

The challenges in managing a case of refractory and overwhelming shock caused by Systemic Capillary Leak Syndrome

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Abstract

Introduction: Systemic Capillary Leak Syndrome (SCLS) or Clarkson syndrome is a rare condition characterised by vascular hyperpermeability. The frequency and severity of disease flares is highly variable. The disease is associated with significant morbidity and mortality. We describe a fulminant episode in a patient known to have the condition.

Case Report: A forty-four-year-old woman with known SCLS self-presented with malaise and dyspnoea. Over twelve hours she developed refractory shock despite aggressive volume resuscitation and vasopressor use. She ultimately succumbed to the condition despite aggressive treatment which included fasciotomies of all four limbs for compartment syndrome, a laparostomy for suspected abdominal compartment syndrome, steroids, IV immunoglobulin and haemofiltration.

Conclusion: SCLS should be considered in the context of hypotension, haemoconcentration, and hypoalbuminaemia in the absence of albuminuria. The underlying pathophysiology is not yet fully elucidated but results in dramatic vascular leak. Management of acute SCLS episodes can prove extremely challenging for both the intensivist and the anaesthetist. Our patient resembled the archetypal patient identified by Bayard Clarkson and exemplified how precipitous the clinical deterioration can be during these episodes. Abdominal compartment syndrome has not previously been reported. Supportive care in an intensive care setting is the only established treatment. There are still no proven pharmacotherapies to modulate the course of acute episodes of this disease.

Keywords: Shock states; Capillary leak; Compartment syndrome.

Introduction

Systemic Capillary Leak Syndrome (SCLS) or Clarkson syndrome is a rare disorder characterised by inexplicable episodes of endothelial hyperpermeability resulting in a shocked state with hypotension, haemoconcentration and hypoalbuminaemia [1]. The condition was first described by Bayard Clarkson in the 1960s [2]. Since then, over 250 additional cases have been described in the literature [3]. Compartment syndrome is frequently reported. In a recent systematic review it was found in 31% of patients and 64% of these patients required fasciotomies [3]. Abdominal compartment syndrome has not previously been described in the absence of recent intra-abdominal surgery [4]. Unlike our case cerebral oedema is also rarely seen [3, 5]. We describe a fulminant SCLS episode in a patient admitted to our institution. We also discuss our improving knowledge of the pathogenesis of the condition and current treatment strategies.

Case Report

A 44-year old Caucasian woman self-referred to the Emergency Department with malaise and progressive dyspnoea on exertion. She described a three-day prodrome of flu-like symptoms, nausea and lethargy that coincided with menses. On examination the patient was alert and orientated and not in obvious distress. Although normotensive, cold peripheries were noted. Point of care blood gas analysis revealed a metabolic acidosis (BE-13.4) with incomplete respiratory compensation. There was haemoconcentration (Hb 21.6 g/dl) with normal inflammatory markers. Other laboratory investigations including serum biochemistry and liver function tests were normal. Sequential Organ Failure Assessment (SOFA) score was 3 (due to reduced daily urine output).

Following a presentation in 2008 which required admission to the Intensive Care Unit (ICU) for invasive ventilation, our patient had been diagnosed with Systemic Capillary Leak Syndrome (SCLS) [6].

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During this episode she suffered a cardiac arrest, but had made a complete recovery. She had previously suffered less severe episodes prior to her eventual diagnosis. SCLS was a diagnosis of exclusion following extensive investigation during quiescent periods. This included complete resolution of the haemoconcentration observed during flares, normal complement studies and serum electrophoresis revealing the characteristic M paraprotein. Apart from occasional mild exacerbations her disease was largely quiescent, controlled on a regime of montelukast, theophylline and salbutamol. The patient had no other significant medical history.

Over several hours the patient experienced recurrent episodes of hypotension and tachycardia. These were initially responsive to crystalloid boluses. Given the absence of an obvious infective focus and similarities (including the triad of hypotension, haemoconcentration and hypoalbuminaemia) to previous episodes a presumptive diagnosis of an exacerbation of SCLS was made. When hypotension persisted despite fluid administration she was transferred to the ICU for vasopressor support. She remained alert and orientated but had notable cool peripheries with a prolonged capillary refill. Despite continued aggressive fluid resuscitation her shocked state continued to deteriorate with increasing noradrenaline requirements, rising lactates (2 to 6 mmol/L) and negligible urine output (<100 ml in the preceding 4 hours).

By twelve hours into admission, the patient had received over 10 litres of crystalloid in the form of lactated Ringer's solution. She had become increasingly oedematous and persistent haemoconcentration was reflected by a haemoglobin of 23.9 g/dl. She now reported severe bilateral lower limb pain, worse on movement. On examination her calves were tense with absent pedal pulses. Following immediate review by the vascular surgery service who measured compartment pressures exceeding 30 mmHg a diagnosis of bilateral compartment syndrome was made. Urgent transfer to theatre for bilateral lower limb fasciotomies was arranged. Prior to this high volume continuous veno-venous haemofiltration (CVVH) with a 2-litre exchange was instituted. This was done both in anticipation of compartment syndrome-related rhabdomyolysis and to manage her evolving acute kidney injury. General anaesthesia was induced cautiously to minimise haemodynamic disturbance with fentanyl 250µg, ketamine 80 mg and propofol 50mg. The airway was then secured using a McGrath videolaryngoscope. There was marked upper airway oedema but remarkably ventilation was unaffected. Viable bulging calve muscles were noted on fascial release. Given the marked airway oedema and unpredictable clinical trajectory the decision was made to keep the patient intubated.

Following return to ICU the patient's condition continued to deteriorate precipitously. A Mean Arterial Pressure (MAP) >60 mmHg was maintained with difficulty through escalating vasopressor doses and continued fluid administration. Bedside transthoracic echocardiogram revealed evidence of intravascular volume depletion with no significant pericardial effusion. Vasopressin and adrenaline infusions were added. It was also hoped that adrenaline would provide β_2 agonism as an adjunctive treatment. Abdominal distention, rising lactates (>8 mmol/L) and anuria raised the possibility of abdominal compartment syndrome. Intra-abdominal pressures of 23 mmHg measured via the bladder confirmed this diagnosis. The patient was returned to theatre for laparostomy and completion fasciotomy of her lower limbs (thighs). Peak serum Creatine Kinase reached 33,431 U/L.

By this time multi-organ failure was established. Noradrenaline,

vasopressin and adrenaline infusions were needed to maintain an adequate blood pressure. Pulse pressure variation continued to show profound intravascular volume depletion. The patient was grossly oedematous, anuric and metabolically deranged despite continuous hemofiltration. She was also coagulopathic (PT 29.6, APTT 74.5, fibrinogen 1.03) with copious serosanguinous ooze noted coming from her surgical wounds. Concerningly at this point her pupils were only sluggishly reactive to light raising the possibility of cerebral oedema. Specific therapies aimed at reversing the capillary leak including systemic glucocorticoids (Hydrocortisone 200 mg) and intravenous immunoglobulin (IVIG) 2 g/kg were unsuccessful. Hydrocortisone was given in ED and IVIG following the patient's initial fasciotomies. Both were continued daily. Although alternative diagnoses were considered unlikely empiric antibiotic therapy (IV tazocin and gentamicin) was commenced in the ICU.

Care continued in the hope of resolution (including bilateral upper limb fasciotomies), but the patient's condition remained refractory to treatment. In consultation with her family a decision was made to switch the focus of care to comfort measures.

Discussion

Idiopathic systemic capillary leak syndrome (SCLS) or Clarkson's disease was first described in 1960 by Bayard Clarkson [2, 7]. He reported recurrent inexplicable episodes of shock and generalised oedema in a previously healthy female patient in her thirties. Attacks were often preceded by a non-specific prodrome of nausea and malaise. Generalised oedema with hypotension and shock would quickly ensue. Resolution would occur spontaneously after several days. Following two years of observation this patient succumbed to a severe episode.

Our knowledge of this condition has improved since then. SCLS is characterised by stereotypic attacks of varying intensity resulting in hypotension, haemoconcentration and hypoalbuminaemia in the absence of albuminuria [1]. Over 250 cases have been described in the literature to date. This has recently surged owing to increased awareness with over 130 cases reported between 2010 and 2016 [1]. Most reported cases have been in Caucasian adults, however this likely reflects sampling bias. Some recent reports of cases in children have been published [8]. There is no sex predominance [1]. In most patients there is no discernible trigger; in others viral infections, heat exposure and extended travel have been implicated [1, 7]. A fatal case of SCLS was recently associated with acute COVID-19 infection [9]. Most patients report a prodrome of fatigue and flu-like illness preceding the onset of attacks. The diagnosis of SCLS is rarely established at first presentation as the features overlap with more common conditions including sepsis, anaphylaxis, adrenal insufficiency, hereditary angioedema and even polycythaemia rubra vera [2].

The onset of an attack is characterised by dramatic vascular leak causing hypotension and anasarca [2]. The duration, severity and frequency of these attacks is highly variable. Classically visceral spaces such as the lungs are spared. This leak phase often ends as abruptly as it starts with the excess extravascular fluid being mobilised from the peripheries into the intravascular space. Both phases of the disease process can result in morbidity and death [1]. Intravascular volume depletion can result in acute renal failure and thrombosis. Fluid accumulation within tissues can cause compartment syndrome and cardiac tamponade. Acute fluid reabsorption can cause pulmonary oedema.

Using albumin-binding dyes, Clarkson demonstrated vascular hyperpermeability, a feature of acute attacks of SCLS [2]. He also demonstrated the existence of a paraprotein in patients' sera which persisted during quiescent periods. This paraprotein (typically IgGκ isotype, as in our patient) is found in 70% of those with SCLS, its role remains uncertain [1, 10]. Acute sera has been shown in vitro to provoke endothelial hyperpermeability, unlike sera taken from patients during quiescent periods [10, 11]. At a cellular level acute sera disrupts endothelial gap junctions and promotes cellular retraction. Vascular Endothelial Growth Factor and Angiopoietin-2 have been identified as possible molecular mediators [11].

The mainstay of treatment of acute severe attacks is titrated intravenous fluid administration and vasopressor support to maintain organ perfusion. Ideally this should occur in an ICU setting where additional organ supports including mechanical ventilation and CRRT can be instituted as needed. Clinicians should anticipate complications such as compartment syndrome and pulmonary oedema. Steroids, aminophylline infusions and high dose IVIG are used to abort acute attacks without particularly solid evidence [12]. A recent case report implicated nitric oxide in acute attacks and suggested a role for methylene blue [13]. The evidence for prophylactic pharmacotherapy is better established and includes IVIG infusions, oral theophylline and terbutaline [14]. IVIG in

particular has been associated with improved survival in monoclonal gammopathy-associated SCLS [15].

In conclusion, SCLS is a rare and potentially devastating condition. It is difficult to diagnose as it mimics other more common conditions. In undiagnosed patients it should be considered in the presence of the classic triad (especially after multiple presentations): hypotension; haemoconcentration; and hypoalbuminaemia in the absence of albuminuria. In patients known to have SCLS early ICU involvement is advisable. Cumulative fluid therapy has been associated with mortality in SCLS patients admitted to ICU [12], although this may simply reflect severity. Permissive hypotension with earlier pressor use may be appropriate. During acute episodes patients with SCLS may require surgical intervention and can prove extremely challenging. Our patient was distinctive in some respects: her course was fulminant and refractory to aggressive therapy; she resembled the archetypal Clarkson patient including the onset of symptoms at time of menses; and the development of presumed cerebral oedema during the course of her acute illness [5, 16]. Supportive care in an ICU environment is the only well-established treatment for acute SCLS episodes at present.

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