CASE REPORT

Severe capillary leak syndrome with cardiac arrest triggered by influenza virus infection

Lotte Ebdrup,1 Kirk Druey,2 Trine Hyrup Mogensen1,3,4

SUMMARY

Systemic capillary leak syndrome (SCLS), also known as Clarkson syndrome, is a rare disease with a potential fatal outcome. The clinical picture involves leakage of fluid and protein from the bloodstream into peripheral tissues, resulting in hypoalbuminaemia, elevated haematocrit, oedema and hypotension. The spectrum of the symptoms ranges from discrete swelling/oedema of extremities to fulminant cardiogenic shock. We present a case with a 52-year-old man diagnosed with SCLS after being resuscitated from cardiac arrest, which was complicated by compartment syndrome. The severe episode of capillary leak was potentially triggered by influenza virus infection. With the benefit of hindsight, he presented with symptoms of SCLS 2 years prior the major acute episode. Here we describe this case and review some aspects of the literature on SCLS, with particular focus on the pathogenesis, treatment/prophylaxis and long-term physical and psychological complications.

BACKGROUND

Systemic capillary leak syndrome (SCLS), also known as Clarkson syndrome, is a rare disease with a potentially fatal outcome. The syndrome was first described by Dr Clarkson in 1960 in a patient with recurrent episodes of hypotension, subcutaneous swelling, anasarca and increasing haematocrit.1 Due to the central role of vascular leakage in the pathogenesis, the disease was named idiopathic SCLS (or Clarkson disease). Since then, more than 350 cases of SCLS have been described in the literature.2 3 However, the fundamental pathogenesis of this entity remains largely unresolved. The diagnosis is made based on the presence of a triad of hypotension (systolic blood pressure <90 mm Hg), haemoconcentration (haematocrit >49%–50% in men and 43%–45% in women) and hypoalbuminaemia (<3.0 g/dL).2 A characteristic of SCLS is the presence of paraprotein (M component) in blood, also known as gammapathy of unknown significance (MGUS), in the majority of patients, although it is not required for the diagnosis of SCLS.

Due to the rarity of the disease and a general lack of recognition by clinicians, SCLS is probably underdiagnosed. The disease is sporadic and has been described most commonly in middle-aged Caucasians with an equal sex distribution, although cases have been reported in ethnic groups from around the world. The typical acute SCLS episode presents as hypotensive shock with intravascular volume depletion and haemoconcentration. Most patients rapidly develop peripheral oedema (anasarca) and hypoalbuminaemia followed by resuscitation with intravenous fluids due to plasma extravasation. Renal failure can occur due to acute kidney injury (AKI) during this ‘leak’ phase. Pleural, pericardial effusion, ascites and oedema of the gastrointestinal tract are sometimes present. Forty-eight to 96 hours later, fluids are mobilised from peripheral tissues into plasma with renormalisation of circulation and diuresis.3 The severity of attacks varies, and patients with severe episodes may also experience separate milder attacks characterised by fatigue, weakness, mild oedema and muscle discomfort. Similarly, the frequency of attacks is highly individual/variable, ranging from several mild attacks per week to up to intervals of 5–10 years between flares.4 Complications of acute vascular leak in SCLS include acute renal failure, thrombosis/pulmonary embolism and compartment syndrome, which may lead to sensorimotor neuropathy, foot drop or amputation.

CASE PRESENTATION

Here we describe a 52-year-old man admitted to the intensive care unit (ICU) of our university hospital in February 2016 after 2–3 days of diffuse abdominal pain, which increased in intensity 5–6 hours prior to collapse, unconsciousness and cardiac arrest. Medical history included evaluation in the haematology department, October 2014, for a 2-month history of headache and several days of pain and swelling in both calves, polyarthalgia, and a normal blood pressure; evaluation with ultrasound of the lower extremities, CT scan of thorax and abdomen and bone marrow histopathology (negative for JAK3 mutation) were negative. The following 1.5 years before the acute admission, the patient had experienced two episodes of moderate, unexplained swelling of legs or arms and complained of persistent headache; moreover, he was diagnosed with a mild depression and granted partial disability; allowing him to work fewer hours/week because of this (still undiagnosed) condition.

On admission to the ICU, the patient had cardiac arrest with pulseless electrical activity, hypotension, severe hypovolaemia and extreme hypoalbuminaemia (0.8 g/dL), increased haemoglobin (25.8 g/dL) and haematocrit (0.56), all of which normalised within 6 hours (table 1). Coronary angiography was performed, which revealed patent coronary arteries and no underlying cardiac pathology that could account for his presentation. CT scan of the thorax, abdomen and cerebrum was without pathology. No pericardial or pleural effusions were visible. Massive fluid extravasation causing swelling of
Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Table 1  Blood tests in 2014, 2016 (major leak) and 2017 (follow-up)

|          | Normal range | 2014         |          | 2016         |          | 2017         |
|----------|--------------|--------------|----------|--------------|----------|--------------|
|          |              | October      | February | 12th         | 14th     | 06th         |
|          |              | 4th          | 6th      | 08:00        | 14:00    | 06:00        |
| Albumin  | 3.6–4.5 g/dL | 3.6          | 3.8      | 0.8 L        | 3.2 L    | 2.8 L        |
| Haemoglobin | 13.8–17.2 g/dL | 19.3 H    | 8.3      | 25.8 H       | 10.3 L   | 11.9 L       |
| EVF      | 40–50%       | 51 H         | 39       | 56 H         | 30 L     | 35 L         |
| Creatinine | 60–105 μmol/L | 94          | 83       | 227 H        | 191 H    | 259 H        |
| Sodium   | 137–145 mmol/L | 137        | 141      | 141          | 147 H    | 144          |
| Potassium | 3.5–4.6 mmol/L | 4.6         | 4        | 3.7          | 3.2 L    | 4.6          |
| Phosphate | 0.71–1.23 mmol/L | 4.09 H   | 2.89 H   | 2.59 H       |          |              |
| ALT      | 10–70 U/L    | 19          | 23       | 398 H        | 458 H    | 380 H        |
| TNT      | 14 ng/L      | 219 H       | 829 H    | 827 H        |          |              |
| Creatine kinase | 50–270 U/L | 254 H    |          |              |          |              |
| Myoglobin | <75 μg/L     | 273 H       | 10936 H  |              |          |              |
| CRP      | <8 mg/L      | 6.4         | 2.9      | 5.5          | 3.7      | 43 H         |
| Leukocytes | *10^9/L     | 5.7         | 3.3      | 12.9 H       | 8.4      | 8.5          |
| Thrombocytes | *10^9/L   | 211         | 174      | 106 L        | 106 L    | 98 L         |
| Lactate, arterial | 0.5–2.5 mmol/L | 8.2 H     | 14.8 H   | 4.7 H        |          |              |
| D-dimer  | <0.5 mg/L    | <20 H       | >20 H    | 7.0 H        |          |              |
| INR/PP   | <1.2–10.6–1.3 | /1.2       | /1.2     | 3.6 H        | 1.7 H    | 1.1          |
| APTT     | 25–38 s      | >150 H      | >134 H   | 45 H         |          |              |
| M-spike (plasma) mg/dL |          | Positive 100 | Positive (kappa IgG) 520 |
| Kappa chain | 0.33–1.94 mg/dL | 48 H     |          |              |          |              |
| Lambda chain | 0.57–2.63 mg/dL | 2.07      |          |              |          |              |
| Ratio kappa/lambda | 0.26–1.65 | 2.31 H     |          |              |          |              |
| Complement C1q | 0.24–0.61 μg/mL | 0.35      |          |              |          |              |
| Complement C3c | 90–180 mg/dL | 0.499 L    | 129 (2016) |          |          |              |
| Complement C4 | 10–40 mg/dL | 0.088 L    | 30 (2016) |          |          |              |
| IgA      | 80–490 mg/dL | 109         | 140      |              |          |              |
| IgG      | 610–1490 mg/dL | 530 L     | 1600 H   |              |          |              |

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; CRP, C reactive protein; EVF, erythrocyte volume fraction; H, high; INR, international normalized ratio; L, low; TNT, troponine T.

INVESTIGATIONS
The most severe manifestations of SCLS are hypovolaemic shock and cardiac arrest. A history of localised oedema and increased haematocrit should alert the clinician and prompt further diagnostic. Serum albumin levels, haematocrit and blood pressure should be monitored frequently during an attack. M-component (blood and urine), complement C3/4, C1-esterase inhibitor levels and function must be measured, together with other parameters to exclude or confirm other diagnoses.

The patient was evaluated at the National Institutes of Health 18 months after the acute episode. Lab tests were repeated, including beta-2-microglobulin, C3/4, quantitative immunoglobulins and immunofixation electrophoresis (table 2). Cardiac MRI was normal.

DIFFERENTIAL DIAGNOSIS
Polycthemia vera was considered 2 years prior to the major capillary leak event.

In the acute phase, other reasons for shock (septic, cardiogenic, bleeding and so on) must be ruled out. Other rare causes of hypotension may include neuroendocrine tumours, inferior vena cava syndrome or coagulopathy. Likewise, hereditary angio-oedema may share features with SCLS and should be excluded by measuring C1 esterase inhibitor levels. Infections with filoviruses (e.g., Ebola and
The pathogenesis of SCLS remains poorly understood, but the central pathology may include vascular endothelial dysfunction. Sera obtained from acute flares of SCLS reduce barrier function of healthy microvascular endothelial cells, whereas convalescent sera from the same patients do not. This suggests the presence of soluble mediators precipitating vascular leakage during acute SCLS flares. While allergic triggers are not typically associated with SCLS attacks, increasing evidence suggest that inflammation is often linked to leak episodes, and up to three out of four patients reported a virus-like prodromal illness preceding the leak. These included viral infections, such as influenza virus, respiratory syncytial virus and West Nile virus. Previously, a case report described the occurrence of SCLS triggered by influenza virus infection in a 40-year-old woman. This patient’s presentation differed somewhat from ours, in that the respiratory symptoms of influenza were more prominent, and she did not experience cardiac arrest. Moreover, elevated proinflammatory mediators, including interleukin-6, were measured during acute attacks. Intense physical exercise and exhaustion has been linked to disease flares in patients with SCLS, suggesting a potential role for metabolic stress in the induction of vascular barrier disruption. A genetic component has also been considered, although no specific mutations have been uniformly associated with SCLS so far. One small genome-wide association study suggested a potential genetic link and identified a candidate susceptibility locus, but the number of patients included was too small to reach firm conclusions. Given the central common aspect of abnormal endothelial physiology, several studies have sought to address the abnormalities in angiogenic permeability factors, such as vascular endothelial growth factor A angioptioid 2, which are increased transiently in sera during attacks. Intriguingly, because most patients do not have residual oedema during asymptomatic intervals, these findings suggest that endothelial barrier dysfunction is also transient, manifesting only around disease flares.

One important question relates to the potential pathogenic role of the paraprotein present in most patients with SCLS. Purified IgG does not recapitulate the effects of acute SCLS sera on endothelial cells, suggesting that MGUS is an associated epiphenomenon and not directly related to pathogenesis. The risk of progression to myeloma is not increased compared with other patients with MGUS. Altogether, the pathogenesis underlying abnormal endothelial barrier function may involve both an intrinsic susceptibility to inflammatory mediators as well as extrinsic factors such as the paraprotein.

The treatment of acute episodes of SCLS remains primarily supportive as several strategies including corticosteroids, antihistamines, high dose aminophylline and anticytokine compounds (eg, infliximab) have been used with limited success. A recent multicentre study of patients with SCLS admitted to the ICU demonstrated that therapy of acute flares with high-volume intravenous fluids was independently associated with poorer outcomes. Although a beneficial effect of IVIG (1–2 g/kg) during acute leaks has been suggested based on the study of a few patients, overall, its efficacy in the acute setting has not been established. In contrast, prophylactic administration of IVIG on a monthly basis clearly reduces the severity and frequency of episodes in most patients. A recent study provided evidence of increased survival of patients with SCLS receiving IVIG compared with those not treated with IVIG; it should be considered as current standard of care for this disease. Dosing varies from 0.4 g/kg/month to 2 g/kg/month in different studies, although definite target peak or

### Table 2: Evaluation at National Institutes of Health

| Albumin | Normal range | September 2017 |
|---------|--------------|----------------|
| 4.3–5.5 g/dL | 4.6 |
| Haemoglobin | 13.8–17.2 g/dL | 16 |
| EVF | 36%–48% | 49 |
| M-spike (plasma, gamma) | mg/dL | 400 |
| Kappa light chain | 0.33–1.94 mg/dL | 1.81 |
| Lambda light chain | 0.57–2.63 mg/dL | 0.98 |
| Ratio kappa/lambda | 0.26–1.65 | 1.85 |
| Complement C3 | 90–180 mg/dL | 116 |
| Complement C4 | 10–40 mg/dL | 16 |
| IgG | 700–1600 mg/dL | 2412 |
| Tryptase | <11.5 ng/mL | 2.8 |
| Beta-2-microglobulin | 0.9–1.7 ng/mL | 2.0 |

Within normal range: creatinine, sodium, potassium, ALT, creatine kinase, APTT, INR, IgG and IgM.

APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; EVF, erythrocyte volume fraction; H, high; INR, international normalized ratio; L, low.
trough levels have been defined. Currently, a dose of 1–2 g/kg/month is recommended, and due to the favourable side effect profile, IVIG is mostly recommended as monotherapy due to questionable/uncertain effect of other therapies (thepophysalmine and terbutaline) combined with considerable side effects of those drugs. The mechanism of action of high-dose IVIG is currently unknown but may include anti-idiotypic effects on the paraprotein, neutralisation of proinflammatory cytokines and/or immunomodulatory effects, which have been described previously.  

Fatigue appearing as a pronounced periattack symptom is well established. However, whether subtler mental fatigue and cognitive disturbances occur in chronic or mild forms of SCLS with less severe leaks is not well understood. Typically, central nervous system oedema does not accompany acute episodes of SCLS, although patients are at increased risk of thromboembolic stroke due to haemoconcentration and increased serum viscosity. Our patient was diagnosed with mild depression prior to the major attack and cardiac arrest, and currently, he still suffers from mild cognitive symptoms and chronic headache. We speculate that minor long-term cognitive symptoms may be associated with SCLS in some patients.

### Learning points

- Localised oedema of unknown origin or episodes of increased haematocrit of unknown origin, consider systemic capillary leak syndrome (SCLS).
- In confirmed SCLS, IVIG prophylaxis (1–2 g/kg/month) is the standard of care.
- SCLS may be associated with several clinical symptoms and sequelae, including fatigue, muscle pain, depression and recurrent episodes with minor or major leaks.
- Better understanding of the genetics and immunology underlying the exaggerated microvascular endothelial response to inflammation and physical stress leading to capillary leak syndrome may improve treatment and prophylaxis of the disease.

### Conclusions

Further studies on the clinical attributes of SCLS as well as the basic molecular and cellular mechanisms of the disease will hopefully provide insight into this intriguing and serious medical condition. Understanding the genetic, immunological and pathophysiological mechanisms will help guide clinicians on treatment of acute attacks. Early recognition of this entity and prompt initiation of prophylaxis with IVIG will prevent further morbidity and potential fatalities in patients with SCLS.

**Acknowledgements** We would like to thank the patient and his family for contributing to this manuscript.

**Contributors** LE and THM diagnosed and cared for the patient. KD performed a second opinion evaluation of the patient and advised on follow-up and prophylactic treatment. THM drafted the first version of the manuscript; all authors read and approved the final version of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

### References

1. Clarkson B, Thompson D, Honwirth M, et al. Cylcical edema and shock: due to increased capillary permeability. Am J Med 1960;29:193–216.
2. To TS, Chun KJ, Hong SJ, et al. Clinical presentation, management, and prognostic factors of idiopathic systemic capillary leak syndrome: a systematic review. J Allergy Clin Immunol Pract 2018;6:609–18.
3. Druzy KM, Parkih SM. Idiopathic systemic capillary leak syndrome (Clarkson disease). J Allergy Clin Immunol 2017;140:663–70.
4. Gousseff M, Amau L, Lambert M, et al. The systemic capillary leak syndrome: a case series of 28 patients from a European registry. Ann Intern Med 2011;154:464–71.
5. Pinetón de Chambrun M, Luyt CE, Beloncè F, et al. The clinical picture of severe systemic capillary-leaf syndrome episodes requiring ICU admission. Crit Care Med 2015;43:1216–23.
6. Xie Z, Ghosh CC, Patel R, et al. Vascular endothelial hyperpermeability induces the clinical symptoms of Clarkson disease (the systemic capillary leak syndrome). Blood 2012;119:4321–32.
7. Hsu P, Xie Z, Frith K, et al. Idiopathic systemic capillary leak syndrome in children. Pediatrics 2015;135:e730–e735.
8. Sousa A, Leś O, Escaló-Vergé L, et al. Influenza A virus infection is associated with systemic capillary leak syndrome: case report and systematic review of the literature. Antivir Ther 2016;21:181–3.
9. Xie Z, Chan E, Yin Y, et al. Inflammatory markers of the systemic capillary leak syndrome (Clarkson disease). J Clin Cell Immunol 2014;5:1000213.
10. Durand Bedhu M, Rouget A, Recher C, et al. A systemic capillary leak syndrome (Clarkson syndrome) in a patient with chronic lymphocytic leukemia: A case report in an out-of-hospital setting. Case Rep Emerg Med 2016;2016:1–3.
11. Xie Z, Nagarajan V, Sturdevant DE, et al. Genome-wide SNP analysis of the systemic capillary leak syndrome (Clarkson disease). Rare Dis 2013;1:e27445.
12. Dowden AM, Rulfo OJ, Aziz N, et al. Idiopathic systemic capillary leak syndrome: novel therapy for acute attacks. J Allergy Clin Immunol 2009;124:1111–3.
13. Lambert M, Lauray D, Chahulla E, et al. High-dose intravenous immunoglobulins dramatically reverse systemic capillary leak syndrome. Crit Care Med 2008;36:2184–7.
14. Xie Z, Chan EC, Long LM, et al. High-dose intravenous immunoglobulin therapy for systemic capillary leak syndrome (Clarkson disease). Am J Med 2015;128:91–5.
15. Pinetón de Chambrun M, Gousseff M, Maunin W, et al. Intravenous immunoglobulins improve survival in monoclonal gammopathy-associated systemic capillary-leak syndrome. Am J Med 2017;130:1219.e19–1219.e27.
16. Dézsi L, Horváth Z, Vécsei L. Intravenous immunoglobulin: pharmacological properties and use in polymyopathies. Expert Opin Drug Metab Toxicol 2016;13:434–58.
