hospital because of persistent dyspnea. She did not present with fever, and the serum CRP level declined to the normal range on illness day 36. She did not need oxygen supplementation; however, her SpO_2 decreased to less than 90% with just a 30-m-walk on illness day 43. In addition, the CT on illness days 23 and 43 showed the presence of GGOs and consolidations in both lungs (Fig. 3B and C). A pulmonary function test on illness day 44 also showed a reduced DLCO. We performed bronchoscopy on illness day 45. The BAL fluid from right B^5 (recovery rate 67%, 101/150 mL) showed a cell count of 3.0×10^5 cells/mL with 93.5% macrophages, 3.5% lymphocytes, 1.5% neutrophils, and 1.5% eosinophils. The PCR of SARS-CoV2 RNA from the BAL fluid was negative. A microscopic examination of the TBLB from right B^3 and B^4 revealed an interstitial and intra-alveolar infiltration of lymphocytes and macrophages as well as fibroblastic connective tissue proliferation. We did not find severe fibrotic changes, eosinophil or neutrophil infiltrations, and lung structure disorganization (Fig. 4). We diagnosed the patient as secondary organizing pneumonia after COVID-19. We initiated an oral administration of prednisolone 60 mg/day (1 mg/kg/day) on illness day 51. After, her symptoms and oxygen saturation rapidly improved. On illness day 58, her SpO_2 remained higher than 95% on room air when she walked a distance of more than 100 m. Furthermore, the CT on illness day 57 showed a remarkable improvement of consolidations and GGOs (Fig. 3D). Pulmonary function tests showed the DLCO of predicted values increased from 49.6% on illness day 44 to 71.7% on illness day 58, before and after the prednisolone treatment, respectively (Table 1). On illness day 58, we decreased prednisolone dose to 30 mg/day (0.5 mg/kg/day), and she was discharged on illness day 65. We tapered prednisolone dose to 20 mg/day on illness day 86 without recurrence.

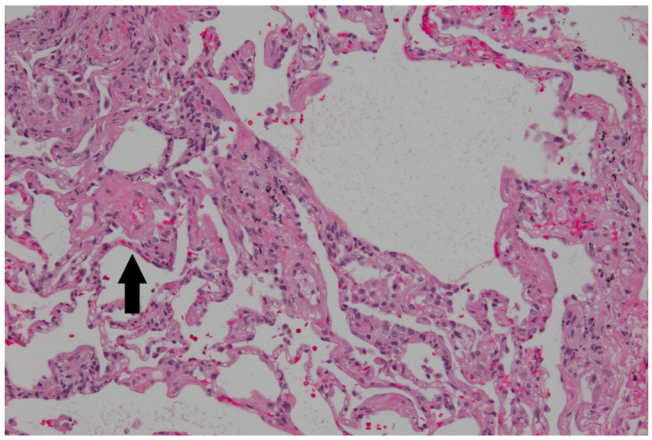

Fig. 4. Histopathological findings of TBLB in case 2 (hematoxylin and eosin stain; × 10). Arrow indicates interstitial and intra-alveolar infiltrations of lymphocytes and macrophages. There were fibroblastic connective tissue proliferations in the interstitium.

3. Discussion

We reported two cases that pathologically showed secondary organizing pneumonia after COVID-19. To the best of our knowledge, there was only one report of pathologically confirmed secondary organizing pneumonia after COVID-19 [10]. Our two cases and the previous Korean case commonly showed radiological improvements after the treatment of corticosteroids. However, our cases were different from the previous case in terms of following two clinical courses: 1) our diagnosis was based on TBLB, while the previous case was based on invasive surgical biopsy, and 2) we objectively confirmed improvements of pulmonary lung function before and after the treatment of corticosteroids in case 2.

Secondary organizing pneumonia may be responsible for the

Table 1
Results of pulmonary function test before and after administration of corticosteroids in case 2.

Parameter	before steroids[a]	after steroids[b]
Spirometry		
VC (L)	1.66[85.9][c]	1.57[81.5]
FEV1 (L)	1.29[80.6]	1.43[89.3]
FEV1/FVC (%)	79.1	86.7
Lung volume		
TLC (L)	3.07[113.7]	3.66[135.6]
RV (L)	1.41[133.9]	2.09[198.2]
RV/TLC	46[132.7]	57.1[164.6]
Diffusion capacity		
DLCO (mL/min/mmHg)	7.09[49.6]	10[71.7]
DLCO/VA (mL/min/mmHg/L)	2.79[69.9]	3.36[84.3]

DLCO: diffusing capacity of the lungs for carbon monoxide; FEF50%: forced expiratory flow at 50% of forced vital capacity; FEV1: forced expiratory volume; RV: residual volume; TLC: total lung capacity; VC: vital capacity.

[a] Results before initiation of corticosteroids (on illness day 44).

[b] Results 7 days after initiation of corticosteroids (on illness day 58).

[c] Values in square brackets mean % of predicted.

persistent respiratory failure in patients recovering from COVID-19. Findings of CT and pulmonary function tests in our two cases correspond to those reported in previous studies of organizing pneumonia: however, symptom, inflammation reaction, and low proportion of lymphocytes in the BAL fluid were not typical [8,9]. Conversely, organizing pneumonia could not be excluded from clinical findings alone [8]. For example, a previous study showed that 35% of patients with organizing pneumonia did not present fever, and another study revealed that 24% of patients did not present an elevation of serum CRP level [9,11]. Considering the risk of complications, it is not practical to perform TBLB for all the cases suspected of organizing pneumonia. However, we should not hesitate histological analysis from TBLB specimen for unclear or critical cases. We should consider organizing pneumonia as a sequela after COVID-19. TBLB is an option when the diagnosis of organizing pneumonia is difficult only from radiological and microbiological findings.

Secondary organizing pneumonia after COVID-19 is also a reversible condition owing to a sufficient treatment of corticosteroids. Systemic corticosteroid treatments have been shown to decreased COVID-19 mortality. Dexamethasone was recommended for use in the acute phase [12,13]. However, there was no evidence regarding systemic corticosteroid treatments for patients with persistent respiratory failure in patients recovering from acute COVID-19 infection. We used corticosteroids for our two cases because aside from being effective for cryptogenic organizing pneumonia, they are also typically used for secondary organizing pneumonia [8,9]. Both of our patients had objectively improved in terms of oxygenation, CT findings, and DLCO. We initiated a prednisolone dose of 1 mg/kg/day for 1 week according to the guideline for the treatment of cryptogenic organizing pneumonia [14]. Owing to the rapid improvement of our patients after the introduction of prednisolone, we decreased the prednisolone dose to 0.5 mg/kg/day 1 week after in order to shorten the duration of corticosteroid treatment. Further studies are needed to find the optimal initial dose and tapering schedule for secondary organizing pneumonia after COVID-19.

In conclusion, we present two cases of secondary organizing pneumonia after COVID-19, in which systemic corticosteroids improved patients' oxygenation, radiological findings and pulmonary function. We should consider secondary organizing pneumonia as a differential diagnosis when respiratory failure persists among patients after COVID-19.

Author contributions

Kensuke Kanaoka, Seigo Minami, Shoich Ihara, Tsunehiro Tanaka and Kiyoshi Komuta were involved in treatment and care of these patients. Hironao Yasuoka performed pathological diagnosis of organizing pneumonia. Kensuke Kanaoka drafted the report. All authors read and critically reviewed the report and approved the final submitted version.

Declaration of competing interest

All authors declare no potential conflicts of interest related to the publication.

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