



Diagnostic and therapeutic considerations in idiopathic systemic capillary leak syndrome: a case report

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Background: Systemic capillary leak syndrome (SCLS) is a rare disorder which leads to severe shock. Typically, endothelial dysfunction leads to massive leakage of fluids from the intravascular compartment to the interstitial space, causing hemoconcentration, hypoalbuminemia, hypotension and potential organ failure. The syndrome may be idiopathic or triggered by disease, such as viral infections. The syndrome is often unrecognized and besides resuscitation, no effective treatments are known.

Case Description: Here we describe a 46-year-old female with recurrent episodes of shock due to unrecognized SCLS, with the second episode being triggered by an asymptomatic COVID-19 infection. She was, besides resuscitation, treated with high dose vasopressors and intravenous immunoglobulins (IVIG). The case is complicated by compartment syndrome with infected muscle necrosis and eventually amputation of both lower legs. Moreover, the patient still has a chronic kidney insufficiency. In this case report we will discuss pitfalls and potential therapeutic options in SCLS treatment.

Conclusions: Vasopressor use may aggravate ischemic complications in a hypovolemic condition and its use should therefore be discouraged in these patients. Cardiac output monitoring should be considered early. The use of IVIG might be beneficial in the acute phase as well as in preventing future episodes of shock. Whether the use of bevacizumab is also of value is yet unclear.

Keywords: Clarkson's disease; systemic capillary leak syndrome (SCLS); intravenous immunoglobulins (IVIG); bevacizumab; case report

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Introduction

Systemic capillary leak syndrome (SCLS) was first described by Bayard Clarkson in 1960 (1). It is characterised by increased capillary permeability leading to severe shock, hemoconcentration, hypoalbuminemia. The disease is rare and under recognized. Whereas in other forms of shock a restrictive fluid balance might be beneficial, in SCLS resuscitation remains the most important aspect of treatment. In this case reports we therefore describe the main diagnostic considerations of SCLS and discuss therapeutic pitfalls. We present the following case in accordance with the CARE reporting checklist (available

at <https://jecm.amegroups.com/article/view/10.21037/jecm-22-22/rc>).

Case presentation

A 46-year-old female patient with a medical history of core rod myopathy, cholecystectomy and hypothyroidism visited the emergency department twice in a period of two months. Written informed consent for publishing this report was obtained. First, she presented because of diffuse muscle weakness (legs more than arms) and a mild shortness of breath for a week. In the emergency

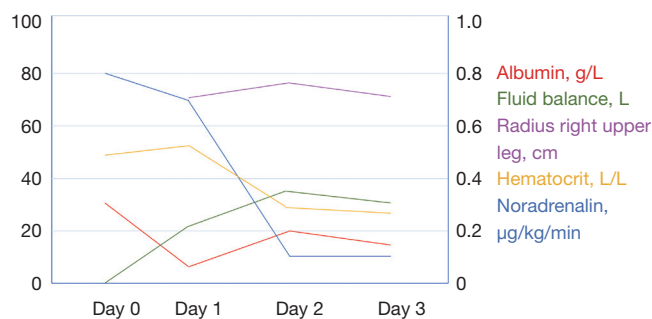


Figure 1 Overview of fluid balance, leg circumference, albumin levels, haematocrit and vasopressor doses.

Table 1 Overview of fluid balance, leg circumference, albumin levels, haematocrit and vasopressor doses

Test	Day 0	Day 1	Day 2	Day 3
Albumin (g/L)	29	6	20	16
Hematocrit (L/L)	0.48	0.59	0.32	0.26
Fluid balance (L)	0.1	21	35	32
Radius right upper leg (cm)	-	69	74	71
Noradrenalin (µg/kg/min)	0.8	0.7	0.1	0.1
Platelet count	302	144	87	71

department she was hypotensive (78/50 mmHg), anuric and collapsed several times. Laboratory results demonstrated a markedly elevated hematocrit (0.59 L/L), leukocytosis ($19.6 \times 10^9/L$, mostly neutrophil granulocytes, without lymphocytosis, lymphopenia or eosinophilia), mildly decreased kidney function and a slightly elevated lactate (2.7 mmol/L). Despite resuscitation with 8 L of fluid (NaCl 0.9%), the patient remained hypotensive. She was admitted to the medium care unit for vasopressor therapy (norepinephrine). The patient developed a normal anion gap (hyperchloremic) metabolic acidosis and after another three litres of fluids (NaHCO₃ 1.4% and Ringer's lactate) vasopressors were stopped. Within 24 h the patient was discharged to the internal medicine ward and kidney function recovered completely. She was discharged six days after admission. Since there were no signs of cardiac dysfunction on echocardiography, no pulmonary embolism on CT-angiography, no sepsis or anaphylaxis, this episode of shock was diagnosed as hypovolemic due to mild nausea, vomiting and diarrhoea. At that time, no other explanation could be found. One month later, she visited the emergency department with similar symptoms. Besides diffuse weakness

and collapse there was a mild cough. She had tested positive for COVID-19 just two days before (despite being fully vaccinated). On examination there was hypotension (90/70 mmHg), mild tachycardia (110/min), anuria and mild tachypnoea (23 breaths per minute) without other respiratory problems. Despite aggressive fluid resuscitation with 12 L of fluids and additional vasopressor therapy, the patient remained hemodynamically unstable and laboratory results revealed hemoconcentration (haematocrit from 0.45 to 0.59 L/L) lactic acidosis and hypoalbuminemia (Figure 1, Table 1). The patient was admitted to the ICU. Due to the large amount of fluids administered pulmonary edema was likely to occur in the following days. Therefore, the patient was intubated to prevent clinical deterioration due to pulmonary edema. Within the next 24 h, the cumulative positive fluid balance increased to 38 L (crystalloids and NaHCO₃ 1.4%). For a short period of time high doses of vasopressors (noradrenaline 0.5 µg/kg/min and vasopressin 0.04 IE/min) were given as well, without effect on blood pressure.

Laboratory results showed no signs of adrenal insufficiency, no clues for systemic mastocytosis or hereditary angioedema or hypothyroidism (Table 2).

After ruling out cardiogenic, distributive and obstructive forms of shock, we diagnosed the patient with SCLS. Besides typical haemoconcentration, hypoalbuminemia and clinical capillary hyperpermeability, we additionally detected a IgG type κ Myeloma protein (M-protein), which is associated with SCLS.

Next, treatment with intravenous immunoglobulins (IVIg) (1 g/kg) was initiated and twenty-four hours later, hemodynamics stabilized.

Fluid administration was stopped and because of the highly positive fluid balance and its potential severe complications, diuretics were given and continuous renal replacement therapy (CRRT) was started to remove excessive fluids. Nonetheless, the ICU stay was complicated by development of compartment syndromes in both arms and legs with creatinine kinase (CK) levels up to 46,000 U/L, for which fasciotomy was performed four days after admission. Our patient had decreasing platelet levels which might have been a clue for disseminated intravascular coagulation (DIC) and although our patient had the clinical signs of a compartment syndrome, limb ischemia due to DIC could not be excluded. In the end we concluded that the presence of muscle necrosis of the left leg was due to a combination of compartment syndrome, the high dose of vasopressor agents used and possibly DIC. In the recovery

Table 2 Diagnostic laboratory measurements on admission

Laboratory results on admission	Result [reference]
Complement component 4 (mg/L)	123 [100–400]
Immunoglobulin G (g/L)	6.37 [7–16]
Immunoglobulin A (g/L)	1.43 [0.7–4]
Immunoglobulin M (g/L)	1.17 [0.4–2.3]
Total protein (g/L)	35 [60–80]
Myeloma protein (g/L)	2.7
Tryptase ($\mu\text{g/L}$)	2.2 [<11.4]
Thyroid-stimulating hormone (mE/L)	2.54 [0.26–4.2]
Cortisol ($\mu\text{mol/L}$)	0.75 [0.19–0.55]

phase the patient remained on renal replacement therapy for a couple of weeks, but in the end her kidney function recovered to an estimated clearance of 30 mL/min. Her hospital stay was prolonged due to infected muscle necrosis, eventually leading to amputation of both legs. After approximately 2.5 months of admission, the patient was discharged for rehabilitation. In the rehabilitation clinic IVIG is given subcutaneous every four weeks.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Idiopathic SCLS, also called Clarkson's disease, was first described by Bayard Clarkson in 1960 (1). He characterised the syndrome as recurrent episodes of shock with haemoconcentration, increased capillary permeability leading to edema and eventually organ failure. The aetiology of the disease was unclear, however, he did find abnormal gamma globulins and described recurrent viral infections prior to the episodes of shock. Nowadays, SCLS is characterised by a prodromal phase (this phase may be absent in idiopathic SCLS), a leak phase and a recovery phase. In the prodromal phase there is a trigger for the systemic leakage. This is most frequently a viral infection, however also stem cell transplantation,

anti-cancer treatment [for example SS1P, IL-1, IL-2, anti-CD22 (2), GM-CSF and checkpoint inhibitors (3-5)], physical exertion and snake bites can induce severe systemic capillary leakage (6). Since the COVID-19 pandemic, relapses of SCLS (7), as well as new onset SCLS have been reported (8). As for our patient, we did not find a clear trigger for the first episode, whereas the second episode could have been triggered by a COVID-19 infection.

The pathophysiology of SCLS includes an increase in capillary permeability to medium sized proteins and plasma. As a consequence, proteins and fluid leak from the intravascular into the interstitial space, resulting in hypotension, edema and hypoalbumenia. The larger red blood cells remain intravascular, resulting in marked hemoconcentration. In most cases this leads to hypovolemic shock. The increase in capillary permeability is thought to be due to cytokines released by various stimuli. These cytokines might disrupt adherend junctions between cells, increasing vascular permeability even more. However, studies at a cellular level are scarce. One study demonstrated elevated vascular endothelial growth factor (VEGF), which is involved in regulating adherence junctions, and angiopoietin-2 (Ang2) levels in SCLS patients (9). Besides cytokines, up to 90% of SCLS patients have a monoclonal gammopathy of unknown significance (MGUS), as already described by Clarkson (10).

Despite the clinical characteristics often seen in SCLS, there are no strict criteria to diagnose this syndrome. Literature suggests the following clinical characteristics and laboratory findings support the diagnosis of SCLS (Table 3).

The corner stone in the treatment of SCLS is fluid resuscitation. This is different from several other forms of shock where a restrictive fluid management and a more liberal use of vasopressors seems beneficial. SCLS patients have severe hypovolemia and the use of vasopressor agents without adequate fluid therapy may be detrimental. The choice of vasopressor therapy is important as well, as vasopressin proved to give more peripheral muscle necrosis (11). Besides frequent laboratory measurements (haematocrit, albumin, lactate), echocardiography can be used to monitor the effect of resuscitation. Furthermore minimal-invasive monitoring, such as pulse contour analysis, or invasive monitoring, for example with a Swan-Ganz catheter, can be used to evaluate fluid responsiveness. Intubation should be considered early in the disease to avoid a difficult intubation because of oedema in the pharynx and larynx. To avoid complications due to excessive fluid administration, it is important to initiate

Table 3 Findings suggesting SCLS

Major	Minor
Hemoconcentration (despite fluid resuscitation)	Elevated VEGF
Hypovolemic shock	Elevated angiotensin 2
Hypoalbuminemia	Present M-protein/MGUS
Generalised edema	
Other forms of shock ruled out	

SCLS, systemic capillary leak syndrome; VEGF, vascular endothelial growth factor; M-protein, myeloma protein; MGUS, monoclonal gammopathy of unknown significance.

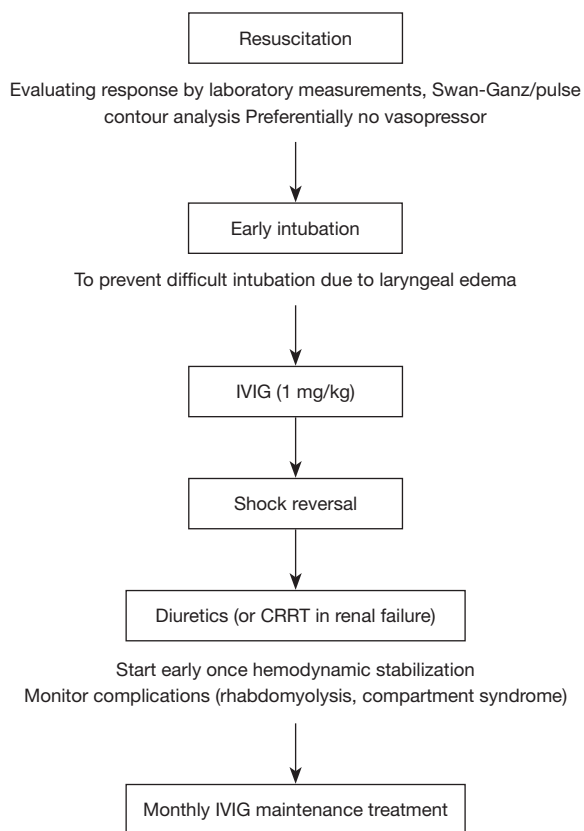


Figure 2 Decision making tool for the treatment of SCLS. SCLS, systemic capillary leak syndrome; IVIG, intravenous immunoglobulins; CRRT, continuous renal replacement therapy.

diuretic treatment or renal replacement therapy as soon as vascular hyperpermeability decreases. Besides symptomatic treatment with fluids, no other effective treatments are known. In several case reports a potential benefit of IVIG is described (12). However, their mechanism of action remains

unknown and a benefit on survival due to IVIG treatment could not be found (13). Besides, IVIG is associated with acute kidney injury. In our patient clinical improvement may be due to IVIG treatment or the natural course of the disease. The acute kidney injury in our patient already occurred before starting IVIG treatment. However, it may have been a contributing factor.

Since several patients also had elevated VEGF levels, additional treatment with bevacizumab was also proposed. Bevacizumab, used in the treatment of several forms of cancer, acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors. This inhibition leads to a reduction in microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues. Since adherence junctions dissolve in response to VEGF (14), possibly aggravating capillary leak, it was postulated that bevacizumab could possibly diminish this phenomenon. Last year, two case reports described successful treatment with bevacizumab. The first patient was a young female suffering from idiopathic capillary leak syndrome (CLS), resembling our patient. Her treatment included IVIG on days 3–4, a subsequently bevacizumab on day 5 (15). The second patient was an infant after stem cell transplantation who developed CLS with response one day after administration of bevacizumab (16). Conversely, another report showed no benefit of bevacizumab in the context of CLS after stem cell transplantation in a 58-year-old woman (17). This may be due to the different pathogenesis of SCLS in children and adults. In murine studies canagliflozin was able to prevent vascular hyperpermeability, and thus might be a hopeful new therapeutic agent (18). It remains to be elucidated to what extent recovery can be attributed to bevacizumab, earlier interventions including IVIG, or the natural course of CLS. However, any shortening of the leakage phase could attenuate the risk of complications. Adjunct treatment with bevacizumab could be considered, further research however is warranted. We advocate a treatment regimen with mainly resuscitation, early intubation to prevent difficult intubation due to laryngeal edema, IVIG in persistent shock, CRRT when necessary and early use of diuretics when shock reverses (Figure 2).

Complications in the disease course of SCLS may be due to the disease itself or because of the treatment. Both hypotension and volume depletion may lead to acute organ failure whereas high dose of vasopressors (in combination with hypovolemia) may lead to ischemia and worsen organ failure. Moreover, IVIG is associated with renal failure.

Because of the large amounts of fluids given, compartment syndrome of all extremities is also frequently seen (12). Compartment syndrome may even be a presenting symptom of SCLS (19).

Idiopathic SCLS is a recurrent syndrome. In patients with recurrent episodes of SCLS, β_2 -agonists (e.g., theophylline) or monthly treatment with IVIG (1–2 g/kg) prevented attacks in about half of the patients and could therefore be beneficial (20). No other preventive treatment has proven beneficial yet. Possibly there is a role for bevacizumab in the future, but further research is necessary.

In conclusion, SCLS is a rare disorder that is characterised by hypovolemic shock with hemoconcentration despite resuscitation, hypoalbuminemia, and progressive organ failure. This diagnose needs to be considered in patients in which hemoconcentration occurs despite extensive fluid resuscitation. Since vasopressor use may aggravate ischemic complications in a hypovolemic condition its use is discouraged in these patients. In addition, the use of IVIG might be beneficial. Whether the use of bevacizumab is also of value is yet unclear.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-22/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-22/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the

patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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