RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Case report)

Rheumatology Advances in Practice 2022;00:1–3
https://doi.org/10.1093/rap/rkac063
Advance Access Publication 26 July 2022

Whatever 'smells' like COVID-19 is not always COVID-19

Key message

- Interstitial lung disease associated with anti-synthetase syndrome (anti-PL7) can mimic post-coronavirus disease 2019 syndrome.

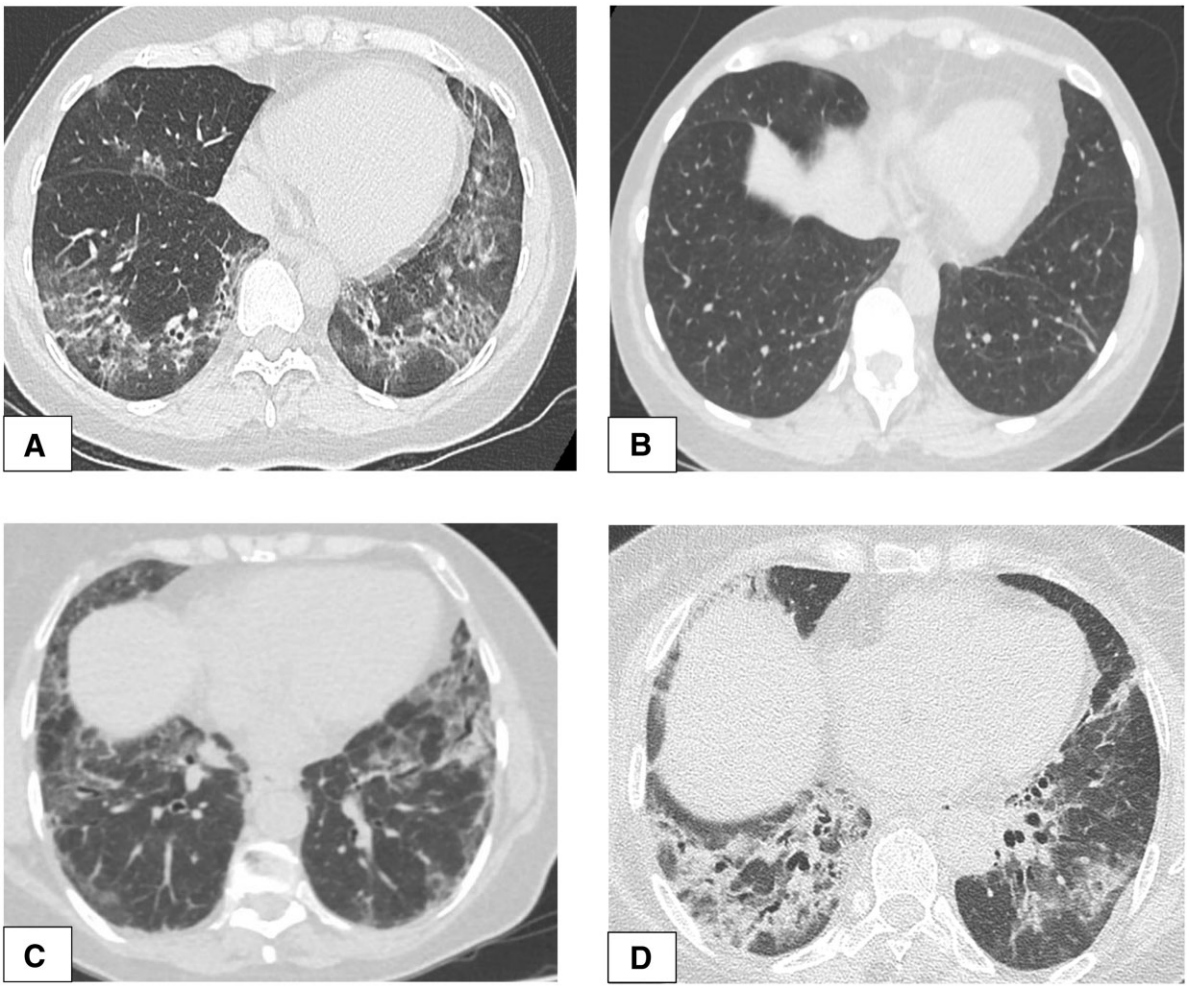
Dear Editor, Evidence on coronavirus disease 2019 (COVID-19) sequelae is accumulating, and pulmonary fibrosis can be a severe manifestation of post-acute lung injury [1]. It remains unclear to what extent fibrosis-like CT features represent irreversible lesions [2]. The importance of a thorough assessment of patients with features suggestive of post-COVID-19 interstitial lung disease (ILD) needs to be highlighted, in order to avoid misdiagnoses. Herein, we describe three patients referred for evaluation of post-COVID-19 ILD, in whom the final diagnosis was ILD associated with anti-synthetase syndrome.

The first case was a 45-year-old woman, a former smoker, without past medical history and unvaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The patient reported ageusia, anosmia and diarrhoea 1 month before she presented to her physician complaining about dyspnoea. A PCR test for SARS-CoV-2 was negative. Low-grade fever and dyspnoea persisted during the next month, and the lung CT revealed ground glass opacities (GGOs) (Fig. 1A). Bronchiectasis and subpleural reticulations in the lower lobes were also described. The working diagnosis was post-COVID-19 ILD, and the patient was referred for further evaluation. Pulmonary function testing demonstrated a diffusion capacity of carbon monoxide of 56% of the predicted value, with normal forced vital capacity (98% of predicted). Bronchoalveolar lavage showed lymphocytosis, with 900 000 cells/ml; 66% macrophages, 26% lymphocytes and 6% eosinophils. Inflammatory markers and creatine phosphokinase were normal. Although she had no clinical evidence of myositis, progression of the CT findings over a span of ∼3 months and the absence of parenchymal consolidation led to an order for an autoantibody panel, which revealed the presence of anti-PL7 antibodies. The final diagnosis was anti-synthetase syndrome, positive for anti-PL7. The patient received prednisolone (1 mg/kg), with a clear improvement of lung CT (Fig. 1B).

The second case was a non-smoking 61-year-old woman, unvaccinated against SARS-CoV-2, with arterial hypertension and diabetes type II. In October 2020, she experienced mild COVID-19 disease, confirmed by a PCR test. Two months later, she experienced breathlessness and coughing, with a diagnosis of pericarditis, and she was treated with colchicine and aspirin. Owing to the persistence of the cough for >1 month, she had a chest CT, which showed GGOs and traction bronchiectasis (Fig. 1C). A post-COVID-19 ILD was suspected. At that time, the patient mentioned dyspnoea, myalgias in the lower limbs, and dry mouth and eyes. Pulmonary function testing demonstrated a restrictive pattern, with forced vital capacity 72% of predicted and diffusion capacity of carbon monoxide 60% of predicted. Blood tests revealed slightly increased CRP (10 mg/l). Bronchoalveolar lavage showed 340 000 cells/ml; 87% macrophages, 11% neutrophils and 2% lymphocytes. Lacrimal secretion was reduced (Schirmer test <5 mm in each eye), and biopsy of the minor salivary glands showed mild sialadenitis, with a focus score greater than one. Oral sicca was absent. Serology uncovered positive anti-PL7 and anti-DFS 70 antibodies. Electrophysiological examination revealed bilateral deltoid muscle involvement and motor axonal impairment of the lower limbs. Blood creatine phosphokinase level was normal. Typical features of anti-synthetase syndrome were absent. The final diagnosis was anti-synthetase syndrome, positive for anti-PL7, with lung and muscle involvement, overlapping with SS. She was treated with prednisolone (0.5 mg/kg) and MMF as a CS-sparing agent, with partial improvement.

The third patient was a non-smoking 69-year-old woman, fully vaccinated against SARS-CoV-2. The disease history started 6 months before her referral, when she complained of coughing and dyspnoea. At disease onset, she was diagnosed with COVID-19 because of CT scan presentation with peribronchovascular and subpleural consolidation, although PCR for SARS-CoV-2 was negative. The symptoms remained, leading to a diagnosis of post-COVID-19 ILD. A few months later, breathlessness increased, and a new CT scan showed extension of GGOs, peribronchovascular consolidation and traction bronchiectasis (Fig. 1D). At her referral, physical examination revealed crackles bilaterally, periungual erythema, and mechanic's hands. Pulmonary function testing revealed a forced vital capacity of 50% of predicted and diffusion capacity of carbon monoxide of 30% of predicted. Blood tests showed lymphopenia and anaemia, and muscle enzymes were normal. Autoimmune tests revealed anti-PL7 and anti-Ro52 positivity. Electromyography showed no muscle involvement. The patient had respiratory failure and received pulses

Fig. 1 Chest CT, prone images



(**A**) Case 1. Ground glass opacities, traction bronchiectasis and mild subpleural reticulation in lower lobes. (**B**) Case 1. Clear improvement of the abnormalities 1 month after initiation of CS treatment. (**C**) Case 2. Interstitial lung abnormalities 9 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; subpleural ground glass opacities, with consolidation and traction bronchiectasis. (**D**) Case 3. Ground glass opacities, peribronchovascular consolidation and traction bronchiectasis in lower lobes.

of methylprednisolone, followed by oral prednisolone in combination with i.v. CYC, with partial improvement.

We describe three patients with anti-synthetase syndrome, positive for anti-PL7, who were referred for post-COVID-19 ILD. Misdiagnosis between post-COVID-19 ILD and anti-synthetase syndrome is not surprising, because the CT pattern combining GGOs and consolidation is highly suggestive of COVID-19, but can be observed in many other conditions, including myopathies. There are data about myositis-associated lung abnormalities mimicking acute COVID-19 [3]. In fact, several pathological features of COVID-19, such as epithelial and endothelial alterations, are common to autoimmune ILD [4].

Apart from the well-known similarity of CT features in CTD-related ILD and COVID-19-related lesions, it has been described how we could differentiate between CTD-related ILD and COVID-19 [5, 6]. Consolidations in a round shape and GGOs are proposed to be suggestive of COVID-19 in the absence of typical fibrotic abnormalities [5]. Subpleural sparing, absence of parenchymal consolidation and fibrosis inside GGOs might suggest a diagnosis of CTD-related ILD [6].

New-onset autoimmune disease after COVID-19 has also been described, including nine patients diagnosed with myositis after COVID-19, but none was characterized by anti-PL7 positivity [7]. However, causality between SARS-CoV-2 infection and autoimmune disease development should be attributed with caution.

These cases illustrate that even during a pandemic, it is essential to apply rigorous diagnostic algorithms when evaluating patients with ILD. Post-COVID-19 ILD should not be a dustbin diagnosis. Worsening of symptoms should lead to consideration of an

alternative diagnosis. Autoimmune screening, including myositis-associated autoantibodies, should be performed in patients with persistent ILD in a post-COVID-19 context [2, 8].

Funding: Eirini Vasarmidi was funded by European Respiratory Society, Fellowship ID number: LTRF202101-00863.

Disclosure statement: The authors have declared no conflicts of interest.

Consent: Informed patient consent was obtained for the publication of this paper.

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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Accepted 14 July 2022

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