COVID-19 in Patients With Connective Tissue Disease-related Interstitial Lung Disease

To the Editor:

Infection with the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manifests in a myriad of ways, ranging from asymptomatic disease to pneumonia and acute respiratory distress syndrome. Advanced age and underlying cardiovascular/pulmonary conditions appear to increase the risk for COVID-19 complications. Patients with connective tissue disease–related interstitial lung disease (CTD-ILD) may represent a vulnerable patient population for COVID-19 given their diminished pulmonary reserve. To our knowledge, there are no prospective data reporting outcomes of SARS-CoV-2 infection in patients with CTD-ILD. We herein present all known cases (n = 4) of COVID-19 in patients with CTD-ILD at the University of California Los Angeles (UCLA) between January 2020 and August 2020. Ethics approval was not obtained for this study. The UCLA Institutional Review Board does not consider case studies to be research as defined by federal regulations. We obtained all patients’ written informed consent to publish the material.

Case 1: Systemic sclerosis–related ILD. EL is a 55-year-old Latina female with pulmonary hypertension and progressive systemic sclerosis–related (SSc) ILD receiving mycophenolate mofetil (MMF) 1 g twice per day for 5 years (Table 1). In early April 2020, the patient developed fevers, malaise, sore throat, cough, and dyspnea after exposure to her son-in-law who tested positive for SARS-CoV-2 by nasopharyngeal swab. She self-quarantined, discontinued AZA (Table 1). On Day 15, her dyspnea worsened, and she was admitted to the hospital for hypoxia. Her labs were notable for the following: white blood cell count 4.0 × 10³/uL, lymphocyte count 0.4 × 10³/uL, ferritin 1960 ng/mL, C-reactive protein (CRP) 11 mg/dL, and erythrocyte sedimentation rate 52 mm/h. She was treated with inhaled racemic epinephrine, magnesium sulfate, and oxygen. One day after admission, her oxygen saturation remained within normal limits on ambient air. Her symptoms resolved after 3 weeks. Her friend who did not have CTD-ILD also tested positive for SARS-CoV-2 by nasopharyngeal swab and died 5 days later. Two months after her initial illness, EL regained her baseline supplemental oxygen requirements of 3–5 L. On April 24, she tested positive for IgG antibodies to SARS-CoV-2. A high-resolution computed tomography (HRCT) scan of the chest demonstrated overall unchanged moderate to severe ILD without evidence of ground glass opacity or consolidations. MMF was reinitiated, and the patient has experienced no subsequent sequela of COVID-19 in the 3 months following her illness.

Case 2: SSc-ILD. RD is a 66-year-old Latina female with obesity, diabetes mellitus, and SSc-ILD taking mycophenolic acid (MPA) 760 mg twice per day for 1 year (Table 1). In early March 2020, she accompanied her friend on a 15-h flight and shared a room with her on a 10-day cruise. On Day 4 of the cruise, they both developed fevers, myalgias, nausea, diarrhea, cough, loss of taste, and dyspnea. Upon disembarking from the cruise, she self-quarantined, discontinued MPA, and received support care at home. Her oxygen saturation remained within normal limits on ambient air. Her symptoms resolved after 3 weeks. Her friend who did not have CTD-ILD and was not receiving immunosuppression developed worsening dyspnea, prompting intubation in the emergency department, where she tested positive for SARS-CoV-2 by nasopharyngeal swab and died 5 days later. Two months after her initial illness, RD tested positive for IgG antibodies to SARS-CoV-2. MPA was reinitiated, and the patient has experienced no subsequent sequela of COVID-19 in the 4 months following her illness.

Case 3: Rheumatoid arthritis–ILD. SP is a 70-year-old white female with rheumatoid arthritis (RA) and mild ILD taking azathioprine (AZA) 50 mg daily for 3 years (Table 1, Figure 1A). On March 16, 2020, the patient developed fevers, progressive cough, dyspnea, malaise, and nausea after her husband returned from a ski trip to Vail, Colorado, USA. Both she and her husband tested positive for SARS-CoV-2 by nasopharyngeal swab. She self-quarantined and discontinued AZA (Table 1). On Day 15, her dyspnea worsened, and she was admitted to the hospital for hypoxia. Her labs were notable for the following: white blood cell count 4.0 × 10³/uL, lymphocyte count 0.4 × 10³/uL, neutrophil count 3.4 × 10³/uL, ferritin 1960 ng/mL, C-reactive protein (CRP) 11 mg/dL, and erythrocyte sedimentation rate 44 mm/h. Her oxygen saturation remained within normal limits on ambient air. Her symptoms resolved after 3 weeks. Her husband tested positive for IgG antibodies to SARS-CoV-2. MMF was reinitiated, and the patient has experienced no subsequent sequela of COVID-19 in the 3 months following her illness.

Table 1. Baseline characteristics of patients with CTD-ILD prior to COVID-19 infection.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Race/ethnicity</th>
<th>SSc-ILD</th>
<th>ILD duration, yrs</th>
<th>Radiographic ILD pattern</th>
<th>Autoantibodies</th>
<th>FVC% predicted</th>
<th>DLCO% predicted</th>
<th>TLC% predicted</th>
<th>Immunomodulatory treatment and dosage</th>
<th>Duration of immunomodulatory treatment, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 (EL), SSc-ILD</td>
<td>Female</td>
<td>Latina</td>
<td>55</td>
<td>5</td>
<td>UIP</td>
<td>ANA, Scl-70</td>
<td>52</td>
<td>12</td>
<td>4</td>
<td>MMF 1 g BID</td>
<td>5</td>
</tr>
<tr>
<td>Case 2 (RD), SSc-ILD</td>
<td>Female</td>
<td>Latina</td>
<td>66</td>
<td>7</td>
<td>UIP</td>
<td>ANA, Scl-70</td>
<td>65</td>
<td>53</td>
<td>66</td>
<td>MPA 760 mg BID</td>
<td>3</td>
</tr>
<tr>
<td>Case 3 (SP), RA-ILD</td>
<td>Female</td>
<td>White</td>
<td>70</td>
<td>4</td>
<td>UIP</td>
<td>ANA</td>
<td>150</td>
<td>74</td>
<td>126</td>
<td>AZA* 50 mg daily</td>
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</tr>
<tr>
<td>Case 4 (MF), SSc-ILD</td>
<td>Female</td>
<td>White</td>
<td>56</td>
<td>12</td>
<td>UIP</td>
<td>ANA</td>
<td>50</td>
<td>66</td>
<td>72</td>
<td>MMF 1 g BID</td>
<td>4</td>
</tr>
</tbody>
</table>

* This patient also received rituximab 1000 mg intravenously on Day 0 and Day 15, five months prior to COVID-19. ANA: antinuclear antibodies; AZA: azathioprine; CCP: cyclic citrullinated peptide; COVID-19: coronavirus disease 2019; CTD: connective tissue disease; DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; MMF: mycophenolate mofetil; MPA: mycophenolic acid; NSIP: nonspecific interstitial pneumonia; RA: rheumatoid arthritis; SSc: systemic sclerosis; TLC: total lung capacity; UIP: usual interstitial pneumonia.
with SSc-ILD undergoing treatment with TCZ also experienced a milder course of COVID-19⁶. In a small, retrospective study of 28 ILD patients with COVID-19 (10 of whom had CTD), increased levels of IL-6, IL-1β, and IL-2R were associated with worse clinical outcomes; however, information regarding the underlying CTD and background ILD-targeted therapy was not provided⁷. While further research is needed to understand the best management approach in a patient with CTD-ILD and SARS-CoV-2 infection, background immunomodulatory with MMF/MPA therapy may protect patients from CSS.

Case 4: SSc-ILD. MF is a 56-year-old white female with SSc-ILD receiving MMF 1 g twice per day for 4 years (Table 1). In late July 2020, the patient developed fevers, malaise, and fatigue after exposure to her son, who tested positive by nasopharyngeal swab for SARS-CoV-2. She tested positive for SARS-CoV-2 by nasopharyngeal swab, self-quarantined, discontinued MMF, and received supportive care at home. After 2 weeks, her symptoms resolved, and she reported no change in her respiratory status. At that time, her laboratory tests were notable for a white blood cell count 6.2 × 10³/µL, lymphocyte count 1.8 × 10³/µL, neutrophil count 3.5 × 10³/µL, ferritin 220 mg/mL, CRP 0.4 mg/dL, and ESR 42 mm/h. MMF was reinitiated, and the patient has experienced no subsequent sequela of COVID-19 in the 3 months since her initial hospitalization for COVID-19, she has fully recovered, and her HRCT demonstrates complete resolution of COVID-19 pneumonia (Figure 1C).

Figure 1. Serial axial HRCT images of patient SP (case 3). (A) Obtained June 9, 2019 (10 months prior to COVID-19 infection), demonstrating lower lung predominant subtle subpleural reticulation and textured ground glass attenuation with mild architectural distortion consistent with early CTD-ILD. (B) Obtained during hospitalization for COVID-19 on April 4, 2020, demonstrating mid to lower lung predominant coalescent air space consolidation and ground glass attenuation consistent with COVID-19 pneumonia. (C) Obtained 3 months after hospitalization on July 7, 2020, demonstrating interval resolution of coalescent air space consolidation and ground glass attenuation in both lungs. COVID-19: coronavirus disease 2019; CTD-ILD: connective tissue disease–related interstitial lung disease; HRCT: high-resolution computed tomography.

REFERENCES
3. de Lathouder S, Gerards AH, de Groot ER, Valkhoff M, Aarden LA. Mycophenolic acid and methotrexate inhibit cytokine production...
