OBSERVATIONS: CASE REPORTS

Severe Exacerbations of Systemic Capillary Leak Syndrome After COVID-19 Vaccination: A Case Series

Background: Flares of systemic capillary leak syndrome (SCLS) release plasma into peripheral tissues, which typically leads to hypotensive shock and multiple organ dysfunction (1). Anasarca and compartment syndromes may develop as a result of excessive intravenous (IV) fluid administration (2). Between episodes, patients are typically asymptomatic. The diagnosis of SCLS is based on characteristic clinical findings that include hypotension, hemoconcentration, and hypoalbuminemia. Prophylaxis with IV immunoglobulin (IVIG) is disease sparing and improves survival (3).

We describe 3 patients who had severe flares of SCLS immediately after receiving standard doses of the COVID-19 vaccines that have emergency use authorization from the U.S. Food and Drug Administration. These events were classified as non–dose-related, unexpected, and serious adverse events according to the World Health Organization.

Objective: To alert clinicians to the possibility of SCLS-like events immediately after COVID-19 vaccination.

Case Reports: Patient demographic characteristics and hospital experiences are detailed in Table 1, and the results of selected laboratory tests are summarized in Table 2.

Patient 1 was diagnosed with SCLS with monoclonal gammopathy of unknown significance in 2006 after 2 characteristic episodes. She declined IVIG treatment but had no disease relapses during 15 years of treatment with oral theophylline and terbutaline. In March 2021, she presented to the emergency department of Exeter Hospital 2 days after receiving a single dose of the Ad26.COV2.S vaccine (Janssen). She had hypotension and tachycardia and developed protracted shock and anasarca. Results of blood cultures and nasal swab polymerase chain reaction tests for SARS-CoV-2 were negative. After she developed additional SCLS-related complications and continued to deteriorate, care was discontinued on hospital day 7.

Patient 2 had a normal vaginal delivery in 2002 followed by hypotension and edema, which was attributed to amniotic fluid embolism. In 2018, she had another episode of hypotension (systolic blood pressure was approximately 50 mm Hg) and anasarca after several days of upper respiratory symptoms. This episode was attributed to sepsis, although blood culture results were negative. In February 2021, she presented to the emergency department of Virginia Hospital Center 2 days after receiving the second dose of the mRNA-1273 vaccine (Moderna). She had hypotension and tachycardia and later developed shock and anasarca. Results from a nasal swab polymerase chain reaction test for SARS-CoV-2 and a screen for other common respiratory pathogens (Table 1) were negative. All symptoms resolved with supportive treatment. Treatment with IVIG was started; monoclonal gammopathy of unknown significance (IgG κ) was detected during an asymptomatic period.

Patient 3 had syncope and seizures in December 2020 and again in February 2021. His neurologic work-up, which included an electroencephalogram and magnetic resonance imaging of the brain, was normal. In April 2021, he presented to the local emergency department 1 day after receiving the second dose of the BNT162b2 vaccine (Pfizer-BioNTech). He had tachycardia and developed status epilepticus and was transferred to Maine Medical Center. During transport, he developed a cardiac arrest with pulseless electrical activity, which responded to cardiopulmonary resuscitation and epinephrine. Blood and urine cultures were negative, as were results from multiple nasal swab polymerase chain reaction tests for SARS-CoV-2. Monoclonal gammopathy of unknown significance was not detected by serum or urine immunofixation during the hospitalization.

Table 1. Patient Demographic Characteristics and Hospital Experiences

Parameter	Patient 1	Patient 2	Patient 3
Age, *y*	68	46	36
Sex	Female	Female	Male
Race	White	White	White
Presenting signs and symptoms	Nausea/vomiting, syncope, hypotension, and tachycardia*	Influenza-like symptoms†, hypotension, and tachycardia‡	Syncope, hypotension, and tachycardia§
Hospital course	Protracted hypotensive shock; anasarca, acute kidney injury, disseminated intravascular coagulation, bilateral lower-extremity compartment syndromes, and widespread digital necrosis	Hypotensive shock, anasarca‖, bilateral lower-extremity pain but not compartment syndrome, deep venous thrombosis, and a pericardial effusion	Status epilepticus, cardiac arrest, anasarca, acute kidney injury, disseminated intravascular coagulation, pulmonary edema, and pleural effusions on hospital day 3
Treatments	IV fluids, vasopressors, antibiotics, stress-dose corticosteroids, renal replacement, IVIG (1 g/kg of body weight), and bilateral lower-extremity fasciotomies	IV fluids¶, vasopressors, antibiotics, and stress-dose corticosteroids	IV fluids, anticonvulsants, 4 vasopressors, antibiotics, and stress-dose corticosteroids
Disposition	Died on hospital day 7	Discharged on hospital day 7	Discharged on hospital day 10

IV = intravenous; IG = immunoglobulin.
* The patient's systolic blood pressure was approximately 60 mm Hg, and heart rate was 120 beats/min.
† Nasal swab specimen negative for all of the following respiratory pathogens tested: adenovirus; coronaviruses 229E, HKU1, NL63, and OC43; human metapneumovirus; human rhinovirus/enterovirus; influenza A and B; parainfluenza 1-4; respiratory syncytial virus; *Bordetella pertussis*; *Chlamydophila*; and *Mycoplasma pneumoniae*.
‡ The patient's systolic blood pressure was 49 mm Hg, and heart rate was 130 beats/min.
§ The patient's heart rate was 180 beats/min with atrial fibrillation; blood and urine culture results were negative.
‖ The patient gained 18 kg of weight; blood culture results were negative.
¶ Included 7 L of crystalloid and albumin boluses.

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Table 2. Laboratory Abnormalities

Variable*	Normal Range†	Patient 1	Patient 2	Patient 3
Hemoglobin level, *g/L*	112–157	201	233	199
Hematocrit	0.341–0.449	0.62	0.686	0.628
Platelet count, $\times 10^9$/*L*	150.00–440.00	350.00	213.00	174.00
Albumin level, *g/L*	35–52	11	20	23
Creatinine level				
μmol/L	48.63–106.1	229.01	132.63	212.21
mg/dL	0.55–1.2	2.59	1.5	2.4
Aspartate aminotransferase level, *U/L*	5–34	4491	47	541
Lactate level, *mmol/L*	0.5–2.2	10.9	7.7	10.9
Creatine kinase level, *μkat/L*	0.48–2.8	1092.8	23.19	55.58
Erythrocyte sedimentation rate, *mm/h*	0–25	ND	1	ND
IgG level, *g/L*	7.00–16.00	ND	<2.70	1.10

ND = not done.
* Data represent peak (hemoglobin, hematocrit, creatinine, aspartate aminotransferase, lactate, and creatine kinase), minimum (albumin and IgG), or admission (platelets and erythrocyte sedimentation rate) values reported during the vaccine-related hospitalization.
† Based on National Institutes of Health Clinical Center guidelines.

Discussion: We describe 3 patients with SCLS or a history suggestive of SCLS who developed life-threatening flares 1 to 2 days after COVID-19 vaccination. We believe these patients identify SCLS as a risk factor for the development of serious adverse reactions after COVID-19 vaccination. However, we recognize that these observations do not rule out other causes of these flares. For example, infection-related symptoms precede 44% to 64% of all acute flares (1,4), and flares have been reported with SARS-CoV-2 infection (5). However, we were unable to identify any of these other triggers.

Systemic capillary leak syndrome is a rare disease, and persons without a diagnosis of SCLS or a history suggestive of SCLS are unlikely to develop a flare after COVID-19 vaccination. However, some persons with unexplained episodes of hypotension and edema may have undiagnosed SCLS. In addition, we note that none of the 3 patients we describe were receiving IVIG prophylaxis when they were vaccinated and that we have received no reports of SCLS flares after COVID-19 (or other antiviral) vaccinations among our 78 patients with SCLS, most of whom are receiving IVIG prophylaxis. Therefore, we recommend that patients with a diagnosis or a suspected diagnosis of SCLS should receive IVIG prophylaxis before vaccination.

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