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Case Report

Pfizer–biontech COVID-19 RNA vaccination induces phosphatidylserine autoantibodies, cryoglobulinemia, and digital necrosis in a patient with pre-existing autoimmunity[☆]

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ABSTRACT

We describe a 64-year-old Caucasian female with a history of Raynaud's disease, hand arthritis, photosensitivity, Sjogren's syndrome and leukocytoclastic vasculitis who presented with progressively worsening fingertip necrosis that began three days after receiving a first dose of Pfizer–BioNTech COVID-19 RNA vaccine. Our workup revealed cryoglobulinemia, hypocomplementemia, elevated antinuclear antibodies (ANA) and IgM antiphospholipid autoantibodies (aPL) directed against phosphatidylserine (aPL-PS), suggesting a diagnosis of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). The patient failed to develop anti-spike IgG antibodies up to two months following vaccination. Disease progression was halted by plasmapheresis, anticoagulation, and immune suppression. We conclude that the vaccine RNA moiety may induce SLE manifesting in APS, cryoglobulinemia, hypocomplementemia, and digital necrosis.

Introduction

Systemic vasculitides are heterogeneous disorders that share the common feature of vascular inflammation. They vary depending on which organs are involved, which size of blood vessels is affected and how severe the inflammation is. In the end, there is diminished blood flow, alterations in the vascular system, and eventual occlusion with variable ischemia, necrosis, and damage to tissues. Cryoglobulinemic vasculitis is a small vessel vasculitis that is characterized by the presence in the serum of one or more immunoglobulins that precipitate below core body temperatures and re-dissolve upon rewarming [1].

Vasculitides have been linked to infectious agents, connective tissue diseases, malignancies, drugs, and toxins among other still unknown factors. Various forms of vasculitides have also been observed and reported as adverse events following immunization after different vaccines [2]. The Pfizer–BioNTech COVID-19 vaccine is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the pre-fusion spike glycoprotein of SARS-CoV-2, the virus that causes COVID-19 [3]. To our knowledge, there has not been any described case of worsening of vasculitis following administration of the vaccine.

Case presentation

A 64-year old Caucasian female presented to our emergency department with painful fingertip discoloration on 3/20/2021. Her past med-

ical history included Raynaud's disease, hand arthritis, and Sjogren's syndrome diagnosed in August 2020. Two months prior to admission, in January of 2021, she presented to with purpuric rash over her lower extremities, which was diagnosed as biopsy-proven leukocytoclastic vasculitis and treated with a prednisone taper by her dermatologist for 2 weeks.

On 03/03/21 she received a 1st COVID-19 vaccine. On 03/11/21 she saw her dermatologist for the bluish discoloration of her fingertips, when her right third distal phalanx started to turn black for the first time, which was accompanied by overall worsening upper extremity Raynaud's disease. She was again started on prednisone, 10 mg daily, which did not help with the fingertip lesions. Eventually, the patient presented to the Upstate Emergency Department (ED) on 03/20/21 with stabbing pain and decreased sensation in all her fingertips. She was hemodynamically stable. Nasopharyngeal SARS-CoV-2 RNA RT-PCR test was negative. On physical exam, there was a bluish discoloration of all fingertips, the right third distal phalanx was showing signs of necrosis, and purpuric rash was seen on her legs (Fig. 1). Rheumatological work-up revealed photosensitivity, malar rash, bilateral symmetrical leg purpura, positive ANA, low complement levels with undetectable C4, elevated IgM antiphospholipid antibody directed to phosphatidylserine (aPL-PS), cryocrit of 14% (Table 1), suggesting systemic lupus erythematosus (SLE) with antiphospholipid syndrome (APS) and cryoglobulinemia. Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and HIV were all nonreactive.

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Table 1
Laboratory test results of the patient.

Laboratory test name	Results upon admission	Results upon discharge	Reference range
Serum creatinine	0.86	0.71	0.5–0.9 mg/dL
Total protein	6.6	-	6.4–.3 g/dL
AST	26.0	-	< 32 U/L
ALT	15.0	-	< 33 U/L
WBC	6.7	11.2	4–10 ³ /μL
Hemoglobin	11.1	9.4	11.5–15.5 g/dL
Platelets	437.0	338	150–400 10 ³ /μL
PT INR	0.97	2.11	-
PTT	25.6	-	24–33 s
Anticardiolipin IgA	< 1.4	-	< 20 CU
Anticardiolipin IgG	< 2.6	-	< 20 U/mL
Anticardiolipin IgM	< 1.0	-	< 20 U/mL
Antiphosphatidylserine IgA	1.0	-	0–20 APS IgA
Antiphosphatidylserine IgG	1.0	-	0–11 GPS IgG
Antiphosphatidylserine IgM	85	-	0–25 MPS IgM
β2 Glycoprotein IgA	< 4.0	-	< 20 CU
β2 Glycoprotein IgG	< 6.4	-	< 20 U/MN
β2 Glycoprotein IgM	< 1.1	-	< 20 U/mL
dRVVT	1.101	-	< 1.20
Hexagonal phase phospholipid neutralization	0.1	-	< 8.0 s
Platelet neutralization	0.0	-	< 1.0 s
ANA, Nucleolar Pattern	< 80	-	< 80 (dilution)
ANA, Homogenous	< 80	-	< 80 (dilution)
ANA speckled patterned	640	-	< 80 (dilution)
Anti-cyclic citrullinated peptide antibody	2	-	0–20 units
Anti-centromere antibody	167	-	0–99 AU/mL
Cryoglobulin	Positive at 14%	Positive at 1%	Negative
Anti-dsDNA antibody	2	-	0–99
Anti-histone antibody	19	-	0–99
Anti Jo-1 antibody	10	-	0–99 AU/mL
Neutrophil Cytoplasmic Antibody	Negative	-	Negative
Rheumatoid factor	463	-	< 14 IU/mL
Anti SCL-70 antibody	31	-	0–99
Anti-Smith antibody	15	-	0–99 AU/mL
Anti-SSA antibody	9	-	0–99 AU/mL
Anti-SSB antibody	25	-	0–99 AU/mL
C3-complement	101	-	90–180 mg/dL
C4-complement	< 4	3	10–40 mg/dL
Total complement	< 10	-	> 41 U/mL
HBV core antibody	Non-reactive	-	Non-reactive
HBV surface antigen	Non-reactive	-	Non-reactive
HCV antibody	Non-reactive	-	Non-reactive
HIV antibody	Non-reactive	-	Non-reactive
Serum IgA	96	-	70–400 mg/dL
Serum IgG	323	-	700–1600 mg/dL
Serum IgM	124	-	30–230 mg/dL
ESR	59	< 1	< 30 mm/hr
C-reactive protein	34.0	< 3.0	< 8.0 mg/L
SPEP total protein	6.2	-	6.4–8.3 g/dL
SPEP albumin	3.48	-	3.8–5.7 g/dL
SPEP alpha1 globulin	0.26	-	0.08–0.23 g/dL
SPEP alpha2 globulin	1.06	-	0.45–0.92 g/dL
SPEP beta2 globulin	0.87	-	0.5–1.03 g/dL
SPEP gamma globulin	0.52	-	0.54–1.03 g/dL
SPEP M-spike	0.03	-	0 g/dL
Serum immunofixation	IgMκ paraprotein at β/γ interface	-	-
UPEP	Protein concentration too low for fractionation	-	-
Urine immunofixation	No paraprotein detected	-	-
Blood flow cytometry	No evidence of leukemia or non-Hodgkin lymphoma cells	-	-
COVID-19 Spike IgG (04/15/2021)	-	negative	Negative

ANA, antinuclear antibody; dRVVT, diluted Russell viper venom time; SR, Erythrocyte sedimentation rate; CRP, C-reactive protein; HIV, human immune deficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; SSA, Sjogren syndrome A; SSB, Sjogren's syndrome B; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; WBC, white blood cell;

She was started on intravenous methylprednisolone (500 mg/day for 3 days) and heparin infusion. The purpuric rash on her legs resolved but the discoloration and pain in the fingertips worsened with necrosis affecting all fingertips. Therefore, therapeutic plasma exchange (TPEX) was initiated for removal of cryoglobulins. Patient received TPEX (6 sessions every other day) after which her cryocrit dropped to 1%. She was also given intravenous epoprostenol that improved her skin color and reduced fingertip pain. She was discharged home on 4/6/2021.

Discussion

COVID-19 infection is still relatively a new and poorly understood disease. The Pfizer–BioNTech COVID-19 vaccine is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a pre-fusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. It can protect its recipient from a SARS-CoV-2 infection by formation of antibodies and provide T-cell immunity against a SARS-CoV-2 infection



Fig. 1. Induction of digital necrosis by Pfizer–BioNTech COVID-19 RNA vaccination. **A,** Digital necrosis and bilateral leg vasculitis upon presentation to the ED on 3/11/2021. **B,** Progressive demarcation of fingertip necrotic lesions upon follow-up office visit on 4/21/2021.

[3]. Clinical trials are still underway to monitor for primary and secondary outcomes.

Multiple skin manifestations related to COVID-19 infection have been described so far ranging from morbilliform rash, urticaria, vesicular eruptions, acral lesions, chilblains, to livedoid lesions among others and the exact pathogenesis of which is still poorly understood [4,5]. However, to our knowledge, there have not been yet any described cases of worsening of vasculitis, APS, cryoglobulinemia, following Pfizer–BioNTech COVID-19 vaccine.

Although vasculitis has been reported following intravesical instillations of bacillus Calmette–Guerin [6], hepatitis B vaccine [7], influenza and pneumococcal vaccine [8], none of these vaccines were associated with the production of aPL-PS that has been suggested as a possible factor in thromboembolic complications of COVID-19 [9]. Remarkably, the present case provides initial evidence that Pfizer–BioNTech COVID-19 RNA vaccine itself is capable of inducing SLE, aPL-PS, APS, and cryoglobulin-associated vasculitis that eventually rapidly progressed to digital skin necrosis in the absence of COVID-19 immunity.

Cryoglobulinemia vasculitis is a small vessel vasculitis with a characteristic finding of cryoglobulins in the patient’s serum. Type I cryoglobulins are single monoclonal immunoglobulins associated with a B-cell

lymphoproliferative disorder. When cryoglobulins are polyclonal immunoglobulin IgG with monoclonal IgM that have rheumatoid factor activity, they are called type II cryoglobulins. The third type of cryoglobulins are polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Types II and III are called sometimes mixed cryoglobulinemia. Cryoglobulin levels are quantified by determining the cryocrit as the percentage of the total serum volume following incubation at 4 °C for 72 h [10].

Our patient was diagnosed with type II cryoglobulinemia vasculitis that led to digit necrotic changes. Although the patient already had vasculitic changes in her legs months prior to her vaccination, her finger discoloration and necrotic changes only started to show few days after receiving her Pfizer–BioNTech COVID-19 RNA vaccine. It is also true that cryoglobulinemia vasculitis can be triggered by some infections mainly hepatitis C and that other forms of vasculitides can be associated with infections such as hepatitis B, Human immunodeficiency virus (HIV), erythrovirus B19, cytomegalovirus, varicella-zoster virus and human T-cell lymphotropic virus (HTLV)-1 among others [11], but the Pfizer–BioNTech COVID-19 vaccine is a not a live attenuated vaccine and our case delineates the possibility of induction of aPL-PS by the RNA itself which was not described before in other vaccines. Since the patient failed to develop anti-COVID-19 spike IgG, we conclude that the vaccine RNA or antigen induced the APS. This raised the possibility that the vaccine RNA may have stimulated the innate arm of the immune system and thus triggered autoimmunity and SLE flare [12]. It is also plausible that the RNA encoded spike protein itself may have triggered the production of aPL-PS, as autoimmunity to phosphatidylserine may itself serve as a mediator of inflammation in COVID-19-induced disease pathogenesis [13].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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