Systemic capillary leak syndrome (SCLS) after receiving BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine

Masatoshi Inoue, Yu Yasue, Yoichi Kobayashi, Yutaka Sugiyama

Nephrology, Tajimi Hospital, Tajimi, Japan

Correspondence to
Dr Masatoshi Inoue;
inoue.masatoshi333@gmail.com

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SUMMARY

Systemic capillary leak syndrome (SCLS), also known as Clarkson's disease, is a rare disorder of unknown aetiology. Since SCLS was first described in 1960, fewer than 500 cases have been reported. SCLS is diagnosed by the classic triad of hypotension, haemoconcentration and hypoalbuminaemia resulting from fluid extravasation. Some reports show that SCLS may sometimes occur as a side effect of adenoviral vector COVID-19 vaccines, although there is only one report (two cases) of SCLS after receiving a messenger RNA vaccine. Survival rates for SCLS are very poor without treatment, so it is crucial for clinicians to recognise this disorder. A middle-aged woman who presented with generalised malaise and anasarca after receiving the BNT162b2 COVID-19 vaccine was diagnosed with SCLS. Treatment with methylprednisolone and intravenous immunoglobulin was commenced and her symptoms resolved. We expect that this case report will add to the existing literature on this rare disorder and the side effects of vaccinations.

BACKGROUND

Systemic capillary leak syndrome (SCLS), also known as Clarkson's disease, is a rare disorder of unknown aetiology. Since SCLS was first described in 1960, fewer than 500 cases have been reported in the medical literature. SCLS is diagnosed by the classic triad of hypotension, haemoconcentration and hypoalbuminaemia resulting from fluid extravasation.[1] This 'leak' phase lasts several days, and the 'post-leak' phase usually begins from 48 hours to 1 week after the onset of shock, in which fluids are mobilised from the peripheral tissues into the intravascular space, followed by normalisation of blood pressure and diuresis.[2] Anasarca and compartment syndromes may develop as a result of excessive intravenous fluid administration during the 'post-leak' phase.[3]

Monoclonal gammopathy of uncertain significance (MGUS) is present in 68%–85% of patients with SCLS, but a pathogenic role of paraprotein remains unclear.[4] Typically, SCLS can be triggered by upper respiratory infections such as influenza,[5 6] West Nile virus[7] and so on. Recently, five cases of SCLS triggered by COVID-19 were reported.[8 9] SCLS is considered a cytokine-mediated disease, so the benefit of steroids presumably relates to their ability to reduce the expression of multiple cytokines[10]; however, the reason that steroids are ineffective in some cases of capillary leak syndrome is unknown.[11] Currently, intravenous immunoglobulin (IVIg) is the most promising therapy for both acute treatment[12] and long-term prevention.[13]

CASE PRESENTATION

A woman in her 40s presented to the local emergency department with a 1-day history of generalised malaise, chest discomfort and anasarca. Four days earlier, she had received the second dose of the BNT162b2 messenger RNA (mRNA) COVID-19 vaccine (Pfizer-BioNTech). She was not on any medications and had no known allergies, alcohol abuse, prior episodes of oedema, or family history of oedema or sudden death. When she received the first dose of the COVID-19 vaccine 3 weeks before the second one, she was aware of mild generalised malaise, which resolved spontaneously in a few days. She receives influenza vaccine every year and never had problems. She had hypotension (<60 mm Hg) and tachycardia (130 beats per minute). After receiving 5 L of intravenous fluid, she remained in shock and was transferred to our hospital. When she arrived at our hospital, her consciousness was lucid, and her body temperature was 37°C, blood pressure was 86/52 mm Hg, respiratory rate was 23 per minute, heart rate was 129 beats per minute and oxygen saturation was 99% (oxygen 2 L/min via nasal cannula). Chest X-ray and whole-body CT were unremarkable. Echocardiography showed normal myocardial function. Her serum haemoglobin level was elevated (241 g/L; normal 137–168 g/L) and her serum albumin level declined (18 g/L; normal 41–51 g/L) (table 1). Blood cultures and multiple nasal swab PCR tests for COVID-19 were all negative. We admitted her to the intensive care unit, treating her with 5 L of intravenous fluid over the next 24 hours and norepinephrine. The following day, monoclonal gammopathy of unknown significance (IgG λ) was detected. In view of these clinical features and results, we diagnosed her with SCLS. Therefore, treatment with methylprednisolone (mPSL) 1000 mg/day for 3 days and IVIg 50 g (1 g/kg) was commenced. Urine output increased to 5500 mL/day on day 4 and the intravenous fluid was withdrawn. Ultrasonography and contrast-enhanced CT revealed thrombi in the femoral vein and inferior vena cava (5 cm in length, 2 mm in diameter, homogeneous, low echo) on day 5. Anticoagulation therapy using intravenous unfractionated heparin was administered. D-dimer level declined (3200 µg/L; normal 1–1000 µg/L) on day 8 and follow-up ultrasonography showed a

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Table 1 Laboratory investigations of the patient

Laboratory test	Test results		
	Refering hospital	12 hours	60 hours
Haemoglobin, g/L (normal 116–148 g/L)	241	109	95
Haematocrit, % (normal 35.1%–44.4%)	72.3	32	27.7
White cell count, $\times10^9$/L (normal 3.0–8.6$\times10^9$/L)	55.9	20.7	8.4
Neutrophil count, $\times10^9$/L (normal 1.8–7.5$\times10^9$/L)	43	16.1	7.47
Lymphocyte count, $\times10^9$/L (normal 1.0–4.8$\times10^9$/L)	10	3.73	0.58
Platelets, $\times10^9$/L (normal 158–348$\times10^9$/L)	143	120	82
Creatinine, µmol/L (normal 46–79 µmol/L)	19.2	10.4	4.6
Lactate level, mmol/L (normal 0.5–2.0 mmol/L)	3.91	1.11	1.11
D-dimer level, µg/L (normal 0–1000 µg/L)	ND	3300	10 700
Brain natriuretic peptide level, ng/L (normal 0–18.4 ng/L)	ND	33.7	485.6

ND, not done.

significant reduction in the thrombi on day 9, so anticoagulation therapy was withdrawn. D-dimer level declined further to 1000 on day 11. All symptoms resolved and laboratory abnormalities improved. The patient was discharged 12 days after admission. She is under regular follow-up without recurrence.

INVESTIGATIONS

SCLS is characterised by hypovolaemic shock as a result of fluid extravasation. Serum albumin level is low, and haemoglobin level and haematocrit are remarkably high. In several days, fluids rapidly return to the blood vessels and pulmonary oedema usually arises. As a result, death from SCLS typically occurs during this phase, and intravascular volume and chest X-ray should be monitored frequently. MGUS is observed in most of the patients with SCLS, so M-component tests (blood and urine) and bone marrow examination should be done.

DIFFERENTIAL DIAGNOSIS

In the acute leak phase, other causes of hypovolaemic shock must be ruled out. Blood and urine culture is essential to exclude sepsis, and whole-body CT should be done. Serum tryptase levels and whether urticaria is present are useful to rule out anaphylaxis. Haemoglobin levels and haematocrit are remarkably high, so haemorrhagic shock can be ruled out. There are no specific diagnostic criteria for SCLS; however, the classic triad of hypotension, haemoconcentration and hypoalbuminaemia could support the diagnosis of SCLS if other causes of hypovolaemic shock have been ruled out.

TREATMENT

The patient received over 10 L of intravenous fluid per day. The following day, we started mPSL 1000 mg/day for 3 days and IVIg 50 g (1 g/kg). Anticoagulation therapy is also necessary if a thrombus formed in the deep veins. After acute therapy, we continued IVIg 0.6 g/kg/month as prophylaxis therapy.

OUTCOME AND FOLLOW-UP

Presently, 2 months have passed since she was discharged. She is under regular monthly follow-up and she is receiving IVIg 0.6 g/kg/month without recurrence. She has not yet received the third dose of the COVID-19 vaccine. We are planning to hospitalise her for monitoring before vaccination.

DISCUSSION

In this paper, we describe a female patient presenting with generalised malaise, chest discomfort and anasarca after receiving the BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine who was diagnosed with SCLS. The Medicines and Healthcare products Regulatory Agency in the UK reported 13 cases of capillary leak syndrome in the context of more than 49 million doses of the ChAdOx1 COVID-19 vaccine (Oxford-AstraZeneca), and advise that the ChAdOx1 COVID-19 vaccine is not used in people who previously experienced episodes of capillary leak syndrome.[14] The European Medicines Agency also issues that SCLS may occur as a side effect of the ChAdOx1 COVID-19 vaccine and Ad26.COV2.S vaccine (Johnson & Johnson-Janssen), both of which are adenoviral vector vaccines.[15] To our knowledge, however, there is only one report of SCLS after receiving the BNT162b2 COVID-19 vaccine (an mRNA vaccine; Pfizer-BioNTech) in the world.[16] There is a case report of SCLS after receiving an influenza vaccine.[17] Although it is unknown what components of a vaccine trigger exacerbations, we consider that any kind of antiviral vaccine can trigger SCLS. The mechanism of IVIg in patients with SCLS is not yet known. IVIg has been widely used for the treatment of MGUS-associated diseases such as neuropathy.[18] Because MGUS is present in 68%–85% of patients with SCLS, we believe that SCLS and MGUS are somehow related, but details are unknown. The median annual attack frequency in subjects treated with IVIg is lower (0, range 0–3.3; 40 patients) than with theophylline or terbutaline (2.25, range 0–20; 27 patients).[2] As far as we know, there are no reports of SCLS flares after COVID-19 or any other antiviral vaccinations among patients with SCLS who are receiving IVIg prophylaxis. The dosage of IVIg is generally 0.4–2 g/kg/month and she was light (height: 164 cm, body mass index: 18.0), so we started IVIg 0.6 g/kg/month as prophylaxis therapy.[19] We also recommend that patients with SCLS receive IVIg as the first line in prevention therapy. Although international guidelines recommend at least 3 months of anticoagulation in all patients after acute venous thromboembolism, we withdrew anticoagulation therapy. Because she is at low risk of thrombosis, we think the vein thrombosis occurred as a result of haemoconcentration with the SCLS 'leak' phase, so we consider that preventing the SCLS 'leak' phase by IVIg will prevent thrombosis. The causal relationship between COVID-19 vaccine and SCLS has not been established and further research is needed.

CONCLUSIONS

There are no specific diagnostic criteria for SCLS, so it may be challenging to recognise this disease. This is the first case report in Japan of SCLS after vaccination, although there are a few cases of oedema, hypotension and shock after vaccination.[20] We are concerned that there are patients with SCLS who are misdiagnosed as another disorder. Prognosis is still uncertain, but patients who survive the initial severe SCLS episode are estimated to have a 10-year survival rate greater than 70%.[7] Clinicians should consider SCLS in patients with unexplained anasarca, haemoconcentration and hypotension following any kind of antiviral vaccine. Since the causal relationship between COVID-19 vaccine and SCLS has not yet been established, more research is needed.

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Patient's perspective

"The whole experience was very frightening for me. I thought I had a cold until I went to the hospital. It is true I am afraid of vaccination, but I am planning to get a third dose of the COVID-19 vaccine. Of course, I will get IVIg prophylaxis before vaccination. I am happy that doctors all over the world are learning from my case, and I hope all SCLS patients will not be mislabeled and will get adequate treatment."

Learning points

- Hypotension, haemoconcentration, hypoalbuminaemia and anasarca are crucial features of systemic capillary leak syndrome (SCLS).
- Intravenous immunoglobulin is the most promising therapy for both acute treatment (1–2 g/kg) and long-term prevention (0.4–2 g/kg/month) of SCLS.
- SCLS could be associated with both adenoviral vector vaccines and messenger RNA vaccines.
- Anticoagulation therapy is also necessary if a thrombus formed in the deep veins in the acute leak phase due to haemoconcentration and increased serum viscosity.

Contributors All persons who meet the authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in *BMJ Case Reports*. Conception and design of study: MI, YY, YK, YS. Acquisition of data: MI. Analysis and/or interpretation of data: MI. Drafting the manuscript: MI. Revising the manuscript critically for important intellectual content: MI, YY, YK, YS. Approval of the version of the manuscript to be published: MI, YY, YK, YS.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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