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Case Report

Post-COVID-19 interstitial lung disease presenting with profound hypoxemia: Report of three cases demonstrating a good response to high-dose corticosteroid therapy

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which leads to critical pneumonia, although the clinical courses vary. In some cases, COVID-19 pneumonia causes secondary pulmonary fibrosis, which can retain radiological changes and prolong respiratory symptoms. Interstitial lung disease (ILD) secondary to COVID-19 is thought to be caused by multiple pathologies, such as excessive cytokines and abnormal repair processes elaborated by lung cells (epithelium, mesenchyme, and alveolar macrophages) after lung injury rather than viral invasion itself. Immunosuppression therapy may improve chronic respiratory symptoms and radiological changes in post-COVID-19 ILD, although the treatment is not yet established. Herein, we report three patients with post-COVID-19 ILD who presented with profound hypoxemia that had a good response to high-dose corticosteroid therapy. Further and larger studies are needed to establish post-COVID-19 ILD.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a global problem. COVID-19 leads to acute and critical pneumonia, although the clinical courses vary [1–3]. Pulmonary fibrosis secondary to COVID-19 is an essential problem because it might prolong or even deteriorate respiratory symptoms in patients recovering from COVID-19, and pulmonary fibrosis in COVID-19 is thought to be due to an abnormal repair process following lung injury caused by an excessive inflammatory response, abnormality of lung epithelium, mesenchyme, and macrophages, and mechanical injuries in alveoli [4–6]. Since cytokine storms are crucial in the pathogenesis of COVID-19 pneumonia, immunosuppressive agents may also improve interstitial lung disease (ILD) secondary to COVID-19 [7,8], although proper therapeutic strategies have not yet been established.

Here, we report three cases of post-COVID-19 ILD presenting with profound hypoxemia, which demonstrated a good response to high-dose corticosteroid therapy.

2. Case reports

2.1. Case 1: male, 63 years old

The patient underwent coronary artery bypass graft (CABG) for angina pectoris at 61 years old and was also diagnosed with type 2 diabetes mellitus; in addition, he was a current smoker (82 pack-years). He noticed fever, and eight days after the onset of this symptom, he experienced dyspnea and was diagnosed with COVID-19 (the SARS-CoV-2 PCR test result was positive). He was treated with dexamethasone (6 mg/day, for ten days), baricitinib (4.0 mg/day, for 14 days), and remdesivir (200 mg/day on the first day, 100 mg/day from the second to the fifth day). His condition gradually improved, and he was discharged on the 26th day after the onset of COVID-19. However, on the 28th day, he was readmitted to our hospital because of recurrence of dyspnea. Physical examination revealed clear consciousness, low-grade fever (37.1 °C), and hypoxemia (SpO2 84% on room air). The laboratory test indicated high levels of ILD markers (KL-
The computed tomography (CT) image revealed bilateral consolidation with subpleural distribution, traction bronchiectasis, and irregular reticulation (Fig. 1 and E1). From the findings, we diagnosed post-COVID-19 ILD and started corticosteroid pulse therapy (at a dose of 500 mg of methylprednisolone every 12 hours, six times in total) with antibiotics. Following the initial therapy, corticosteroid therapy was continued (at a dose of 1.0 mg/kg/d of prednisolone, also see in Fig. 1). Such therapy could prevent

Table 1
Patient’s laboratory data at the point of post-COVID-19 interstitial lung disease onset.

| Hematology | Case 1 | Case 2 | Case 3 | Biochemistry | Case 1 | Case 2 | Case 3 | Immunology | Case 1 | Case 2 | Case 3 |
|------------|--------|--------|--------|--------------|--------|--------|--------|------------|--------|--------|--------|
| WBC (/μL)  | 11930  | 14670  | 8800   | AST (IU/L)    | 110    | 18     | 24     | CRP (mg/dl) | 14.09  | 20.73  | 4.84   |
| Neut       | 89.3%  | 80.6%  | 70.3%  | ALT (IU/L)    | 154    | 35     | 23     | KL-6 (U/L)  | 1462   | 595    | 4680   |
| Lym        | 5.6%   | 7.4%   | 12.1%  | ALP (IU/L)    | 481    | 216    | 280    | SP-D (ng/ml) | 161    | N/M    | 482    |
| Mo         | 4.1%   | 11.2%  | 11.2%  | LDH (IU/L)    | 336    | 239    | 343    | IgA (mg/dl) | 314    | 444    | 566    |
| Baso       | 0.5%   | 0.5%   | 5.9%   | BUN (mg/dl)   | 10     | 14     | 12     | IgG (mg/dl) | 1260   | 940    | 1298   |
| RBC (X10⁶/μL) | 398   | 405    | 463    | CK (IU/L)     | 66     | 23     | 44     | C3 (mg/dl)  | 185    | 163    | 141    |
| Hb (g/dl)  | 11.7   | 12.3   | 14.7   | TP (g/dl)     | 6.5    | 6.4    | 6.7    | C4 (mg/dl)  | 41     | 34     | 20     |
| Pt (X10³/μL) | 131   | 232    | 257    | Ferritin (ng/ml) | 137   | 127    | 137    | C-ANCA (U/mL) | 1.0   | 2.1    | 1.0    |
| WBC (μL)   | 11930  | 14670  | 8800   | Na (mEq/l)    | 137    | 127    | 137    | MPO-ANCA (U/mL) | 1.0   | 1.0    | 1.0    |
| Neut       | 89.3%  | 80.6%  | 70.3%  | Cl (mEq/l)    | 100    | 94     | 99     | Auto-Antibody, Names | Neg | Neg    | Neg    |
| Lym        | 5.6%   | 7.4%   | 12.1%  | Ca (mg/dl)    | 8.8    | 8.3    | 9.3    | HbA1c (%, NGSP) | 6.8  | 8.2    | 7.6    |
| Mo         | 4.1%   | 11.2%  | 11.2%  | LDH (IU/L)    | 126    | 238    | 106    | NT-pro BNP (pg/ml) | 517 | N/M    | 397    |
| Baso       | 0.5%   | 0.5%   | 5.9%   | BUN (mg/dl)   | 126    | 238    | 106    | Complement, Total (CH50/mL) | Neg | Neg    | Neg    |
| RBC (X10⁶/μL) | 398   | 405    | 463    | Ferritin (ng/ml) | 137   | 127    | 137    | C-ANCA (U/mL) | 1.0   | 2.1    | 1.0    |
| Hb (g/dl)  | 11.7   | 12.3   | 14.7   | Na (mEq/l)    | 137    | 127    | 137    | MPO-ANCA (U/mL) | 1.0   | 1.0    | 1.0    |
| Pt (X10³/μL) | 131   | 232    | 257    | FBS (mg/dl)   | 162    | 238    | 106    | Anti-nuclear antibodies | Neg | Neg    | Neg    |
| WBC (μL)   | 11930  | 14670  | 8800   | Na (mEq/l)    | 137    | 127    | 137    | HbA1c (%, NGSP) | 6.8  | 8.2    | 7.6    |
| Neut       | 89.3%  | 80.6%  | 70.3%  | Cl (mEq/l)    | 100    | 94     | 99     | NT-pro BNP (pg/ml) | 517 | N/M    | 397    |
| Lym        | 5.6%   | 7.4%   | 12.1%  | Ca (mg/dl)    | 8.8    | 8.3    | 9.3    | Complement, Total (CH50/mL) | Neg | Neg    | Neg    |
| Mo         | 4.1%   | 11.2%  | 11.2%  | LDH (IU/L)    | 126    | 238    | 106    | C-ANCA (U/mL) | 1.0   | 2.1    | 1.0    |
| Baso       | 0.5%   | 0.5%   | 5.9%   | BUN (mg/dl)   | 126    | 238    | 106    | MPO-ANCA (U/mL) | 1.0   | 1.0    | 1.0    |
| RBC (X10⁶/μL) | 398   | 405    | 463    | Ferritin (ng/ml) | 137   | 127    | 137    | Anti-nuclear antibodies | Neg | Neg    | Neg    |
| Hb (g/dl)  | 11.7   | 12.3   | 14.7   | Na (mEq/l)    | 137    | 127    | 137    | HbA1c (%, NGSP) | 6.8  | 8.2    | 7.6    |
| Pt (X10³/μL) | 131   | 232    | 257    | FBS (mg/dl)   | 162    | 238    | 106    | NT-pro BNP (pg/ml) | 517 | N/M    | 397    |

N/M; not measured, Neg; Negative, ARS; aminoacyl tRNA synthetase, RNP; ribonucleoprotein, CCP; cyclic citrullinated peptide.
deterioration of respiratory failure and improve hypoxemia. The patient was discharged on the 55th day after the onset of COVID-19. He continued steroid tapering in an outpatient setting and was weaned from oxygen therapy on the 69th day.

2.2. Case 2: male, 75 years old

The patient was being treated for hypertension and was a past smoker (40 pack-years). He experienced cough and dyspnea, and four days after the onset of these symptoms, he noticed fever and was diagnosed with COVID-19 (the SARS-CoV-2 antigen test result was positive). The patient exhibited hypoxemia and was hospitalized. He was treated with dexamethasone (6 mg/day, for ten days) and remdesivir (200 mg/day on the first day, 100 mg/day from the second to the fifth day). The fever improved, although the hypoxemia worsened from the 10th day to the 12th day after the onset of COVID-19. The hypoxemia was improved on the 13th day. However, on the 17th day, the fever recurred (38.7 °C), and the hypoxemia (SpO₂ 94% on nasal cannula O₂ 2 L/min) also deteriorated. The laboratory test indicated high C-reactive protein (CRP, 20.73 mg/dl) and KL-6 (595 U/L) values (Table 1). The high HbA1c (8.2%, NGSP) level indicated that the patient had diabetes mellitus. Chest X-ray showed new bilateral peripheral infiltrates, and CT imaging revealed bilateral consolidation with subpleural distribution, suggesting organizing pneumonia (Fig. 2 and E2). We started corticosteroid pulse therapy (at a dose of 500 mg of methylprednisolone every 12 hours, six times in total) based on acute exacerbation of ILD. Following the pulse therapy, we continued corticosteroid therapy using betamethasone (at the dose of 4.0 mg per day, also see in Fig. 2). The hypoxemia was resolved immediately after high-dose corticosteroid treatment. The corticosteroid was tapered, and the patient was discharged on the 28th day. On the 47th day, he complained of dyspnea, although hypoxemia was not observed (SpO₂ 93% on room air). The laboratory test indicated an increase in CRP (5.99 mg/dl) and KL-6 (723 U/L) values, and the corticosteroid dose was increased. However, the patient’s dyspnea worsened, and he was hospitalized on the 54th day. The radiological changes were improved over those on the 19th day, but hypoxemia was observed (SpO₂ 89% on room air). There was no evidence of pulmonary embolism or heart failure, and he was introduced to long-term oxygen therapy and discharged on the 62nd day. In outpatient settings, the patient’s symptoms improved gradually, and he restarted the steroid tapering and was weaned from oxygen therapy on the 102nd day.

2.3. Case 3: male, 59 years old

The patient had undergone CABG for myocardial infarction at 47 years of age and was also treated for hypertension, hyperlipidemia, and type 2 diabetic mellitus; moreover, he was a past smoker (27 pack-years). He noticed fever and dyspnea, was admitted to an emergency hospital and was diagnosed with COVID-19 (the SARS-CoV-2 PCR test result was positive). The patient had severe hypoxemia and was intubated, and intermittent positive-pressure ventilation (IPPV) was started. He was treated with dexamethasone (6 mg/day, for ten days) and remdesivir (200 mg/day on the first day, 100 mg/day from the second to the fifth day). Additionally, he was administered sulbactam/ampicillin because of aspiration pneumonia (from the sixth to the 12th day). The patient’s condition improved, and he was weaned from IPPV on the 9th day after the onset of COVID-19. He was managed using high-flow nasal cannula oxygen therapy (HFNC) from the 10th day to the 14th day, and his radiological changes and respiratory failure improved (Fig. 3 and E3). He was transferred to our hospital on the 17th day. Physical examination revealed clear consciousness, low-grade fever (37.2 °C), and hypoxemia (SpO₂ 91% on nasal cannula O₂ 4 L/min). However, after...
transfer, the hypoxemia deteriorated, and we performed further examinations. The laboratory test indicated CRP elevation (4.84 mg/dl) and extremely high levels of ILD markers (KL-6: 4680 U/L, SP-D: 482 U/L) (Table 1). On CT imaging, compared to that on the 11th day, bilateral consolidation had respread, and traction bronchiectasis and irregular reticulation were observed (Fig. 3 and E3). From these findings, we diagnosed post-COVID-19 ILD and started corticosteroid pulse therapy (at a dose of 500 mg of methylprednisolone every 12 hours, six times in total). Following the initial therapy, corticosteroid therapy was continued (at a dose of 1.0 mg/kg/d of prednisolone, also see in Fig. 3). The patient was treated using HFNC from the 21st day to the 38th day. Although severe hypoxemia was prolonged, he was weaned from HFNC and continued rehabilitation. The hypoxemia and radiological changes gradually improved, and the corticosteroid dose was tapered. The patient was discharged on the 61st day after the onset of COVID-19.

3. Discussion

These three patients showed profound hypoxemia after COVID-19; at that time, CT images indicated pulmonary fibrosis, and laboratory tests revealed high levels of ILD markers (KL-6: 4680 U/L, SP-D: 482 U/L) (Table 1). On CT imaging, compared to that on the 11th day, bilateral consolidation had respread, and traction bronchiectasis and irregular reticulation were observed (Fig. 3 and E3). From these findings, we diagnosed post-COVID-19 ILD and started corticosteroid pulse therapy (at a dose of 500 mg of methylprednisolone every 12 hours, six times in total). Following the initial therapy, corticosteroid therapy was continued (at a dose of 1.0 mg/kg/d of prednisolone, also see in Fig. 3). The patient was treated using HFNC from the 21st day to the 38th day. Although severe hypoxemia was prolonged, he was weaned from HFNC and continued rehabilitation. The hypoxemia and radiological changes gradually improved, and the corticosteroid dose was tapered. The patient was discharged on the 61st day after the onset of COVID-19.

Fig. 3. The figure shows the clinical course in Case 3. Oxygen at 1–4 L/min was administered using a nasal cannula, 5–7 L/min was administered using a simple face mask, and 7–10 L/min was administered using a nonrebreather face mask. IPPV; Intermittent positive pressure ventilation, HFNC; High-flow nasal cannula, DEX; Dexamethasone, mPSL; Methylprednisolone, PST; Prednisolone, S/A; Sulbactam/ampicillin (the dose was not confirmed), AZM; Azithromycin. The images are indicated as representative chest X-rays and CT images.
there are no signs of worsening of ILD.

We administered corticosteroid pulse therapy in all three cases. Corticosteroid pulse therapy has strong potential to suppress the inflammatory response and promote faster clinical recovery from symptoms than oral therapy through not only systemic effects but also nongenomic glucocorticoid activities [19, 20]. When comparing our three patients, patients 1 and 3 had similar clinical features: acute and prolonged hypoxemia, high KL-6 levels, and CT imaging indicating traction bronchiectasis and irregular reticulation without macronodular honeycombing (Figure E1 and E3). The radiological features were consistent with nonspecific interstitial pneumonia patterns with acute exacerbation of ILD, so we administered corticosteroid pulse therapy based on the treatment of acute exacerbation of ILD [21]. On the other hand, patient 2 had relatively short-term and mild hypoxemia and a lower KL-6 level. CT imaging showed mainly organizing pneumonia patterns (Figure E2) [22]. However, the patient had high-grade fever, dyspnea, and a high CRP level; therefore, we administered corticosteroid pulse therapy with the expectation of early systemic inflammatory improvement. An adaption of corticosteroid pulse therapy needs to be further discussed to avoid complications associated with exposure to a large amount of corticosteroids. Serological markers and radiological interstitial lung patterns might be treatment strategies for pulmonary fibrosis secondary to COVID-19.

Interestingly, all three patients had diabetes mellitus (DM). DM has the potential to be associated with ILD [23], and impaired glucose tolerance might be one of the risk factors for pulmonary fibrosis secondary to COVID-19. To develop treatments for fibrosis secondary to COVID-19, we need further studies, especially regarding the molecular mechanisms.

Authorship statement

Kiyoshi Uemasu: Writing- Original draft, Review and editing, Obtaining the informed consent of the patients described in the case report, Review of patient’s medical file.
Yuto Yasuda: Writing - Review & Editing & Obtaining the informed consent of the patient described in the case report.
Yutaka Hirayama: Writing - Review & Editing.
Soichi Arasawa: Writing - Review & Editing.
Daisuke Iwashima: Writing - Review & Editing.
Ken-ichi Takahashi: Writing - Review & Editing, Supervision.

Declaration of competing interest

All the authors have no conflict of interest to declare.

Patient consent statement

This work was performed following local law and ethical considerations. The patients described in this article have provided informed consent for the publication of their cases.

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Appendix A. Supplementary data

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References

[1] Jamil S, Mark N, Carlos G, Cruz CSD, Gross JE, Pannick S. Diagnosis and management of COVID-19 disease. Am J Respir Crit Care Med 2020;201(10):P19–20.
[2] Okahama A, Ishikane M, Hotta M, Sato L, Akiyama Y, Morioka S, et al. Clinical and radiological findings of silent hypoxia among COVID-19 patients. J Infect Chemother 2021;27(10):1536–8.
[3] Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalization: a prospective study. The Lancet Respiratory medicine 2021;9(7):747–54.
[4] Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies. Pulm Med 2020;2020:6179664.
[5] McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol 2021;320(2):L257–L265.
[6] Bogliani C, Ravaglia C, Chioloni M, Rostì G, Dubini A, Pedica F, et al. COVID-19 interstitial pneumonia: histological and immunohistochemical features on cryobiopsies. Respiratation 2021;100:488–98.
[7] Myall KJ, Mukherjee B, Cantasteiri A, Lam JL, Benedetti G, Mak SM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Am Am Thorac Soc 2021;18(5):799–806.
[8] Rosas J, Lianio FP, Cantó ML, Barea JMC, Bener AR, JTA Rabasa, et al. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to coronavirus COVID19: a real-world study. Reumatol Clinica 2020;20(3):1258X(1620). 30271-30276.
[9] Drake TM, Doherty AB, Harrison EM, Quint JK, Adamahi H, Agnew S, et al. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. Am J Respir Crit Care Med 2020;202(12):1565–62.
[10] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology 2020;295(3):715–21.
[11] Yun Y, Wang Y, Hao Y, Xu L, Cai Q. The time course of chest CT lung changes in COVID-19 patients from onset to discharge. Eur J Radiol Open 2021;8.
[12] Ferrara F, Granata G, Pelliccia C, La Porta R, Vittello A. The added value of pitirifedone to fight inflammation and fibrotic state induced by SARS-CoV-2 : anti-inflammatory and anti-fibrotic therapy could solve the lung complications of the infection? Eur J Clin Pharmacol 2020;76(11):1615–8.
[13] Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, Collen JF. Post-COVID-19 pulmonary fibrosis: novel sequelae of the current pandemic. J Clin Med 2021;10(11):2452.
[14] Mandal S, Barnett J, Brill SE, Brown JS, Dennesen EK, Hare SS, et al. Long-COVID: a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021;76(4):396–8.
[15] Miyazato Y, Morioka S, Tsuzuki S, Akashi M, Osanai Y, Tanaka K, et al. Prolonged and late-onset symptoms of coronavirus disease 2019. Open Forum Infect Dis 2020;7(11):soa2507.
[16] George PM, Borratt SL, Condiffe R, Desai SR, Devaraj A, Forrest J, et al. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax 2020;75(11):1099–106.
[17] Vázquez I, Husain-Syed F, Dorfmueller P, Roller FC, Tello K, Hecker M, et al. Severe organising pneumonia following COVID-19. Thorax 2021;76(2):201.
[18] Kosters-Nosal S, Ia&uacute;zubi&aelig;ki D, Chyra M, Kubicki P, Zielinski M, Zora D. A prolonged steroid therapy may be beneficial in some patients after the COVID-19 pneumonia. Eur Respir J 2021;8(11):1945186-1945186.
[19] Sinha A, Bagga A. Pulse steroid therapy. Indian J Pediatr 2008;75(10):1057–66.
[20] Beck IME, Vanden Berghe W, Vermeulen L, Yamamoto KR, Haegeman G, De Bosscher K. Crotstall in inflammation: the interplay of glucocorticoid receptor-based mechanisms and kinases and phosphatases. Endocr Rev 2009;30(7):830–82.
[21] Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J 2021;57(2):356–63.
[22] Mueller-Mang C, Grome C, Schmid K, Stiebelerlhen L, Blancke AA. What every radiologist should know about idiopathic interstitial pneumonias. Radiographics 2007;27(3):595–615.
[23] Rajasuriya V, Gunasekarar K, Surani S. Interstitial lung disease and diabetes. World J Diabetes 2020;11(8):351–7.