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. 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-
6: 1462 U/L, SP-D: 161 U/L) (also see Table 1). 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.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Biochemistry</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Immunology</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/μL)</td>
<td>11930</td>
<td>14670</td>
<td>8800</td>
<td>AST (IU/L)</td>
<td>110</td>
<td>18</td>
<td>24</td>
<td>CRP (mg/dl)</td>
<td>14.09</td>
<td>20.73</td>
<td>4.84</td>
</tr>
<tr>
<td>Neut</td>
<td>89.3%</td>
<td>80.6%</td>
<td>70.3%</td>
<td>ALT (IU/L)</td>
<td>154</td>
<td>35</td>
<td>23</td>
<td>KL-6 (U/L)</td>
<td>1462</td>
<td>595</td>
<td>4680</td>
</tr>
<tr>
<td>Lym</td>
<td>5.6%</td>
<td>7.4%</td>
<td>12.1%</td>
<td>ALP (IU/L)</td>
<td>481</td>
<td>216</td>
<td>280</td>
<td>SP-D (ng/ml)</td>
<td>161</td>
<td>N/M</td>
<td>482</td>
</tr>
<tr>
<td>Mo</td>
<td>4.1%</td>
<td>11.2%</td>
<td>11.2%</td>
<td>LDH (IU/L)</td>
<td>336</td>
<td>239</td>
<td>343</td>
<td>IgA (mg/dl)</td>
<td>314</td>
<td>444</td>
<td>566</td>
</tr>
<tr>
<td>Eo</td>
<td>0.5%</td>
<td>0.5%</td>
<td>5.9%</td>
<td>BUN (mg/dl)</td>
<td>10</td>
<td>14</td>
<td>12</td>
<td>IgG (mg/dl)</td>
<td>1260</td>
<td>940</td>
<td>1208</td>
</tr>
<tr>
<td>Baso</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.9%</td>
<td>Cr (mg/dl)</td>
<td>0.65</td>
<td>0.77</td>
<td>0.64</td>
<td>IgM (mg/dl)</td>
<td>73</td>
<td>91</td>
<td>77</td>
</tr>
<tr>
<td>RBC (X10⁶/μL)</td>
<td>398</td>
<td>405</td>
<td>463</td>
<td>CK (IU/L)</td>
<td>66</td>
<td>23</td>
<td>44</td>
<td>C3 (mg/dl)</td>
<td>185</td>
<td>163</td>
<td>141</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.7</td>
<td>12.3</td>
<td>14.7</td>
<td>TP (g/dl)</td>
<td>6.5</td>
<td>6.4</td>
<td>6.7</td>
<td>C4 (mg/dl)</td>
<td>41</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>Pt (sec)</td>
<td>36.0%</td>
<td>38.0%</td>
<td>43.6%</td>
<td>Alb (g/dl)</td>
<td>2.6</td>
<td>2.7</td>
<td>2.8</td>
<td>Complement, Total (CH50/mL)</td>
<td>29.0</td>
<td>48.8</td>
<td>48.4</td>
</tr>
<tr>
<td>Plt (X10³/μL)</td>
<td>131</td>
<td>232</td>
<td>257</td>
<td>Ferritin (ng/ml)</td>
<td>721</td>
<td>N/M</td>
<td>1285</td>
<td>RF (U/mL)</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Coagulation</td>
<td>K (mEq/l)</td>
<td>3.7</td>
<td>4.3</td>
<td>3.9</td>
<td>MPO-ANCA (U/mL)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (sec)</td>
<td>11.9</td>
<td>N/M</td>
<td>11.7</td>
<td>Cl (mEq/l)</td>
<td>100</td>
<td>94</td>
<td>99</td>
<td>Antiinuclear antibodies</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>36.4</td>
<td>N/M</td>
<td>29.3</td>
<td>Ca (mg/dl)</td>
<td>8.8</td>
<td>8.3</td>
<td>9.3</td>
<td>Antiinuclear antibodies</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>D-Dimer (ng/ml)</td>
<td>2.6</td>
<td>N/M</td>
<td>1.3</td>
<td>FBS (mg/dl)</td>
<td>126</td>
<td>238</td>
<td>106</td>
<td>Antiinuclear antibodies</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>HbA1c (%; NGSP)</td>
<td>6.8</td>
<td>8.2</td>
<td>7.6</td>
<td>Antiinuclear antibodies</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-pro BNP (pg/ml)</td>
<td>517</td>
<td>N/M</td>
<td>397</td>
<td>Antiinuclear antibodies</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

The respiratory symptoms and imaging abnormalities caused by COVID-19 may be prolonged [4,14,15]. Imaging abnormalities are improved without specific treatments in some cases [14], and corticosteroid therapy has the potential to improve respiratory symptoms and radiological changes in persistent post-COVID-19 ILD [7,16]. Although the regimen of corticosteroid therapy for post-COVID-19 ILD has not been established yet, in some case reports, a systemic corticosteroid therapy with prednisolone at a dose of 0.5–1.0 mg/kg/day with or without corticosteroid pulse therapy was performed as an initial therapy [17,18]. Recently, baricitinib and tocilizumab monotherapy or combined therapy was also found to have the potential to improve ILD secondary to COVID-19 [8].

In our patients, high-dose corticosteroid therapy prevented the worsening of post-COVID-19 ILD and improved respiratory failure, and the steroid dose was reduced steadily. We plan to taper off the steroid if...
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 genomic 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 images indicating traction bronchiectasis and irregular reticulation without macrocystic nongenomic glucocorticoid activities [19,20]. When comparing our three cases, patients 1 and 3 had similar clinical features: acute and prolonged hypoxemia, high KL-6 levels, and CT images indicating traction bronchiectasis and irregular reticulation without macrocystic nongenomic glucocorticoid activities [19,20].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.11.010.

References