RESEARCH LETTER

Interstitial pneumonia with autoimmune feature phenotype in patients with COVID-19

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Introduction Several symptoms typical for autoimmune diseases have been described in patients with SARS-CoV-2 infection, including cutaneous rashes, vasculitis, Raynaud syndrome, central or peripheral neuropathy, myositis, and myocarditis.[1,2] The immune system plays a central role in COVID-19 as it is responsible for its clinical manifestations and prognosis of affected patients.[3,4] Autoantibodies against type I interferons in patients with life-threatening COVID-19 were reported.[5] The principal damage is not caused by SARS-CoV-2 itself but by subsequent immune response triggered by the virus. The damage differs depending on an organ and is mainly detected in the lung and manifests as pulmonary vasculitis.[6] Therefore, it would be of interest to investigate whether interstitial lesions in the lungs in the course of SARS-CoV-2 infection could be related to an autoimmune feature. Indeed, there is a consensus statement that provided uniform nomenclature, introducing the term "interstitial pneumonia with autoimmune features," and a set of classification criteria.[7] These criteria include: 1) presence of interstitial pneumonia detected by high-resolution computed tomography and / or surgical lung biopsy; 2) exclusion of alternative etiologies; and 3) lack of typical connective tissue disease according to the diagnostic criteria for a well-defined connective tissue disease. This paper discusses the background behind interstitial pneumonia with autoimmune feature phenotype in patients with COVID-19. Moreover, it offers insight into directions of future research in this area.

Patients and methods In this study, we spontaneously evaluated serum antinuclear antibodies (ANA) in 15 patients hospitalized for COVID-19 pneumonia (TABLE 1). None of them suffered from any autoimmune diseases. At the onset of COVID-19, 6 patients had fever, 10 had cough, and 10 had dyspnea. On admission to the hospital, in 13 patients the disease severity was assessed as moderate, while in 2 as severe. Computed tomography showed ground-glass opacities and bilateral pulmonary infiltrates in all patients; crazy paving was observed in 6 patients. Five patients experienced pulmonary embolism during hospitalization. Before the COVID-19 pandemic, none of the patients had samples collected for autoimmunity testing. Moreover, none of the patients had any rheumatic symptoms or conditions independent of ANA screening test results. All hospitalized patients gave written informed consent for diagnostic procedures, including blood tests. The analysis of laboratory results was retrospective and the institutional ethics committee approval was not required.

Indirect immunofluorescence (IIF) was the first-line tool for ANA screening (ANA1) using the HEp-2 cells (Euroimmun, Lübeck, Germany). Autoantibodies detected on IIF were confirmed by additional specific tests (enzyme-linked immunosorbent assay, line blot ANA3; Euroimmun).[8]

Statistical analysis Quantitative data were described as medians and interquartile ranges (IQRs). Patient characteristics were compared using the Fisher exact test for categorical data, and the Mann–Whitney test for continuous data. A P value of less than 0.05 was considered significant. The statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, California, United States, www.graphpad.com).

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Received: March 14, 2021.
Revision accepted: June 11, 2021.
Published online: June 14, 2021.
Pol Arch Intern Med. 2021; 131 (7-8): 752-754
doi:10.20452/pamw.16029

TABLE 1 Demographic and clinical characteristics as well as laboratory findings of patients with COVID-19 (n = 15) (continued on the next page)

Variable		Value
Demographic and clinical characteristics		
Age, y		64 (58–72)
Sex	Male	13 (86.7)
	Female	2 (13.3)
BMI, kg/m^2		26.2 (22.3–33)
Medical history		
Autoimmune disease		0
Hypertension		11 (73.3)
Diabetes		2 (13.3)
Symptoms at disease onset		
Fever		6 (40)
Cough		10 (66.7)
Dyspnea		10 (66.7)
Computed tomography imaging findings		
Ground-glass opacity		15 (100)
Crazy paving		6 (40)
Bilateral pulmonary infiltrates		15 (100)
Findings on admission		
Disease severity	Moderate	13 (86.7)
	Severe	2 (13.3)
	Critical	0
Blood oxygen saturation, %		94 (90–96)
Pulmonary embolism during hospitalization		5 (33.3)
Subsequent autoimmune testing		
ANA titer	Not detected	3 (20)
	0–160	4 (26.7)
	>160	8 (53.5)
	Median (IQR) for group >160	1:320 (1:320–1:1280)
c-ANCA (+)		0
p-ANCA (+)		1 (6.7)
Subsequent serologic testing		
Anticardiolipin IgG antibodies (+)[a]		2 (13.3)
		6.5 (4.6–10.8)
Anticardiolipin IgM antibodies (+)[b]		7 (46.7)
		13.3 (9.4–24.6)
Anti–β2-glycoprotein I IgG antibodies >20[c]		15 (100)
		1.7 (1.3–1.8)
Anti–β2-glycoprotein I IgM antibodies >20[d]		1 (6.7)
		1.9 (1.5–2.6)
Lupus anticoagulant		Not detected
Laboratory findings on the day of autoimmune testing		
White blood cell count, ×10^3/mm^3		8.4 (6.4–10.9)
Platelet count, ×10^3/mm^3		209 (165–338)
Hemoglobin, g/l		12.9 (11–13.9)
Creatinine, µmol/l		70.9 (52.9–84.4)
eGFR <60 ml/min/1.73 m^2		1 (6.7)
High-sensitivity cardiac troponin I, ng/l		19.9 (5.3–63.8)
Fibrinogen, g/l		4.3 (3.3–5.5)
D-dimer, mg/l		1.5 (0.6–2.5)
Serum ferritin, µg/l		797 (501–1482)

TABLE 1 Demographic and clinical characteristics as well as laboratory findings of patients with COVID-19 (n = 15) (continued from the previous page)

Variable	Value
Procalcitonin, ng/ml	0.02 (0.02–0.18)
High-sensitivity C-reactive protein, mg/l	19.9 (5.3–63.8)

Data are presented as median (interquartile range) or number (percentage).

a Phospholipid unit G

b Phospholipid unit M

c Standard β2 glycoprotein unit G

d Standard β2 glycoprotein unit M

Abbreviations: ANA, antinuclear antibodies; c-ANCA, "classic" antineutrophil cytoplasmic antibodies; BMI, body mass index; eGFR, estimated glomerular filtration rate; Ig, immunoglobulin; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies

Results and discussion Approximately 53% of our patients with interstitial pneumonia were positive for ANA1, with an ANA titer greater than 1:160, as detected by IIF. Additionally, 27% of participants were positive for ANA1, with an ANA titer of 1:160. Among patients with ANA titer greater than 1:160, the median (IQR) was 1:320 (1:320 to 1:1280). A line blot assay did not detect autoantibodies typical for various autoimmune rheumatic diseases. We did not find any differences between COVID-19 patients with interstitial pneumonia with autoimmune features and those without.

In more than half of the patients with COVID-19, interstitial pneumonia was associated with a positive autoimmune feature, with none of the cases fulfilling the diagnostic or classification criteria for specific autoimmune diseases.[9] It is still unknown whether these autoimmune conditions represent transitory postinfectious phenomena, which we termed "interstitial pneumonia with autoimmune feature phenotype", in COVID-19 patients or whether autoantibodies are detectable in serum years before the onset of autoimmune disease. Autoantibody seropositivity may also be found in healthy individuals.[10] The reason for the higher frequency of ANA positivity in our COVID-19 patients (53%) with interstitial pneumonia as compared with the general population[9] is poorly understood. Indeed, up to 20% of healthy women and up to 10% of healthy men are ANA1-positive and most of them will never develop clinical symptoms. It was proposed that a novel immune signature identified in healthy ANA1-positive individuals may protect from T-cell expansion, heightened activation of interferon pathways, and disease transition.[11] It was reported that interleukin 6 levels were elevated in healthy ANA1-positive individuals and that increased T-cell count correlated with elevated gene expression in types I and II interferon signaling pathways in patients with systemic lupus erythematosus, which suggests that dysregulation of these cytokines contributes to autoimmune pathogenesis.[11] A number of reports describing dysregulation of these cytokines in patients with COVID-19 was published.

The current study is not without limitations and the main one is that it was a single time-point study on consecutive patients. The observation concerning the association of COVID-19 interstitial pneumonia with positive autoimmune features should be confirmed in a larger cohort of COVID-19 patients, and a longitudinal assessment of patients with interstitial pneumonia with autoimmune features is necessary to note changes in this immune profile over time. Small cohort studies should be viewed as observations only rather than recommendations for patient evaluation or treatment.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Mastalerz L, Gomółka P, Ćmiel A, et al. Interstitial pneumonia with autoimmune feature phenotype in patients with COVID-19. Pol Arch Intern Med. 2021; 131: 752-754. doi:10.20452/pamw.16029

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