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CASE REPORT

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

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SUMMARY

Systemic capillary leak syndrome (SCLS), also known as Clarkson syndrome, is a rare disease with 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.

rapidly develop peripheral oedema (anasarca) and hypoalbuminaemia following 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.

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).³ A characteristic of SCLS is the presence of paraprotein (M component) in blood, also known as gammopathy 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

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, polycythemia, 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

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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)

		2014		2016			
		October		February			
				12th		13th	
	Normal range	4th	6th	08:00	14:00	06:00	2017
Albumin	3.6–4.5 g/dL	3.6	3.8	0.8 L	3.2 L	2.8 L	4
Haemoglobin	13.8-17.2 g/dL	19.3 H	8.3	25.8 H	10.3 L	11.9 L	16.6
EVF	40–50%	51 H	39	56 H	30 L	35 L	48
Creatinine	60–105 µmol/L	94	83	227 H	191 H	259 H	77
Sodium	137–145 mmol/L	137	141	141	147 H	144	140
Potassium	3.5–4.6 mmol/L	4.6	4	3.7	3.2 L	4.6	4.2
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	47 (June)
TNT	14 ng/L			219 H	829 H	827 H	
Creatine kinase	50–270 U/L				254 H	6266 H	
Myoglobin	<75 µg/L				273 H	10936 H	
CRP	<8 mg/L	6.4	2.9	5.5	3.7	43 H	1.4
Leukocytes	*10 ⁹ /L	5.7	3.3	12.9 H	8.4	8.5	3.7
Thrombocytes	*10 ⁹ /L	211	174	106 L	106 L	98 L	191
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	<1.2/0.6–1.3	/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					0.49 49 L	129 (2016)
Complement C4	10-40 mg/dL g/L					0.08 8 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.

both legs and a compartment syndrome developed, necessitating bilateral fasciotomies. Gastroscopy was performed and showed diffuse bleeding. Renal replacement therapy was initiated for AKI. Within the first 48 hours, inotropic support (milrinone), corticosteroids and broad-spectrum antibiotics (piperacillin/tazobactam) were administered empirically as the primary diagnosis remained cryptic. Because the patient presented with acute hypotension, shock and cardiac arrest during peak influenza season, the patient was tested for influenza A and B following our institutional guidelines and was found to be positive for influenza A by PCR. Accordingly, oseltamivir treatment was initiated. Lab tests revealed positive paraprotein (M component) with increased levels of kappa light chains, initially 100 mg/dL, (most recently 520 mg/dL, [table 1](#)). C-1 esterase inhibitor level was normal.

During the course of the episode, infection and necrosis of the anterior muscle of right lower leg at the fasciotomy site developed, necessitating debridement. As a result, long-term residual peroneal nerve paresis on right side persisted following the attack. During his prolonged hospitalisation, the infections (ventilator associated pneumonia and necrosis/infection of anterior extensor muscle compartment) eventually resolved, renal function was restored and the patient was discharged 41 days after admission.

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

Polycythemia 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 (eg, Ebola and

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Table 2 Evaluation at National Institutes of Health

	Normal range	September 2017	
Albumin	4.3–5.5 g/dL	4.6	
Haemoglobin	13.8–17.2 g/dL	16	
EVF	36%–48%	49	H
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	H
Complement C3	90–180 mg/dL	116	
Complement C4	10–40 mg/dL	16	
IgG	700–1600 mg/dL	2412	H
Tryptase	<11.5 ng/mL	2.8	
Beta-2-microglobulin	0.9–1.7 ng/mL	2.0	H

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

APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; EVF, erythrocyte volume fraction; H, high; INR, international normalized ratio; L, low.

dengue) can also present with features of vascular leak similar to Clarkson disease.

TREATMENT

The patient was started on intravenous immunoglobulin (IVIG) (2 g/kg) at day 34 for the prevention of capillary leak syndrome. Since then, he has received a maintenance dose of IVIG 1 g/kg every 4 weeks with a trough level of IgG around 1500 mg/dL and peak levels the day after IVIG administration of around 3000 mg/dL. In accordance with the current guidelines, the patient receives no other prophylactic treatment.

OUTCOME AND FOLLOW-UP

Presently, 2 years after this major leak episode, the patient is in relatively good clinical condition and is receiving IVIG 1 g/kg every 4 weeks with a trough level of IgG around 1500 mg/dL and peak levels of around 3000 mg/dL. He did, however, experience a few minor episodes of oedema/swelling of extremities interpreted as minor leaks despite prophylaxis with IVIG. Moreover, he has a remaining significant fatigue and mild cognitive disturbances and was diagnosed with mild depression. Another medical issue is that he also suffers from neuropathic pain in both legs and receives physiotherapy on a lifelong regular basis.

Finally, the patient is followed in the Department of Hematology with a diagnosis of MGUS. A bone marrow was performed without signs of malignancy. Paraprotein (M-component), Ig levels and other haematological parameters are measured every 3 months.

DISCUSSION

In this paper, we describe a male patient presenting with cardiac arrest who was subsequently diagnosed with SCLS. The case illustrates several aspects typical of SCLS, including potential trigger by virus infection, presence of a paraprotein, severe rhabdomyolysis and compartment syndrome during the acute phase, and finally persistent fatigue and smaller leaks, despite prophylaxis with IVIG. A recent multicentre study on 59 episodes of acute leaks in 37 patients with SCLS admitted to the ICU revealed that compartment syndrome developed in approximately 20% of episodes, whereas the overall mortality during acute attacks was around 19%.⁵

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.⁶ 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.⁴ These included viral infections, such as influenza virus, respiratory syncytial virus and West Nile virus.⁷ 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.⁸ Moreover, elevated proinflammatory mediators, including interleukin-6, were measured during acute attacks.⁹ Intense physical exercise and exhaustion has been linked to disease flares in patients with SCLS,¹⁰ 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 thus far. One small genome-wide association study suggested a potential genetic link and identified a candidate susceptibility locus, but the number of patient included was too small to reach firm conclusions.¹¹ 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 angiopoietin 2, which are increased transiently in sera during attacks.³ 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.³

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.⁶ 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.^{3 12} 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.⁵ Although a beneficial effect of IVIG (1–2 g/kg) during acute leaks has been suggested based on the study of a few patients,¹³ overall, its efficacy in the acute setting has not been established.⁵ In contrast, prophylactic administration of IVIG on a monthly basis clearly reduces the severity and frequency of episodes in most patients.^{4 14} A recent study provided evidence of increased survival of patients with SCLS receiving IVIG compared with those not treated with IVIG¹⁵; 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

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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 (theophyllamine and terbutaline) combined with considerable side effects of those drugs.³ 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.^{3 16}

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.

Patient's perspective

During the years before my diagnosis I had a number of symptoms which prompted me to seek medical advice. I was referred to several different medical departments and SCLS was obviously a difficult diagnosis to make based on my very diverse symptoms. However, I have often considered why I was seen only by relatively young and inexperienced medical doctors. After my SCLS diagnosis I mostly see experienced doctors and I sometimes wonder, whether it might have made any difference had I met/been seen by a specialist before I experienced a severe attack of life-threatening capillary leakage? Since SCLS is such a rare disease and only sparse literature and documentation on this condition exist, it is essential for me to be involved in decisions regarding prophylaxis and treatment and to have the possibility to discuss and express my concerns and priorities with my doctors. This certainly makes me more comfortable and less worried concerning my disease.

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.

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