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Letter

Infection or Autoimmunity? The Clinical Challenge of Interstitial Lung Disease in Systemic Sclerosis During the COVID-19 Pandemic

To the Editor:

The novel coronavirus disease 2019 (COVID-19) pandemic is a world emergency that may inevitably complicate the clinical scenario of interstitial lung disease (ILD) secondary to systemic sclerosis (SSc)[1,2]. The striking similarities in computed tomography (CT) between the 2 diseases make it difficult to distinguish a worsening of SSc-ILD from a COVID-19 superinfection[2]. For this reason, we present a case of a 67-year-old woman affected by limited cutaneous SSc with anticentromere antibody positivity, characterized by Raynaud phenomenon for 10 years, and skin involvement but no ILD or pulmonary hypertension. She was treated with symptomatic drugs but no immunosuppressive therapy. According to national and local regulations, approval by the ethics committee is not required for a case report. We obtained the patient's informed consent to publish the material.

The patient was seen in January 2020 because of mild fever (37.5°C), malaise, and cough. First, she was treated with ampicillin/minocycline. Due to symptom persistence, she underwent a lung CT, which revealed bilateral, multilobar, rounded ground-glass opacities (GGO), in both the upper and lower lobes (Figure 1A). Initially, the upper lobe involvement raised the suspicion of a pulmonary infection. However, the predominant peripheral, symmetrical, and basal distribution of GGO areas could not rule out the suspicion of early SSc-ILD. Given the ongoing pandemic, a COVID-19 reverse transcription PCR test was performed, with a positive result. Her symptoms spontaneously improved without any additional treatment and she was discharged 3 weeks later. After 8 weeks, a CT confirmed a significant improvement (Figure 1B) and the features seen on the previous CT were considered related to COVID-19 pneumonia. Due to the very limited CT residuals and the complete recovery of the patient, a further control CT was not performed.

This clinical case raises the question of whether CT findings were due to SSc-ILD, COVID-19 pneumonia, or their coexistence. The presence of ILD may expose a patient with SSc to a more severe evolution of the COVID-19 superinfection[1,2]. Few SSc cases with COVID-19 have been reported. Out of 3 patients with SSc (without ILD and treated with rituximab) with COVID-19 pneumonia, 2 evolved to respiratory failure but they fully recovered[3]; the other died, despite intensive care intubation and tocilizumab (TCZ) treatment[4]. Another SSc patient, treated with TCZ, with mild CT features consistent with COVID-19 pneumonia, promptly recovered and, for safety reasons, the therapy was delayed for 1 month[5]. In all these cases, the CT pattern was not discussed. Recently, another case of an SSc patient without ILD was described. He progressed to critical COVID-19 and a CT scan revealed patchy bilateral GGO and grid shadows suggesting interstitial pneumonia[6]. In patients with SSc-ILD, the concern is that some CT features are shared with COVID-19 pneumonia and, in some cases, hard to distinguish[2]; in both diseases, bilateral GGO with subpleural involvement are the most frequent alterations. In the last decades, a multitude of work has described in detail the CT features of SSc-ILD[7]. Over time, GGO is replaced with reticulations and honeycombing (Figure 2D–F). In COVID-19 pneumonia, bilateral GGO usually evolves into consolidations, also in the upper lobes (Figure 2A–C)[8,9], and 3 categories have been identified[9]. In the early stage, GGO is the main sign, usually in the lower lobes (Figure 2A), which can progressively increase and evolve into consolida-

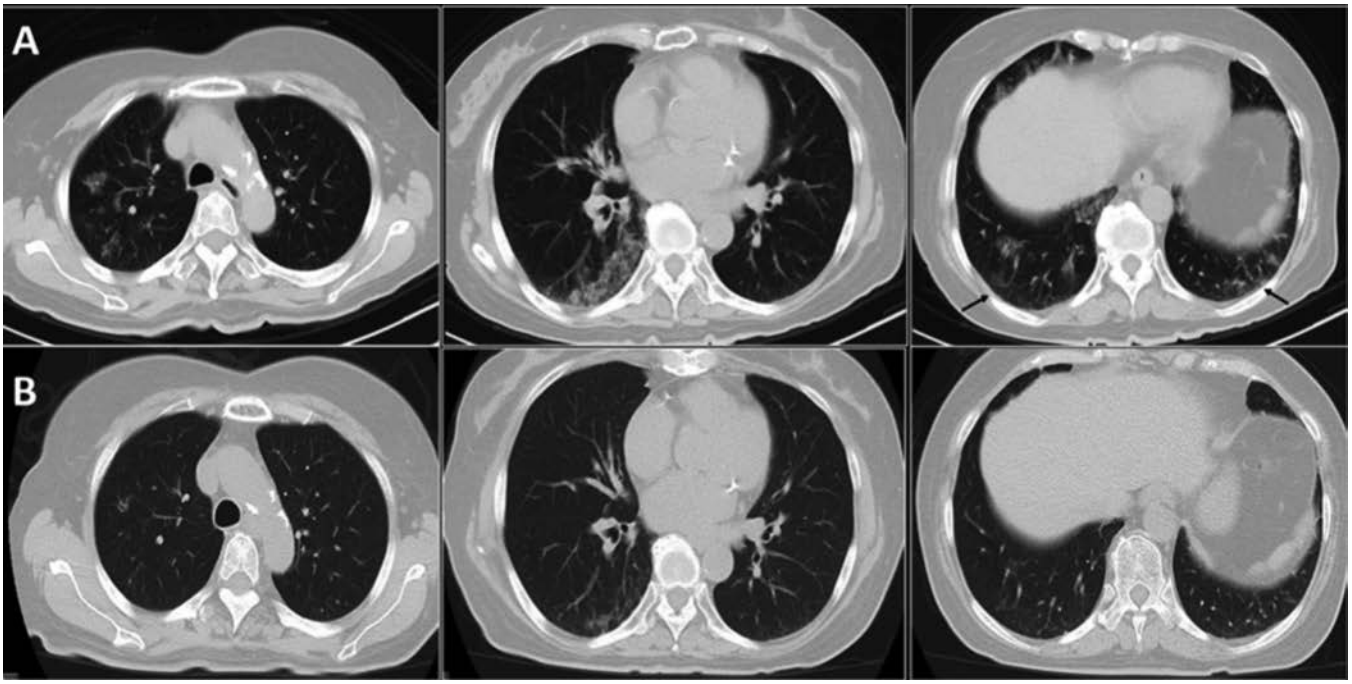

Figure 1. CT scans of a patient with SSc and COVID-19 at presentation and during follow-up. (A) Multiple, bilateral GGO, some with rounded morphology, with a predilection for lower lobes and a peripheral predominance. These features are consistent with a typical radiologic appearance of COVID-19 pneumonia. However, the coexistence of NSIP with SSc cannot be ruled out, especially at lung bases, where GGO are subpleural and symmetric (black arrows). (B) After 8 weeks, GGO are decreased in both extension and density. COVID-19: coronavirus disease 2019; CT: computed tomography; GGO: ground-glass opacities; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis.

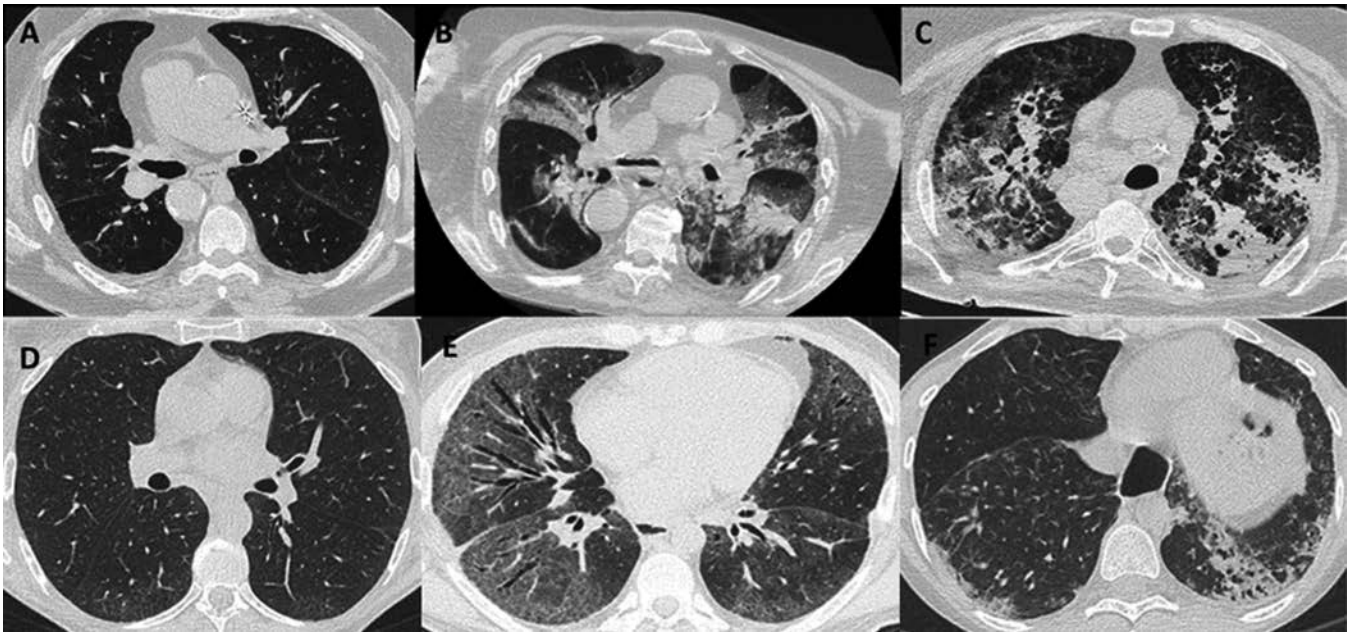

Figure 2. CT scans of (A–C) 3 COVID-19 patients, and (D–F) 3 SSc patients in different phases of disease. (A) Multiple, bilateral GGO, with peripheral predominance in an early phase of disease. (B) Patchy GGO and bilateral consolidations retracting adjacent pleura in a patient in an advanced phase. (C) Wide consolidations, diffuse GGO, and bronchiectasis in a severe case after several days of hospitalization. (D) Typical appearance of ILD in SSc characterized by peripheral GGO with basal predominance. Note in this case the focal GGO in the azygos-esophageal recess and in the contralateral lung next to the descending aorta. (E) Patchy GGO with fine reticulations and traction bronchiectasis bilaterally. Note the unaffected areas next to severely affected areas, similarly to (B). (F) Coarse reticulations in peripheral regions and consolidations along the bronchovascular bundle in the left lower lobe, consistent with SSc-ILD with areas of organizing pneumonia. COVID-19: coronavirus disease 2019; CT: computed tomography; GGO: ground-glass opacities; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; SSc: systemic sclerosis.

tions (Figure 2B–C). In the intermediate stage, interlobular septal thickening and crazy-paving pattern can also appear. In severe cases, extensive consolidations, parenchymal bands, and "white lungs" can be seen. Finally, in the dissipative phase, GGO and consolidations decrease, disappearing or evolving into fibrosis (Figure 2C). At CT evaluation, the early distribution in the superior lobes of patchy GGO, crazy paving, and consolidations are not typical of SSc-ILD and might suggest a COVID-19 infection. Moreover, the rate of progression is different. In SSc-ILD, the progression is from chronic to subchronic, leading to death in several years[7], whereas in COVID-19 pneumonia, an acute stage potentially leads to respiratory failure and death in few days or weeks[10]. From the pathogenetic point of view, SSc-ILD likely originates from a dysregulation of the immune system[7], whereas an acute inflammation contributing to a diffuse alveolar damage lies behind COVID-19 pneumonia[10]. Finally, despite the clinical presentation being similar and characterized by dyspnea, fatigue, and nonproductive cough, the presence of fever and the rapid decrease of respiratory function should suggest high suspicion of a COVID-19 infection[10].

In conclusion, lung CT has a crucial role in the diagnostic algorithm to suspect COVID-19 pneumonia. However, none of the CT features of COVID19 seem to be specific or pathognomonic, being common in other noninfectious diseases, such as in connective tissue disease–associated ILD. Thus, even if COVID-19 pneumonia may show a typical pattern, radiologists should always consider clinical data and keep in mind a tight differential diagnosis, with the support of the rheumatologist. Future research agenda should focus on long-term follow-up of patients infected with COVID-19, to test if the acute viral disease will turn into chronic ILD, and if a COVID-19 infection could operate as a disease-phenotype modifier.

Martina Orlandi[1], MD
Nicholas Landini[2,3], MD
Cosimo Bruni[1], MD
Stefano Colagrande[3], MD
Marco Matucci-Cerinic[1], MD, PhD
Musataka Kuwana[4], MD

[1]Department of Experimental and Clinical Medicine, University of Florence, and Division of Rheumatology AOUC & Scleroderma Unit, Florence, Italy;
[2]Department of Radiology, Ca' Foncello General Hospital, Piazzale Ospedale, 1, Treviso, and Department of Experimental and Clinical Biomedical Sciences, University of Florence-Azienda Ospedaliero-Universitaria Careggi, Florence, Italy;
[3]Department of Experimental and Clinical Biomedical Sciences, University of Florence and Radiodiagnostic Unit n. 2 AOUC, Florence, Italy;
[4]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan.

Address correspondence to Dr. M. Orlandi, Department of Clinical and Experimental Medicine, University of Florence, & Department of Geriatric Medicine, Division of Rheumatology AOUC, Padiglione 28c Ponte Nuovo, piano 1, Via delle Oblate, 4, Florence, Italy.
Email: martina.orlandi@unifi.it.

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