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CASE REPORT

ADVANCED

CLINICAL CASE

Autoimmune Reaction Associated With Long COVID Syndrome and Cardiovascular Disease

A Genetic Case Report

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ABSTRACT

A 35-year-old woman with history of cardiovascular disease presented with shortness of breath, lightheadedness, fatigue, chest pain, and premature ventricular contractions 3 weeks after her second COVID-19 vaccine. Symptoms subsided following catheter ablation and ibuprofen except for chest pain and fatigue, which persisted following ablation and subsequent SARS-CoV-2 infection. The case suggests causal associations between COVID-19 vaccine/infection and recurrence of cardiovascular disease, including long-COVID–like symptoms. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;6:101644) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

LEARNING OBJECTIVES

- To investigate medical history and test results to deduce possible causal relationships between COVID vaccine/infection and exacerbated CVD symptoms.
- To examine CVD and genetic history as factors in determining sensitivity to long COVID.
- To recognize possible causal roles of COVID vaccination/infection in cyclically exacerbated COVID, CVD, and autoimmune symptoms.
- To recognize pericarditis and autoimmune reaction as symptoms of COVID vaccine or long COVID.

HISTORY OF PRESENTATION

A 35-year-old Russian woman presented for evaluation with complaints of fatigue, chest and joint pain, and dyspnea. The patient had a history of cardiovascular disease (CVD), having been hospitalized for 3 days with palpitations and premature ventricular contractions (PVCs) at 1 year and 10 months before her first Pfizer SARS-CoV-2 vaccination. Symptoms resurfaced 3 weeks after patient's second vaccination and worsened progressively, with multiple hospital admissions that included dual cardiac ablations over a 3-month period. Ibuprofen was prescribed for pericarditis 2 months after the second ablation, and 3 weeks later, the patient tested positive for

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ABBREVIATIONS AND ACRONYMS

ANA = antinuclear antibodies

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

PVC = premature ventricular contraction

SLE = systemic lupus erythematosus

SARS-CoV-2. The patient took only vitamin D to combat SARS-CoV-2 infection. Shortly after testing positive for SARS-CoV-2, the patient presented again with chest pain when moving or breathing, joint pain, and dermatitis, symptoms that persisted for 6 months.

PAST MEDICAL HISTORY

CVD was first evident when the patient was hospitalized for 3 days with presyncope, palpitations, and high burden of PVCs, 1 year and 10 months before she was vaccinated for SARS-CoV-2. Three weeks after receiving her second vaccination, the patient experienced lightheadedness, fatigue, frequent presyncope, shortness of breath, and chest pain, and she was admitted to the hospital with high burden of PVCs. Cardiac magnetic resonance showed borderline cardiomegaly with left ventricle enlargement but no evidence of infarct, fibrosis, or amyloidosis. Ejection fraction was 62.3%. Catheter ablation procedures were performed on 2 consecutive days. Symptoms improved after the ablations, and echocardiogram showed trace mitral regurgitation, tricuspid regurgitation, and pericardial effusion (Video 1). Symptoms of chest pain and fatigue were still evident but subsided during 2 to 3 weeks treatment with Advil. GeneCompass genetic analyses exploring 100 genes for CVD and diabetes revealed mutations at 6 potential CVD/diabetes mellitus susceptibility loci—APOC1 (rs4420638), CETP (rs3764261), IL4 (rs2243250), AGT (rs5051), and AGT (rs699) for CVD and SLC30A8 (c.973C) for diabetes mellitus—suggesting moderate risk for developing CVD and/or diabetes mellitus, but no susceptibility genes for immune system disorders. Shortly after testing positive for COVID-19, the patient reported recurrent chest pain when moving or breathing as well as joint pain. The patient has a family history of diabetes, high blood pressure, and cardiac cirrhosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included long COVID-19, arthritis, and systemic lupus erythematosus (SLE).

INVESTIGATIONS

Antinuclear antibody (ANA) immunofluorescence assay screening was positive for autoimmune antibodies with a 1:80 titer and nuclear and homogenous pattern (Table 1). Taken together with the symptoms present at that time (limb/joint pain, dermatitis, fatigue, and shortness of breath) and in accordance with the international consensus for ANA patterns (ICAP), the results are consistent with 3 possible autoimmune-related diagnoses: SLE, chronic autoimmune hepatitis, and juvenile idiopathic arthritis. Based on a double-stranded DNA (dsDNA) antibody test (Table 2), which showed the absence of DS antibody, it can be concluded that the patient does not have SLE. She had normal levels of alkaline phosphatase (52 U/L), aspartate transaminase (20 U/L), and alanine transaminase (9 U/L), which indicate that she does not have autoimmune hepatitis. The patient tested negative for antineutrophil cytoplasmic antibodies, vasculitis proteinase 3, and myeloperoxidase (Table 3). She also tested negative for the following antibodies: cyclic citrullinated peptide (immunoglobulin G [IgG]), complements C3 and C4, B2 glycoprotein I (IgG, immunoglobulin A [IgA], immunoglobulin M [IgM]), phosphatidylserine (IgG, IgM), cardiolipin (IgA, IgG, IgM), Sjogren syndrome type A and B antigens, and Smith and Smith/Ribonucleoprotein antibodies (Table 4). Blood tests revealed normal hormonal and white blood cell levels, slightly elevated low-density lipoprotein cholesterol (LDL-C) (Table 5), and progressively reduced high-density lipoprotein cholesterol (HDL-C) levels over 1 year between 2019 to 2021 (from 79 to 65 mg/dL).

TABLE 1 ANA Screening Results

Result of ANA titer	1:80
Reference range	
<1:40	Negative
1:40-1:80	Low antibody level
>1:80	Elevated antibody level
ANA pattern	Nuclear, homogeneous

ANA = antinuclear antibody.

MANAGEMENT

The patient is currently stable but still presents with severely restricted physical performance, chest pain, joint pain, and fatigue. She has switched from a vegetarian to nonvegetarian diet as a possible avenue to mitigate fatigue (she was tested for low iron and ferritin levels after COVID-19 infection) and continues to take a vitamin D supplement. The patient was

TABLE 2 Double-Stranded DNA Antibody Test Results

Result for DNA (DS) Antibody Test	<1 IU/mL
Interpretation, IU/mL	
≤4	Negative
5-9	Intermediate
≥10	Positive

TABLE 3 ANCA Antibody Test Results

Test Name	In Range	Reference Range
Proteinase 3 antibody	<1.0	<1.0 AI
Value interpretation		
<1.0 AI: no antibodies detected		
≥1.0 AI: antibodies detected		
Myeloperoxidase antibody	<1.0	<1.0 AI
Value interpretation		
<1.0 AI: no antibodies detected		
≥1.0 AI: antibodies detected		

AI = antibody index.

prescribed statin medication for LDL-C and HDL-C but did not take it.

DISCUSSION

The purpose is to alert physicians to the possibility that preexisting cardiovascular disease may sensitize some patients to COVID vaccines and/or infection, leading to recurrent and/or exacerbated CVD and/or long COVID symptoms, including autoimmune reaction. The case timeline is outlined in **Figure 1**. The reappearance of exacerbated CVD (PVCs), hospitalizations, and COVID-like symptoms coinciding with the patient's COVID-19 vaccination schedule suggests a causal relationship. To our knowledge, the patient was not infected at the time of vaccination and had no history of COVID-19 infection. Rare cases of long-COVID-19-like symptoms associated with COVID-19 vaccination have been reported (reviewed by Couzin-Frankel and Vogel[1]), and autoimmune response stimulated by the spike protein antigen has been implicated as the possible culprit.[2,3] The presenting symptoms, as well as results of ANA screening of the patient's blood that do not implicate other autoimmune disease, are consistent with the possibility that the symptoms are driven by the vaccine. Indeed, fatigue and shortness of breath, the major symptoms that were exacerbated after the second vaccination, are the 2 most common symptoms of long COVID. Similarly, exacerbation of chest and joint pain and difficulty breathing subsequent to COVID infection may be causally linked. Patients with preexisting CVD including arrhythmia are at increased risk for developing long COVID and have poorer prognoses.[4,5] The patient's symptoms and presence of autoantibodies are consistent with long COVID.[6] Pericarditis and arrythmias, the 2 main cardiovascular conditions exhibited by the patient, have also been reported in association with long COVID and secondary to an immune reaction to the vaccine.

TABLE 4 List of Antibodies Tested

Test	In Range	Reference Range
Phosphatidylserine AB (IgG), U/mL	<10	<10
Reference range		
<10	Negative	
10-20	Equivocal found in small percentage of healthy population; may be reactive	
>20	Positive: risk factor for thrombosis and pregnancy loss	
Phosphatidylserine AB (IgM), U/mL	<25	<25
Reference range		
<25	Negative	
25-35	Equivocal found in small percentage of healthy population; may be reactive	
>35	Positive: risk factor for thrombosis	
Cardiolipin AB (IgA), APL-U/mL	<20	<20.0
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
Cardiolipin AB (IgG), GPL-U/mL	<2.0	<20
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
Cardiolipin AB (IgM), MPL-U/mL	<2.0	<20
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
B2 glycoprotein (IgG), U/mL	<2.0	<20
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
B2 glycoprotein (IgA), U/mL	<2.0	<20
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
B2 glycoprotein (IgM), U/mL	<2.0	<20
Value	Interpretation	
<20.0	Antibody not detected	
≥20.0	Antibody detected	
Complementary component C3C, mg/dL	91	83-193
Complementary component C4C, mg/dL	21	15-57
SM antibody	<1.0 NEG	<1.0 NEG
SM/RNP antibody	<1.0 NEG	<1.0 NEG
Cyclic citrullinated peptide (IgG), U	<16	<20
Reference range		
Negative	<20	
Weak positive	20-39	
Moderate positive	40-59	
Strong positive	>59	

AB = antibody; APL = IgA Phospholipid; GPL = IgG phospholipid; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MPL = IgM phospholipid ; NEG = negative; RNP = ribonucleoprotein; SM = Smith.

In addition to the confirmed arrhythmias, genetic analyses of the patient's blood revealed the presence of mutations within several CVD-associated high-risk genes. In particular, the rs4420638 variant of *APOC1*

TABLE 5 Cholesterol Blood Test Results

Blood Test Component	Value	Standard Rage	Flag
Cholesterol, total	192 mg/dL	<200 mg/dL	
HDL cholesterol	65 mg/dL	≥50 mg/dL	
Triglycerides	65 mg/dL	<150 mg/dL	
LDL cholesterol	112 mg/dL	<100 mg/dL	H
Cholesterol/HDL ratio	3.0 calc	<5.0 calc	
Non-HDL cholesterol	127 mg/dL	<130 mg/dL	

calc = calculated; H = high; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

is associated with higher LDL-C levels in plasma,[7] and the rs3764261 variant of *CETP* is associated with increased HDL-C and decreased blood pressure.[8] Low serum HDL-C and high LDL-C are established risk factors for coronary artery disease, whereas low HDL-C is associated with poor outcome of patients with COVID-19.[9] It seems possible that the significant decline of HDL-C in the patient's blood that was evident immediately before severe vaccine/COVID-19 symptoms may contribute to enhanced transmission of the COVID spike protein, activation of autoimmune reactions, and long-COVID symptoms.

Genetic results also indicated an absence of gene mutations associated with autoimmune disorders, consistent with COVID-19-induced autoimmune disease symptoms independent of the patient's susceptibility to immune disorders. Cytokine storm is just one of the multiple possible pathways through which the SARS-CoV-2 virus can exacerbate the autoimmune response. During cytokine storm, immune cells are hyperactivated by elevated circulating cytokines and target internal organs. SARS-CoV-2-mediated cytokine storm has been reported to propagate long COVID[10] and is a candidate mechanism for the symptoms described in this case report.

A strength of this case report is the recurrence of severe CVD and long-COVID-like symptoms with autoimmune reaction, coincident with 2 separate COVID-related events, vaccination and infection. The cause and effect are consistent with the known high-risk status of and poorer prognoses of CVD patients for COVID infection and the development of long COVID. Limitations of the study include the selective bias of case studies, which cannot represent entire populations with long COVID and preexisting CVD.

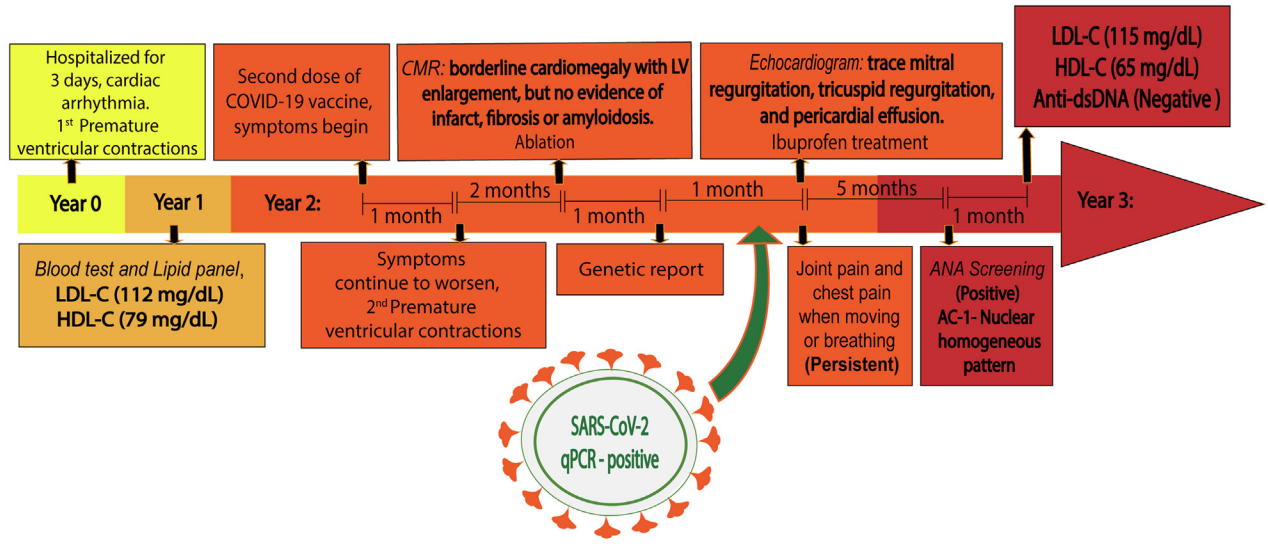
FOLLOW-UP

The patient remains under observation.

CONCLUSIONS

A long-COVID-like condition is supported by patient symptoms, gene analysis, ANA screening, and blood test in association with a CVD and lipid susceptibility

FIGURE 1 Outline of the Case



CMR = cardiac magnetic resonance; dsDNA = double-stranded DNA; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular.

profile. The mechanism may involve COVID-19 spike protein-mediated autoimmune activation. An implication of this study is that COVID vaccine, exacerbated CVD, and long COVID symptoms can be causally associated. Patients with preexisting CVD are at a higher risk of long-COVID-related symptoms relative to patients without preexisting CVD. For future direction, it will be important for doctors and patients to understand possible mechanisms causing long COVID symptoms, especially how the spike protein can instigate an inflammatory response and an autoimmune reaction. It will also be important to determine whether the significant decline of HDL-C in the patient's blood seen before severe COVID-19 symptoms is causally linked to activation of autoimmune reactions and long COVID.

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KEY WORDS arrhythmia, autoimmune disease, long COVID, pericarditis, SARS-CoV-2

APPENDIX For a supplemental video, please see the online version of this paper.