

## Covid-19 in Patients with Connective Tissue Disease-Related Interstitial Lung Disease

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**Short Running Head:** Covid-19 in CTD-ILD

## Introduction

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 [1,2]. 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 CTD-ILD patients at UCLA between January 2020 and August 2020.

### Case 1: Systemic sclerosis (SSc)-ILD

EL is a 55-year-old Latina female with pulmonary hypertension and progressive SSc-ILD on mycophenolate mofetil (MMF) 1g 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 by nasopharyngeal swab for SARS-CoV-2. She self-quarantined, discontinued MMF and received supportive care at home. Her symptoms resolved after 3 weeks, and she required no increase in her baseline supplemental oxygen requirements of 3-5 L. On April 24, she tested positive for IgG antibody 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 re-initiated, 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 SSc-ILD on mycophenolic acid (MPA) 760mg twice per day for 1 year (Table 1), obesity and diabetes mellitus. In early March 2020, she accompanied her friend on a 15-hour 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 on immunosuppression developed worsening dyspnea prompting intubation in the emergency department where she tested positive for SARS-CoV-2 by nasopharyngeal swab and expired 5 days later. Two months after her initial illness, RD tested positive for IgG antibodies to SARS-CoV-2. MPA was re-initiated, and the patient has experienced no subsequent sequela of Covid-19 in the 4 months following her illness.

### Case 3: Rheumatoid arthritis (RA)-ILD

SP is a 70-year-old Caucasian female with RA and mild ILD on azathioprine (AZA) 50mg daily for 3 years (Table 1; Figure 1a). On March 16, the patient developed fevers, progressive cough, dyspnea, malaise, nausea after her husband returned from a ski trip to Colorado. Both her and her husband tested positive for SARS-CoV-2 by nasopharyngeal swab. She self-quarantined and discontinued her azathioprine (Table 1). On day 15, her dyspnea worsened, and she was admitted to the hospital for hypoxia. Her labs were notable for: white blood cell count  $4.0 \times 10^3/\mu\text{L}$ , lymphocyte count  $0.4 \times 10^3/\mu\text{L}$ , neutrophil count  $3.4 \times 10^3/\mu\text{L}$ , ferritin 1960 ng/mL, CRP 11 mg/dL, ESR 64 mm/hr. Her HRCT demonstrated evidence of

Covid-19 pneumonia (Figure 1b). On day 2 of hospitalization, her oxygen requirement and inflammatory markers markedly increased suggesting the evolution of cytokine storm syndrome. She was promptly administered tocilizumab 4mg/kg intravenously. By day 8, her oxygen requirements returned to baseline and her inflammatory markers normalized. In the two months since her initial hospitalization for Covid-19, she has fully recovered, and her HRCT demonstrates complete resolution of Covid-19 pneumonia (Figure 1c).

#### **Case 4: SSc-ILD**

MF is a 56-year-old Caucasian female with SSc-ILD on MMF 1g twice per day for 4 years (Table 1). In late July 2020, the patient developed fevers, malaise, fatigue after exposure to her son who tested positive by nasopharyngeal swab for SARS-CoV-2. MF 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  $6.2 \times 10^3/\text{uL}$ , lymphocyte count  $1.8 \times 10^3/\text{uL}$ , neutrophil count  $3.5 \times 10^3/\text{uL}$ , ferritin 220 ng/mL, CRP 0.4 mg/dL, ESR 42 mm/hr. MMF was re-initiated, and the patient has experienced no subsequent sequela of Covid-19 in the 4 weeks following her illness.

#### **Discussion**

The present cases highlight the diverse spectrum of disease manifestations and outcomes of patients with CTD-ILD and Covid-19. The three SSc patients who had more severe ILD and were taking background immunomodulatory therapy with MMF/MPA had a relatively mild disease course and no exacerbation of their underlying ILD. In contrast, the patient with mild

RA-ILD on low dose AZA therapy developed pneumonia and cytokine storm syndrome. The reasons for these disparate outcomes are unknown. It is conceivable that immunomodulator agents with different mechanisms of action may have varying success in curtailing the intensity of inflammatory response to SARS-CoV-2 infection. For instance, studies have demonstrated that MPA inhibits numerous cytokines implicated as key mediators of cytokines storm syndrome including interferon (INF)- $\gamma$ , interleukin (IL)-4, 13, 8, colony-stimulating factors, and tumor necrosis factor (TNF)- $\alpha$  [3]. A single case study demonstrated that a patient with SSc-ILD undergoing treatment with tocilizumab also experienced a milder course of Covid-19 [4]. In a small, retrospective study of 28 ILD patients with Covid-19 (10 of whom had a CTD), increased levels of IL-6, IL-1 $\beta$ , IL-2R were associated with worse clinical outcomes; however, information regarding the underlying CTD and background ILD-targeted therapy was not provided [5]. 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 cytokine storm syndrome.

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**REFERENCES**

1. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. *Lancet* 2020;395:1014-5.
2. Wu C, Chen X, Cai Y, Xai J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:1-11.
3. de Lathouder S, Gerards AH, de Groot ER, Valkhoff M, Aarden LA. Mycophenolic acid and methotrexate inhibit cytokine production via different mechanisms. *Eur Cytokine Netw* 2002;13:317-23.
4. Mihai C, Dobrota R, Schroder M, Garaiman A, Jordan S, Becker MO, et al. Covid-19 in a patient with systemic sclerosis treated with tocilizumab. *Ann Rheum Dis* 2020;79:668-669.
5. Huang H, Zhang M, Chen C, Zhang H, Weit Y, Tian J, et al. Clinical characteristics of Covid-19 in patients with pre-existing ILD: A retrospective study in a single center in Wuhan, China. *J Med Virol* 2020 [Epub ahead of print].



## FIGURE LEGENDS

**Figure 1. Serial axial HRCT images of patient SP.** Figure 1a was obtained June 9, 2019 (10 months prior to Covid-19 infection), and it demonstrates lower lung predominant subtle subpleural reticulation and textured ground glass attenuation with mild architectural distortion consistent with early CTD-ILD. Figure 1b was obtained during hospitalization for Covid-19 on April 4, 2020, and it demonstrates mid to lower lung predominant coalescent air space consolidation and ground glass attenuation consistent with Covid-19 pneumonia. Figure 1c was obtained two months after hospitalization on July 7, 2020, and it demonstrates interval resolution of coalescent air space consolidation and ground glass attenuation in both lungs.

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

	<b>EL (SSc-ILD)</b>	<b>RD (SSc-ILD)</b>	<b>MF (SSc-ILD)</b>	<b>SP (RA-ILD)</b>
<b>Age (years)</b>	55	66	56	70
<b>Sex</b>	Female	Female	Female	Female
<b>Race/Ethnicity</b>	Latino	Latino	Caucasian	Caucasian
<b>ILD duration (years)</b>	5	7	12	4
<b>Radiographic ILD pattern</b>	UIP	NSIP	UIP	UIP
<b>Auto-antibodies</b>	ANA Scl-70	ANA Scl-70	ANA	ANA CCP
<b>FVC% Predicted</b>	52	65	72	150
<b>DLCO% Predicted</b>	12	53	43	74
<b>TLC% Predicted</b>	44	66	66	126
<b>Immuno-modulatory treatment and dosage</b>	Mycophenolate mofetil 1 g BID	Mycophenolic acid 760 mg BID	Mycophenolate mofetil 1 g BID	Azathioprine* 50 mg daily

<b>Duration of immune- modulatory treatment (years)</b>	5	1	4	3
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\* This patient also received rituximab 1000 mg intravenously on day 0 and 15, five months prior to Covid-19.

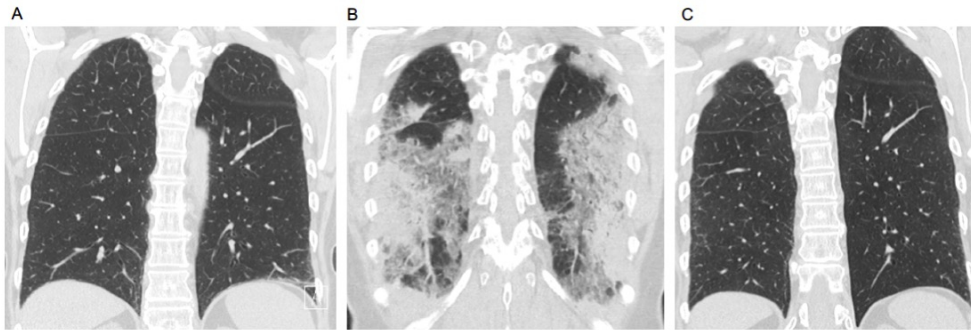


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