Letter to Editor

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COVID-19 as a trigger for autoimmunity: A case of interstitial pneumonia with autoimmune features and prevalence of autoimmune phenomena in patients following COVID-19

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Key points

- We report a case of autoimmune-triggered disease in patient with COVID-19, which is to our knowledge, one of the first cases reported.
- We analyse autoimmune phenomena in a cohort of 34 patients following COVID-19 infection
- Autoimmune-triggered disease exists in patients with COVID-19
- Follow-up of patients with COVID-19 is fundamental.

Dear Sirs,

In the last 7 months, COVID-19 has swept through the world. It is caused by SARS-CoV2-virus, a member of coronaviridae that includes MERS-CoV2 which is responsible for severe respiratory illness and causes acute respiratory distress syndrome [1]. Many patients infected with COVID-19 develop a hyper inflammatory response due to cytokine storm syndrome which associates with high mortality [2]. Recent emerging reports show that coronavirus disease 2019 can serve as a trigger for autoimmunity and lead to autoimmune and auto inflammatory disease [3]. It has also been stated that several patients have developed lung fibrosis following SARS-CoV2 infection, due to autopsy reports [4].

We report the case of a patient with no prior autoimmune disease diagnosis that following COVID-19 infection develops Interstitial Pneumonia with Autoimmune Features (IPAF) and detail the prevalence of autoimmune phenomena in a cohort of 34 patients following COVID-19 infection.

A 74 year-old man (patient X), with the following comorbidities: ex-smoker of 10 years, hypertension, type II diabetes and dyslipidaemia, with no history of autoimmune conditions or respiratory conditions presents dry cough myalgia and 38 degree fever after returning from a work-related trip to Saudi Arabia that required treatment with azithromycin during 3 days. Reverse transcriptase-polymerase chain reaction of nasopharyngeal for SARS-CoV2 was positive, suggesting infection by COVID-19. One month later, the patient came to the emergency room due to increasing dyspnoea and cough. The patient had a temperature of 36.1ºC and a basal oxygen saturation of 98%. On examination, cardiac auscultation was normal and pulmonary auscultation revealed decreased vesicular murmur and light crackles on both lungs. Laboratorial tests revealed lymphopenia (lymphocytes 980 mm^3), C-reactive protein was 24 mg/l and the rest of parameters were normal. Thorax radiography

showed bilateral opacities and excessive buildup of fluid in right hemithorax compatible with pleural effusion. Treatment with antibiotics and corticosteroids was implemented and soon after, the patient was discharged.

Two months later, the patient was again admitted to the hospital due to reports of increased dyspnoea and dry cough, which had started one month after being discharged and coincided with corticosteroids dose reduction. The patient had a temperature of 37°C and a basal oxygen saturation of 88%. Arterial blood gases revealed pH 7.41, pCO_2 37.5, pO_2 58.6, HCO_3 24.1, StO2 89.4%, which showed acute respiratory insufficiency. Laboratorial findings were normal, except for lymphopenia (lymphocytes 880 mm^3) and C-reactive protein of 62 mg/l. Thoracic radiography revealed bilateral pulmonary opacities and a reticular patron predominantly on right hemithorax. A thoracic CT was performed and was compatible with organizing pneumonia (NO) in the context of COVID-19 infection. Treatment with prednisone at 60 mg/day and low molecular weight heparin is implemented, which clinical and analytical improvement which motivated discharge.

The patient is seen in an outpatient clinic in the month of August, reporting increased dyspnoea and dry cough coinciding with reduction of corticosteroids (current dosage 24 mg of methylprednisolone) since discharge. The patient had a basal oxygen saturation of 88% and lung auscultation revealed velcro crackles. Due to previous imaging results, the patients were reinterrogated to check for any signs of connective tissue disease. He denied having any contact with animals or birds did not own bed quilts or feathered pillows and did not have arthralgia or arthritis, sicca syndrome, no Raynaud phenomenon, no photosensibility, no acropaquia and no skin lesions but refers occasional acid reflux. Further laboratorial studies were performed, including ACE determination, rheumatoid factor, alpha-1-antitripsin, antiphospholipid antibodies, complement, avian precipitins, aspergillus, penicillum and micropolyspora and thermoactinomyces precipitins and autoimmunity, including anti-myositis blot. Anti-Nuclear Antibodies (ANA) were positive, with a 1/2560 titre, anti-topoisomerase antibody (anti-Sc70) were also positive, and the rest of the results, precipitins, CK and aldolase was normal. Laboratorial results summed up in **Table 1**.

In October 2020, the patient is consulted again with rheumatology. He has now complaints of arthralgias in both hands and symmetric synovitis on bothhands in second and third metacarpophalangeal joints is evidenced. No signs of sclerodactyly, telangiectasias, puffy hands or calcinosis is noted so far. A spirometry is performed showing a non-obstructive patron and a severe reduction of diffusing capacity for carbon monoxide of 30%. A capillaroscopy is also performed, showing unspecific abnormalities. Thus, all of the evidence points to Interstitial Pneumonia with Autoimmune Features (IPAF) as our patient fills the serologic criteria (ANA and anti-SCl70) and morphologic criteria (suggestive radiology pattern of non-specific interstitial pneumonia with organizing pneumonia by high-resolution computed tomography), and clinical criteria (inflammatory arthritis).

The big question in this case is, will this patient develop an autoimmune-triggered disease, such as a systemic sclerosis-like syndrome? Was the disease undiagnosed because the patient was asymptomatic before the infection and now the disease has progressed triggered by COVID-19? Can COVID-19 infection trigger an autoimmune disease? While we still don't know the implications or consequences of

Table 1. Laboratorial findings of patient X.

White-cell count (mm^3)	8100
Lymphocytes (10^3µL)	890
Platelet count (mm^3)	311.000
Hemoglobin (10^3µL)	13.3
INR (mg/dL)	1.04
Lactate dehydrogenase (U/L)	252
Creatine kinase (U/L)	22
EGFR (ml/min/1.73 m^2)	85
D-Dimer (mg/liter)	461
Serum ferritin (ng/ml)	221
High-sensitivity C-reactive protein (mg/liter)	62.8
Autoimmunity	Positive: ANA: 1/2560, anti-SCL70 + Negative: anti-RNP, centromere, DNAds, Jo1, Ro, La, Sm, Mi2, PM-Scl, PL-12, PL-7, OJ, SRP, PM Scl75, PM Scl100, MDA5, NXP2, SAE1, TIFg

Table 2. Prevalence of positive autoimmunity markers.	
Antinuclear antibody	10 (29%)
Anti-double-stranded DNA antibody	2 (5.9%)
Anti-Scl-70 antibody	1 (2.9%)
Anti-centromere antibody	1 (2.9%)
Anti-neutrophil cytoplasmatic antibody	3 (8.8%)
Anti-SSA/Ro antibody	2 (5.9%)
Anti-SM antibody	1 (8.8%)

COVID-19, there have been several reports of lung fibrosis following SARS-CoV2. Pulmonary fibrosis is a known sequela of severe damage to the lungs from connective tissue disorders, chronic granulomatous diseases, medications, and respiratory infections [5]. Recently, a study by Zhou et al has analysed 21 patients and concluded that autoimmune phenomena exist in people affected by COVID-19 [6]. We have performed a single-centre, observational cohort study by analysing the prevalence of autoimmune phenomena in a cohort of 34 patients infected with COVID-19. Laboratorial findings are in Table 2. The prevalence of antinuclear antibodies was 29%, anti-SM and anti-neutrophil cytoplasmatic antibodies were 8.8%. Out of the 34 patients, 8 patients have developed pulmonary fibrosis, evidenced in follow-up lung CTs, 3 patients have complained about arthralgias and arthritis was evidenced in 2 patients and the rest have remained asymptomatic. All patients are being followed in our outpatient clinic consultation.

There have been cases of Kawasaki-like syndrome in children triggered by SARS-CoV2 [7,8]. We know that infectious diseases have long been consid-ered as one of the triggers for autoimmune and autoinflammatory diseases, mainly via molecular mimicry. Although no link between SARS-CoV-2 and the development of autoimmune diseases has yet to be established, temporal association with the current COVID-19 pandemic and the history of exposure of affected patients to SARS-CoV-2 is heavy argument.

While the development of rheumatic diseases following SARS-CoV2 is currently not described, follow-up of patients with COVID-19 is fundamental, especially if autoimmunity alterations are detected.

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Competing interests

The authors have declared no conflicts of interest

Ethics approval and consent to participate

This study was approved by the Medical Ethical Committee of ComplejoAsistencialUniversitario de León.

Contributorship

CS conceived of the presented idea. CM and ED performed the computations. CM verified the analytical methods. CS, CM, ED, TS supervised the findings of this work. All authors discussed the results and contributed to the final manuscript

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