

PRACTICE | CASES

# Systemic capillary leak syndrome after ChAdOx1 nCOV-19 (Oxford–AstraZeneca) vaccination

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**A** 66-year-old man presented to the emergency department with a 1-day history of generalized malaise, nausea, abdominal pain and dizziness. On presentation the patient's body temperature was 36.5°C, blood pressure 112/78 mm Hg, heart rate 112 beats/min and oxygen saturation 96% (room air), and his respiratory rate was normal. He reported no allergies, no drug or alcohol misuse, and no current use of any medications or over-the-counter products. Two days earlier, he had received his first dose of the ChAdOx1 nCOV-19 (Oxford–AstraZeneca) vaccine.

The patient's medical history included monoclonal gammopathy of uncertain significance (immunoglobulin G [IgG] κ) and a cardiac arrest in 2017. At that time, he presented with generalized weakness and a syncopal episode. Because his hemoglobin level was elevated (210 [normal 130–180] g/L), polycythemia was suspected and phlebotomy was performed. Soon after, the patient became hypotensive and went into pulseless electrical activity arrest. He was successfully resuscitated, recovered without substantial deficits and was discharged home 5 weeks later. His test result for influenza type A was positive, and his shock was attributed to the viral infection.

At this presentation, the patient's hemoglobin level was increased markedly at 224 g/L. He had hypoalbuminemia (28 [normal 34–55] g/L) and an elevated creatinine level (133 [normal 62–115] μmol/L). Coagulation parameters, cardiac and liver enzymes, C-reactive protein and procalcitonin were normal. Screening results for SARS-CoV-2 and extended respiratory virus panel were negative. Examinations using chest radiography, abdominal computed tomography, electrocardiography and focussed assessment with sonography for trauma echocardiography were unremarkable (Table 1 and Table 2).

We started intravenous fluids and empiric treatment with piperacillin–tazobactam, despite the unlikelihood of an infectious process. Twelve hours later, the patient had received more than 6 L of fluid, but his blood pressure had deteriorated to 93/60 mm Hg, his heart rate was 125 beats/min and his polycythemia persisted (hemoglobin 223 g/L). We admitted the patient to the intensive care unit (ICU). In the absence of other causes of impending shock, we diagnosed systemic capillary leak syndrome (SCLS).

## Key points

- Rare cases of systemic capillary leak syndrome (SCLS) have been reported worldwide after vaccination with adenoviral vector and mRNA vaccines against SARS-CoV-2; a number have occurred in patients with a history of SCLS.
- Systemic capillary leak syndrome is a potentially life-threatening immune disorder that is characterized by transient, recurrent episodes of vascular endothelial hyperpermeability that are often triggered by viral upper respiratory infections.
- Hypotension, hemoconcentration, hypoalbuminemia and anasarca are prominent features of SCLS, reflecting the massive leakage of fluids and proteins into peripheral tissues.
- Acute SCLS can rapidly evolve into shock and multiorgan failure, and treatment is mostly aimed at correcting hypovolemia and avoiding end-organ damage; prophylactic monthly administration of immunoglobulins can help prevent further episodes.
- Adenoviral vector vaccines against SARS-CoV-2 are not advised for patients with a history of SCLS.

During the first 24 hours of his admission, the patient received more than 10 L of intravenous fluid, but his hemoglobin and lactic acid levels remained elevated (Table 1), and his creatinine level continued to rise. Central venous pressure was consistently 0–1 mm Hg. He did not need vasopressors and he required oxygen therapy only transiently. He developed substantial anasarca and gained 15 kg. Eventually, his hemodynamic status improved, laboratory abnormalities resolved, and he was discharged 4 days later.

We considered various causes of hypotension, polycythemia and hypoalbuminemia, and eliminated all of them (Table 2). Because his SCLS developed 2 days after vaccination against SARS-CoV-2 and we identified no other triggers, we suspected a possible adverse reaction to the ChAdOx1 nCOV-19 vaccine and reported the reaction to our local department of public health.

## Interpretation

Systemic capillary leak syndrome is a rare disorder associated with recurrent episodes of extravasation of fluid and protein into the interstitial space.<sup>1,2</sup> Fewer than 500 cases have been

**Table 1: Laboratory test results for the patient during his 4-day stay in hospital**

Laboratory test	Test result						
	At admission	4 h	12 h	24 h	48 h	72 h	96 h
Hemoglobin, g/L (normal 130–180 g/L)	224	226	223	184	142	131	136
Hematocrit, % (normal 39%–52%)	65	68.8	68	54.8	41.9	38.4	40
White blood cell count, $\times 10^9/L$ (normal 4.4–11.0 $\times 10^9/L$ )	14.5	19.7	24.5	21.5	11.4	7.6	6.9
Neutrophil count, $\times 10^9/L$ (normal 1.8–7.0 $\times 10^9/L$ )	10.5	15.7	21.3	16.7	7.6	4.6	4.3
Lymphocyte count, $\times 10^9/L$ (normal 1.0–4.0 $\times 10^9/L$ )	2.4	2.2	2.4	3.2	2.5	2.1	2
Platelets, $\times 10^9/L$ (normal 140–440 $\times 10^9/L$ )	222	237	251	202	173	164	174
Albumin, g/L (normal 34–55 g/L)	28	ND	ND	25	ND	ND	38
Creatinine, $\mu\text{mol/L}$ (normal 62–115 $\mu\text{mol/L}$ )	133	133	159	122	90	71	79
Lactate level, mmol/L (normal 0.5–2.2 mmol/L)	ND	ND	3.8	3.3	1.1	ND	ND
D-dimer level, $\mu\text{g/L}$ (normal 0–500 $\mu\text{g/L}$ )	353	ND	ND	ND	ND	ND	ND
Prothrombin time, INR (normal 0.9–1.1)	1.1	ND	ND	ND	ND	ND	ND
Partial prothrombin time, s (normal 20.1–26.4 s)	28.4	ND	ND	ND	ND	ND	ND

Note: ND = not done, INR = international normalized ratio.

reported. Recognizing SCLS may be challenging, because presentation has often been preceded by a prodrome of flu-like symptoms and may be mistaken for sepsis. There are no specific diagnostic criteria for SCLS. Once other causes of shock have been excluded, the classical triad of hypotension, hemoconcentration and hypoalbuminemia supports the diagnosis of SCLS.<sup>2</sup> Together with generalized edema, those 3 features are manifestations of the vascular hyperpermeability and extreme hypovolemia that occur with this syndrome.

The exact pathophysiology of SCLS is mostly unknown. Typically, exacerbations can be triggered by viral upper respiratory infections.<sup>1,3–5</sup> An overwhelming immune response and upregulation of soluble inflammatory and angiogenic mediators during flares appear to be linked to vascular endothelial hyperpermeability.<sup>2</sup> Monoclonal gammopathy of uncertain significance (predominantly IgG  $\kappa$ ) is observed in 68%–85% of patients with SCLS, although a pathogenic role for the paraprotein has yet to be established.<sup>2</sup> Reports exist of patients with SCLS who had a cardiac arrest triggered by influenza type A, similar to the experience of our patient in 2017.<sup>5,6</sup> It is likely that his cardiac arrest at that time occurred during an unrecognized episode of SCLS; he had hypoalbuminemia (29 g/L), hemoconcentration and hypovolemia. However, SCLS was not suspected until this admission.

Our patient's near-fatal episodes illustrate that unrecognized SCLS can be life-threatening; SCLS is associated with an estimated 10-year mortality rate of 25%–34%.<sup>1,4</sup> In addition to shock and renal and cardiopulmonary failure arising from intravascular volume depletion, thromboembolic events and compartment syndrome can occur. Systemic capillary leak syndrome can be classified as grade 1 (hypotension responding to oral hydration), grade 2 (intravenous fluids without hospital admission), grade 3 (life threatening and requiring admission to an ICU) and grade 4 (fatal).<sup>1</sup>

No interventions other than fluid resuscitation have been shown to halt or delay progression of a flare of SCLS.<sup>2</sup> Most episodes are self-limited and resolve within 4 days.<sup>1</sup> The frequency of recurrence of SCLS varies, ranging from once weekly to once every 10 years. Administration of prophylactic monthly intravenous Igs can reduce the frequency of episodes.<sup>1,2</sup>

The World Health Organization (WHO) reports that 3.8 billion doses of vaccines against SARS-CoV-2 have been administered worldwide (as of July 29, 2021; WHO Coronavirus [COVID-19] Dashboard, available at <https://covid19.who.int>). Adverse effects are usually mild and local in nature; however, rare serious adverse reactions can occur, such as pericarditis or myocarditis, anaphylaxis, Guillain-Barré syndrome and thromboembolic events with concurrent low platelet levels (the latter occurring mostly with adenoviral vector vaccines).<sup>7</sup>

In April 2021, the European Medicines Agency (EMA) reported 6 cases of SCLS following receipt of the ChAdOx1 nCoV-19 vaccine (including 1 fatality).<sup>8</sup> Three of those patients had a previous history of SCLS. More than 78 million doses of the ChAdOx1 nCoV-19 vaccine have been administered in Europe, with a reported rate of 1 case of SCLS per 13 million doses.<sup>8</sup> In June 2021, Health Canada issued the first report of SCLS in a patient who had received a ChAdOx1 nCoV-19 vaccine in Canada.<sup>9</sup> The United Kingdom's Medicines & Healthcare products Regulatory Agency (MHRA) reported 8 potential cases of SCLS that occurred shortly after administration of the ChAdOx1 nCoV-19 vaccine.<sup>7</sup> Our patient had a score of at least 4 on the Naranjo Adverse Drug Reaction Probability Scale,<sup>10</sup> making this a possible case of exacerbation of SCLS induced by the ChAdOx1 nCoV-19 vaccine.

Many health agencies have concluded that SCLS, albeit rare, should be considered a serious and potentially fatal adverse effect of the ChAdOx1 nCoV-19 vaccine, and are now advising against its use in patients with known SCLS.<sup>7–9</sup> After the EMA's

**Table 2: Causes of polycythemia, hypoalbuminemia and hypotension and the reasons for exclusion in our patient**

Presentation	Differential diagnosis	Reason for exclusion
<b>Polycythemia</b>		
Primary polycythemia	<b>Inherited:</b> Congenital heart defects	<ul style="list-style-type: none"> <li>• Normal transthoracic echocardiogram</li> </ul>
	<b>Acquired:</b> Polycythemia vera	<ul style="list-style-type: none"> <li>• Absence of Janus kinase 2 (<i>JAK-2</i>) mutation (Val671Phe)</li> </ul>
	Leukemia	<ul style="list-style-type: none"> <li>• Absence of <i>BCR-ABL</i> t(9;22) mutation</li> </ul>
Secondary polycythemia	Chronic hypoxia or cardiopulmonary abnormalities	<ul style="list-style-type: none"> <li>• No clinical symptoms of obstructive sleep apnea and low risk according to the STOP-BANG score</li> <li>• No known chronic pulmonary disease</li> <li>• No obesity hypoventilation syndrome and no daytime hypercapnia</li> <li>• No elevation of erythropoietin level: 4.6 (normal range 5.0–16.0) IU/L</li> <li>• Normal hemoglobin and hematocrit levels between acute episodes</li> <li>• No history of high-altitude travel</li> </ul>
	Erythropoietin-secreting tumours	<ul style="list-style-type: none"> <li>• Level of erythropoietin not high</li> </ul>
Relative polycythemia	Dehydration Capillary leak syndrome	<ul style="list-style-type: none"> <li>• Not excluded</li> </ul>
<b>Hypoalbuminemia</b>	Nephrotic syndrome	<ul style="list-style-type: none"> <li>• No proteinuria, negative urine protein-to-creatinine ratio: undetectable (normal &lt; 0.15 g protein/g creatinine)</li> <li>• No evidence of hyperlipidemia that may be associated with nephrotic syndrome (normal fasting lipid profile)</li> </ul>
	Poor nutrition or liver cirrhosis	<ul style="list-style-type: none"> <li>• Rapid correction of serum albumin levels is inconsistent with hypoalbuminemia from poor nutrition or cirrhosis</li> <li>• No features of liver cirrhosis or ascites on abdominal CT</li> </ul>
<b>Hypotension and shock</b>	Sepsis	<ul style="list-style-type: none"> <li>• Normal procalcitonin level 0.28 (normal 0.00–0.39) µg/L and C-reactive protein level 4.9 (normal 0.0–10.0) mg/L</li> <li>• No evidence of infection on chest radiography and abdominal CT</li> <li>• Two negative results for blood cultures</li> <li>• Negative result for urine culture</li> <li>• Negative result for screening (RT-PCR) test for SARS-CoV-2 (COVID-19 direct diagnostic kit)</li> <li>• Negative result for serology screening test for SARS-CoV-2 IgG</li> <li>• Negative results for screening for common respiratory viruses and pathogens: syncytial respiratory virus; influenza type A (H1 and H3); influenza type B; parainfluenza viruses 1, 2, 3 and 4; human metapneumovirus; entero-rhinovirus, coronavirus NL 63, HKU1, OC43 and 229E; adenovirus; <i>Bordetella pertussis</i> and <i>parapertussis</i>; <i>Chlamydia pneumoniae</i>; or <i>Mycoplasma pneumoniae</i></li> <li>• Negative results for serology screening test for HIV-1 and -2 (p24 combo)</li> </ul>
	Cardiogenic and obstructive shock	<ul style="list-style-type: none"> <li>• Normal FAST ultrasonography in the emergency department</li> <li>• Normal electrocardiogram</li> <li>• Normal transthoracic echocardiography and negative result for exercise stress test (recent outpatient investigations)</li> <li>• Absence of pulmonary edema and raised central venous pressure</li> <li>• Normal cardiac enzymes (troponin &lt; 3 [normal 0–18] ng/L) and D-dimer levels (353 [normal &lt; 500] µg/L)</li> <li>• Negative V/Q</li> </ul>
	Anaphylaxis	<ul style="list-style-type: none"> <li>• Absence of typical clinical signs or symptoms associated with anaphylaxis (e.g., respiratory compromise, rash, pruritus, angioedema or persistent gastrointestinal symptoms)</li> <li>• Normal tryptase level: 3.0 (normal &lt; 11) µg/L</li> </ul>
	Hereditary angioedema	Normal C4 esterase activity (0.20 [normal 0.13–0.40] g/L) and C1 esterase activity (0.97 [normal 0.69–1.42] g/L)
	<b>Other diseases excluded</b>	Cancer drug reactions Hemophagocytic lymphohistiocytosis Viral hemorrhagic fever Snakebite envenomation

Note: CT = computed tomography, FAST = focussed assessment with sonography for trauma, IgG = immunoglobulin G, RT-PCR = reverse transcription–polymerase chain reaction.

July 2021 report of 3 cases of severe SCLS, 2 with fatal outcomes, which were potentially linked to the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen; an adenoviral vector vaccine), similar advice against using the Ad26.COV2.S vaccine in patients with a history of SCLS was made.<sup>8</sup>

In June 2021, a case series described 3 patients who presented with acute SCLS within 2 days of receiving a SARS-CoV-2 vaccine.<sup>11</sup> They all had monoclonal gammopathy of uncertain significance and pre-existing SCLS. The 3 patients received different vaccines: Ad26.COV2.S, mRNA-1273 (Moderna) and BNT162b2 (Pfizer–BioNTech). To our knowledge, no other cases of SCLS have been reported that were associated with mRNA SARS-CoV-2 vaccines, and thus far no warnings or recommendations related to SCLS have been released regarding the mRNA-1273 or BNT162b2 vaccines. Whether exacerbations are triggered by adenoviral vectors themselves or by SARS-CoV-2 antigen (spike protein) remains to be determined.

Administration of mRNA SARS-CoV-2 vaccines can still be used in patients with a history of SCLS, if the benefits are considered to outweigh the risks. After vaccination, physicians and patients must be extra vigilant, because exacerbations can develop quickly and patients may require urgent medical assessment. In our opinion, patients should be monitored closely during the 7–10 days after vaccination with home surveillance of blood pressure, heart rate, weight and urine output; hemoglobin and albumin levels should be measured at least once or twice. We also suggest that prophylaxis with intravenous immunoglobulins be started before vaccination, if not already given monthly.

## Conclusion

We presented the case of a patient with an acute exacerbation of SCLS after ChAdOx1 nCoV-19 vaccination. Early recognition and treatment of acute SCLS is crucial. When a patient presents with generalized edema, malaise, hypotension, hemoconcentration or hypoalbuminemia shortly after administration of a SARS-CoV-2 vaccine, regardless of which vaccine was administered, SCLS should be considered. A history of SCLS is now considered a contraindication to adenoviral vector vaccines against SARS-CoV-2. Health care professionals should report any suspected adverse reactions to SARS-CoV-2 vaccines to their public health agency.

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