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Acute Exacerbation of Interstitial Lung Disease as a Sequela of COVID-19 Pneumonia

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INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of disorders characterized by dyspnea and bilateral infiltrations of the lung. While some cases are idiopathic (e.g., idiopathic pulmonary fibrosis), others are associated with systemic illnesses (e.g., autoimmune disorders), environmental exposures (e.g., asbestosis, hypersensitivity pneumonitis), or drug-induced, among other causes.[1] In general, ILD results from inflammation and excessive accumulation of connective tissue matrices in the interstitium of the lung.[2] Exacerbations with rapid progression resulting in increased dyspnea, increased oxygen supplementation requirements, and respiratory failure have been described in idiopathic pulmonary fibrosis and other types of ILDs.[3] Surgery, aspiration of gastric contents, infection, and other factors has been proposed to contribute to ILD exacerbation. Viral infection has been implicated as an important cause of ILD and of ILD exacerbation, but the viruses involved and the mechanisms triggered during an exacerbation remain poorly elucidated.[4] Recent concerns have been raised by the potential impact of the COVID-19 pandemic on ILD, mainly because of its propensity to cause severe lung injury in older individuals and in individuals with pre-existing lung disease. COVID-19 is caused by the novel β coronavirus SARS-CoV-2.[5] Here, we present a case of a patient with Rheumatoid Arthritis (RA) associated ILD (RA-ILD) recently hospitalized due to COVID-19. We first summarize the case and discuss the literature followed by a discussion of gaps in knowledge in need of further investigation.

CASE

A 60-year-old woman with RA presented with six days of dyspnea on exertion associated with a dry cough. In the weeks prior, the patient noted malaise, subjective fevers, and upper respiratory symptoms. Consistent with guidelines developed to address the COVID-19 pandemic, she reported self-quarantine and keeping her distance away from other family members. In the two days prior to presenting to the hospital, the patient became severely limited in her ability to ambulate within her home resulting in prompt medical evaluation. A review of the patient's history revealed that she was a remote smoker (20 pack-year) and carried diagnoses of type II diabetes mellitus, obstructive sleep apnea (not compliant with treatment), and heart failure with preserved ejection fraction. The patient had also been diagnosed with RA-ILD with Computed Tomography (CT) scan images showing infiltrates with peripheral and basilar predominance and some honey combing, which was interpreted as consistent with a usual interstitial pneumonitis or UIP pattern (Fig. 1A). She was being treated with azathioprine; however, she had recently discontinued the medication prior to the hospitalization due to subjectively stable disease. Most recent pulmonary function tests from 9 months prior showed normal forced vital capacity (2.25 l; 83% predicted) and forced expired volume in first second (1.74 l, 81% predicted), reduced total lung capacity (3.34 l, 67% predicted), and significant reduction in DLCO (10.1 mL/min/mmHg; 47% of expected) consistent with moderate restriction and impaired gas exchange.

Upon arrival to the emergency department, the patient was afebrile, had a heart rate of 97, a respiratory rate of 26 breaths per minute, and a low hemoglobin oxygen saturation of 79% on room air. She was speaking in full sentences and physical examination revealed digital clubbing and velcro-like crackles in both lung bases. Hemoglobin oxygen saturation improved to 97% on 12 L/min of oxygen supplementation via nasal cannula. CT of the chest was notable for progression of ILD compared to prior CT ten months prior in addition to superimposed ground glass opacities in a peripheral and basilar distribution (Fig. 1B). Laboratory data were notable for a lack of leukocytosis, elevated ESR and CRP, and SARS-CoV-2 RNA positive nucleic acid amplification test (NAAT).

Patient was treated for community-acquired pneumonia with ceftriaxone. Because she presented during the early part of the pandemic, she was treated with hydroxychloroquine for COVID-19. Due to concerns for ILD exacerbation, she was also administered methylprednisolone 40 mg IV every 8 h with a quick taper. The patient showed improvement over the next few days and was discharged home requiring 4 L/min of oxygen supplementation. She was also re-started on azathioprine,

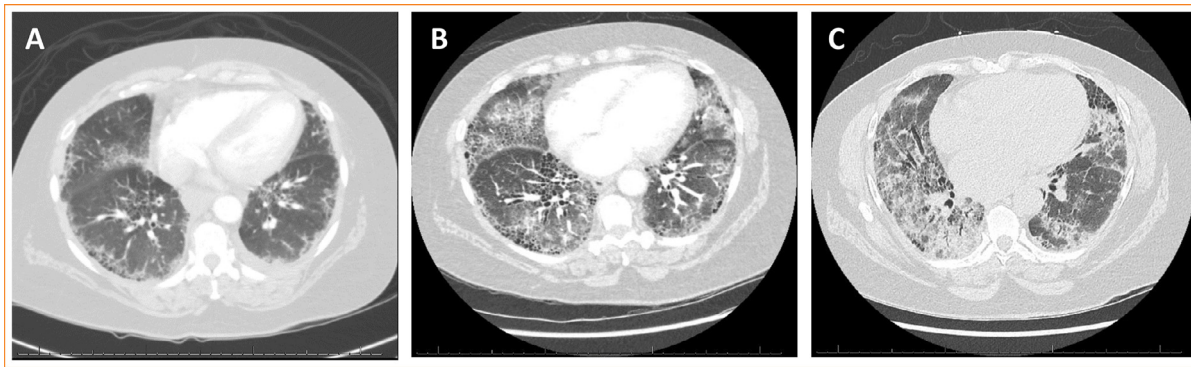

FIGURE 1. Chest CT scan of patient with RA-ILD and COVID-related exacerbation. A, Baseline chest CT scan showing bilateral and peripheral infiltrates with some areas of honey combing interpreted as consistent with UIP pattern. B, Chest CT scan during hospitalization showing bilateral ground glass opacities with underlying ILD. C, Chest CT scan obtained during second hospitalization showing worsening of infiltrates.
Abbreviations: CT, Computed Tomography; ILD, interstitial lung disease; RA-ILD, rheumatoid arthritis associated interstitial lung disease.

although dose was lowered due to concern of co-existing infection.

One-week after discharge, the patient was re-hospitalized because of several days of worsening dyspnea on exertion, sputum production, and a home pulse oximetry showing hemoglobin oxygen desaturation down to 82% despite oxygen supplementation. Oxygenation improved to 98% on 50 L/min at 70% FiO2. A repeat chest CT was notable for interval progression of patchy airspace opacities and consolidations, with no thromboembolism (Fig. 1C). Most inflammatory markers, except CRP, were reduced when compared to the prior hospitalization suggesting her deterioration was not related to COVD-19. She was treated for hospital-acquired pneumonia and given methylprednisolone 40 mg IV every 12 h for possible ILD flare. She was continued with azathioprine. Despite the above, her condition deteriorated, ultimately requiring non-invasive ventilation and transfer to the intensive care unit for surveillance. With continuing antibiotics and corticosteroids followed by taper, the patient improved without requiring intubation and mechanical ventilation. She returned to using 4 L/min of supplemental oxygen and was discharged home with supplemental oxygen. A repeat transthoracic echocardiogram performed after discharge showed mildly decreased left ventricular systolic function with global hypokinesis and estimated ejection fraction of 45–50%. One month after the hospitalization, the patient was still requiring oxygen supplementation and her pulmonary function tests showed deterioration when compared to the prior year (FVC 1.98 L, FEV1 1.65 L, TLC 3.79 L, DLCO 8.2 mL/min/mmHg).

DISCUSSION

We report the case of a woman with RA-ILD who was admitted with acute hypoxemic respiratory failure in the setting of COVID-19. ILD is increasingly being recognized as a manifestation of RA and is associated with significant morbidity and mortality.[6] However, one third of patients are believed to have subclinical disease, which delays diagnosis and intervention. Interestingly, connective tissue disorders like RA are well known to affect women predominantly.[7] However, the development of ILD in the setting of RA is more common in men.[8] Hormonal differences have been suggested, but this requires further investigation.[7]

The co-existence of ILD and COVID-19 has been reported, and others have postulated that patients with COVID-19 respiratory illness may be at risk for developing long-term respiratory problems, such as ILD.[9] In individuals with underlying ILD, COVID-19 has prompted a number of challenges such as diagnostic uncertainty in the setting of underlying chronic lung disease; restricted access to diagnostic procedures, care, and monitoring; and uncertainties about the impact of immunosuppressive agents.[10] Our case of an acute exacerbation of RA-ILD associated with COVID-19 raises a number of important concepts.

First, chronic lung diseases like COPD and ILD are known to render the host susceptible to viral infections, and respiratory viral infections have been linked to ILD and ILD exacerbations even though the exact relationship between viruses and such events is unknown.[11] In general, ILD exacerbations portend a worse prognosis.[12] This case fulfills criteria for ILD exacerbation (subacute worsening of dyspnea and hypoxemia, new pulmonary infiltrates on chest imaging, and absence of cardiac failure, pulmonary emboli, and other potential non-pulmonary causes) and the presence of SARS-CoV-2 infection points to it being the culprit, but a cause and effect relationship is difficult to confirm and other factors could have contributed to the presentation including concerns about medication non-adherence. Nevertheless, others have reported pulmonary fibrosis in patients who have succumbed with infection with a related Coronavirus, SARS-CoV.[13]

Second, as was done in this case, patients with connective tissue related ILD are often treated with corticosteroids and/or other immunosuppressive agents. The same is true for patients with ILD exacerbation. However,

during the early part of the pandemic, there were concerns about the use of corticosteroids in patients with COVID-19 as they were presumed to reduce resistance against the virus. To date, there are no data to support this assumption. In fact, others have reported a case of exacerbation of acute lupus pneumonitis with superimposed COVID-19 where administration of methylprednisolone was perceived as beneficial[14] and a recent meta-analysis suggest that they are likely to be safe and beneficial, particularly in patients with severe respiratory disease.[15]

Third, it is assumed that outcomes in COVID-19 are worse in cases with co-morbidities such as hypertension and diabetes. However, we do not know if coexistent connective tissue disorders like rheumatoid arthritis result in worse prognosis, especially in COVID-19 patients requiring hospitalization. Others have evaluated the presentation of COVID-19 in subjects with rheumatic disorders and found that the presence of respiratory failure was more common in such cases. However, they failed to observe differences in hospital length of stay and mortality rates when compared to COVID-19 patients without rheumatic disorders.[16] Cardiac dysfunction should also be considered, especially since SARS-CoV-2 has been reported to cause myocarditis.[17] Our patient showed a mild deterioration in heart function based on a repeat echocardiogram, but the impact of this change and its cause remain unclear.

Fourth, aging patients with COVID-19 carry a worse prognosis, but the exact mechanisms responsible for this association are unknown. The existing paradigm is that aging compromises the ability of the lung epithelium to regenerate after injury. However, aging has also been linked to the development of ILD through oxidative stress, impaired proteostasis, mitochondrial dysfunction, and immune abnormalities, among other factors.[18] Moreover, in a small study with Rhesus Macaque monkeys infected with SARS-CoV-2, viral replication appeared more active in older animals when compared to young ones, and these monkeys exhibited worse diffuse interstitial infiltrates.[19]

Finally, it is intriguing to hypothesize that COVID-19 infection will lead in some cases to progressive fibrosing lung disease. This, of course, remains speculative, as there are insufficient long-term follow up data. Nevertheless, in such conditions, anti-fibrotic drugs might prove beneficial.[20] This is particularly relevant considering that one such drug, nintedanib, has recently been found to delay progression in several progressive fibrosing lung disorders.[21] It is intriguing to note that the SARS-CoV-2 spike protein contains an Arg-Gly-Asp (RGD) amino acid integrin binding sequence and Coronaviruses contain an N-terminal galectin fold, which might be targeted with novel reagents currently being tested in lung fibrosis.[20]

In short, this case presented a number of challenges, but mostly raised important questions that remain unanswered. For example, what is the link between ILD or ILD exacerbation and COVID-19? Are patients with connective tissue disorders more susceptible to COVID-19? Are immunosuppressive agents helpful in the management of COVID-19 and especially in cases with underlying ILD? Can SARS-CoV-2 lead to irreversible and progressive pulmonary fibrosis and would anti-fibrotic agents be helpful under such circumstances? A close follow up of these patients after recovery from the acute event, with repeated pulmonary function tests and imaging studies, is likely to provide insights in this area. While research continues in the field, it is important that we stress the importance considering COVID-19 in cases with ILD exacerbation.

AUTHOR CONTRIBUTIONS

Fonseca collected data and Summer and Roman assisted with analysis and manuscript writing.

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