Case Reports

Idiopathic systemic capillary leak syndrome (Clarkson's disease) presenting with recurrent hypovolemic shock

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Abstract

A 49-year old male with a past medical history of myocardial infarction and compartment syndromes requiring fasciotomies presented on five occasions with hypovolemic shock. We describe his admissions and presumptive diagnoses which required large volumes of intravenous fluids, admission to intensive care for vasopressors and renal replacement therapy. The presentations were always precipitated by a prodrome of fatigue and pre-syncopal episodes. On his last admission, a diagnosis of Idiopathic systemic capillary leak syndrome (ISCLS), also known as Clarkson's Disease, was reached. He is currently receiving high dose intravenous immunoglobulins on a monthly basis.

Keywords

Shock, capillary, leak, syndrome, Clarkson's.

Key Points

This is the first description of ISCLS or Clarkson's disease locally and we do not expect to see another case given its rarity. This case has significant learning points summarised below:

- Multiple episodes of localised oedema with increased haematocrit are associated with ISCLS or Clarkson's Disease
- The disease may present with recurrent episodes of syncope, chest pain and fatigue and may have a viral-like prodrome. These may progress to a shock-like presentation including hypotension with end-organ damage/failure requiring Critical Care
- It is frequently associated with the presence of a paraprotein
- High-dose prophylactic IVIG (1-2g/kg/month) is the current treatment of choice.
- Patients and staff should be aware of this condition and recognise and treat this promptly with intravenous fluids alongside monitoring for compartment syndrome.

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Introduction

Idiopathic systemic capillary leak syndrome (ISCLS), also known as Clarkson's disease, is a rare disease characterised by recurrent episodes of hypotension, raised haematocrit and peripheral oedema.[1]

The aetiology comprises vascular endothelial dysfunction which results in increased vascular permeability. These episodes of vascular permeability, termed "leaks", can cause massive hypovolemia, shock, kidney injury and increased risk of thrombosis due to relative hyper-viscosity.[2] Significant morbidity and mortality can be associated with acute episodes.

A previous case series suggests that the majority of patients are male (57%) with a median age of onset of 45 years.[3] The classic acute form of Clarkson's disease involves a flu-like prodrome followed by the rapid development of hypovolaemia and peripheral oedema.

Case presentation

A 49-year old male presented to the Emergency Department (ED) with dizziness and chest pain in August 2019. This was his fifth admission. He was independent in his activities of daily living and had never smoked. He had no relevant family history and no drug allergies. His regular medications included ramipril and aspirin.

His past medical history included an anterior ST segment elevation myocardial infarction (STEMI) in 2018 which required angiography and a drug-eluting stent into the left anterior descending artery. Post-procedure, he developed cardiogenic shock and was aggressively treated with intravenous fluids in intensive care. He then developed compartment syndrome in his right arm and both his right and left legs, requiring fasciotomies.

In August 2019, he presented with a three-hour history of central chest pain. He had been feeling

generally unwell for the last 48 hours with multiple pre-syncopal episodes described. His chest pain came on at rest and was initially described as 'mild' before becoming more severe.

His blood pressure was 106/68 mmHg with a heart rate of 96 bpm. He had a normal respiratory rate, oxygen saturations and temperature. He was clammy to touch with cool peripheries. His capillary refill time was 3 seconds. He had bi-basal crackles on auscultation with normal heart sounds. His abdomen was soft with present bowel sounds. He had no clinical evidence of deep vein thrombosis with mild peripheral oedema to his lower limbs.

His electrocardiogram showed no evidence of new ischaemia, demonstrating normal sinus rhythm with inferior Q waves from his previous STEMI. His chest x-ray was clear. Blood results demonstrated an initial troponin of 8 ng/mL (<5 ng/mL) with a white cell count of 46.6 x109/L (4-11 x109/L) [predominant neutrophilia], a C-reactive protein of 2 mg/L (<5 mg/L), and a stage 3 acute kidney injury with a creatinine of 293 mmol/L (60-110 mmol/L). His D-dimer was within a normal range. Additionally, he had evidence of hypoalbuminemia at 32 g/L (35-50 g/L), haemoconcentration with a haemoglobin of 205 g/L (130-180 g/L), and a haematocrit of 65%. A venous blood gas demonstrated a pH of 7.35 (7.35-7.45), a potassium of 5.7 mmol/L (3.5-5.5 mmol/L), lactate of 1.8 mmol/L (0.5-1 mmol/L), base excess of -7 mEq/L (-2 - +2 mEq/L) and bicarbonate of 18 mmol/L (22-29 mmol/L).

He was treated for an infection of unknown source with intravenous piperacillin-tazobactam. He was given 1.5 litres of intravenous fluid in ED over two hours with no effect his blood pressure. A 3-hour troponin taken on the ward returned with a result of 7 ng/mL excluding acute coronary syndrome. He had a pre-syncopal episode where his blood pressure dropped to 79/48 mmHg. He was given a further 2 litres of intravenous fluid over 60 minutes to no effect. Given the similarities to his previous admission to critical care, (March 2019) he was admitted to critical care for further management of his refractory hypotension. He was treated with a further 3 litres of fluid which returned his blood pressure to a normal range. He did not require inotropic support or renal replacement therapy. .

Previous multiple admissions with similar symptoms were noted and further investigations performed. A random cortisol was normal. A short Synacthen test performed for completion was negative. His procalcitonin was normal at 0.27 ng/mL (0.1-0.49 ng/mL), indicating no bacterial infection and antibiotics were stopped. Blood cultures and urine cultures were negative with no growth.

A review of his previous admissions was performed:

1st admission (January 2019)

There was a 4 day prodome with non-specific symptoms and multiple pre-syncopal episodes. He was hypotensive at 96/57 mmHg with a stage 1 acute kidney injury. There were no signs of infection. He was treated with four litres of intravenous fluids over 48 hours. 2nd admission (March 2019).

He presented with syncope and hypotension at 77/54 mmHg. He was peripherally shutdown with weak radial pulses and tachycardic at 108bpm. He had a raised haemoglobin of 212g/L a white cell count of 25.4 x109/L and a stage 2 acute kidney injury. There were no signs of infection. He was admitted to intensive care with refractory hypovolaemic shock and given 6 litres of intravenous fluids and noradrenaline. He required renal replacement therapy. 3rd admission (April 2019)

He presented with a 24-hour prodrome and syncope. He was hypotensive at 98/67 mmHg but not tachycardic, hypoxic or febrile. Investigations were unremarkable. He treated with fluids and discharged with a provisional diagnosis of postural hypotension. 4th admission (June 2019).

He presented with neck pain and chest discomfort. Blood pressure was 106/51 mmHg and heart rate 104 bpm. His examination and investigations were unremarkable with negative troponins. Following a period of observation and review from the medical team he was discharged as a hypotensive episode which resolved spontaneously with no obvious infectious cause.

These episodes summarised in Table 1. On admissions requiring intensive care, his haemoglobin, haematocrit and white blood cells were raised. This would occur alongside hypoalbuminaemia and an acute kidney injury.

Specialists in critical care, haematology, infectious diseases and rheumatology were consulted. A number of differential diagnoses were considered. Hepatitis B/C and human immunodeficiency virus (HIV) tests were negative. An extended autoimmune screen was negative.). Immunological screening showed evidence of an IgG paraprotein (measured at 4g of IgG lambda), normal IgA and low IgM (0.29 (0.5-2.0). His Bence-Jones screen was equivocal with some possible free lambda light chains were present. His serum light chain ratio was normal.

Shock has a wide range of differential diagnoses and is classified into hypovolaemic, cardiogenic, distributive and obstructive. Physiologically, shock is due to circulatory insufficiency with inadequate oxygen delivery due to a problem with either cardiac output or systemic vascular resistance.

With initial raised white cell counts and neutrophilias, the patient was usually treated as presumed sepsis and distributive shock. However, blood and urine cultures and procalcitonin have always been negative. In terms of other causes of distributive shock, there was no evidence of liver failure, neurogenic damage or anaphylaxis and he improved very quickly with fluids which wouldn't occur. Multiple cortisol and negative short Synacthen tests excluded adrenal insufficiency. Thyroid function was also normal.

Obstructive shock was excluded by a normal D-dimer, chest x-ray, and multiple normal echocardiograms. Cardiogenic shock was excluded by these scans, in addition to normal telemetry and troponin values excluding an acute coronary syndrome. His history was not in keeping for other causes of hypovolaemic shock such as gastrointestinal losses, trauma or blood loss.

Comprehensive online searches performed by the advanced critical care practitioners for a combination of recurrent hypovolaemia, haemoconcentration, hypalbuminaemia, the presence of IgG paraprotein and a history of compartment syndrome, suggested a diagnosis of Idiopathic Systemic Capillary Leak Syndrome (ISCLS), also known as Clarkson's disease.

Advice was sought from regional and national immunology colleagues who recommended intravenous immunoglobulin, initially at 2g/kg, on a monthly basis for a year with the dose reduced to 1kg/kg every month for a further year.

The patient is currently in good clinical condition having received several months of IVIG as an outpatient (1g/kg every two weeks). He is followed up by the haematology team. Due to the unique nature of our patient's diagnosis we have given him open access to our ambulatory care unit if he deteriorates so he can receive supportive care. He has not required any further admissions.

Discussion

There are approximately 350 documented cases of ISCLS or Clarkson's disease worldwide.[1] The pathogenesis of the disease is poorly understood. Vascular endothelial dysfunction is suggested as the prime pathological process leading to the presence of soluble mediators on the vascular endothelium which precipitate leakage during acute flares.[2] Vascular endothelial growth factor angiopoietin 2 is a factor involved in flares as its serum levels are transiently raised in sera during attacks.[3] A genetic component has been suggested and a susceptible gene locus identified, but the genome-wide study was too small to reach statistically significant results.[4]

Various case reports and series of patients with Clarkson's Disease demonstrate classical flares in a similar pattern of rapid shock development due to plasma extravasation lasting an average of 3.8 days.[3] No specific trigger has been identified, but in a European

Table 1. Summarising blood results during various admissions. * denotes admission to Critical Care

Investigation	Cardiothoracic ICU admission following STEMI in 2018*	1st admission Jan 2019	2nd admission* March 2019	3rd admission April 2019	4th admission June 2019	5th admission* August 2019
Hb (130-180 g/L)	185	169	212	147	164	205
Haematocrit (0.4-0.54 L/L)	0.537	0.502	0.589	0.451	0.500	0.633
White Cell Count (4-11 x10^9/L)	21.0	14.7	25.4	14.3	12.7	46.6
Neutrophils (2-7.5 x10^9/L)	17.6	11.0	22.4	10.5	10.2	41.6
CRP	11	6	4	2	2	2
Albumin (35-50 g/L)	42	39	35	46	37	32
Urea (2.5-7.8 mmol/L)	5.8	9.4	10.8	7.4	6.4	15.0
Creatinine (64-104 mmol/L)	101	144	176	113	106	293

case registry, 75% of patients experienced a viral-like prodrome immediately prior to attacks.[5] Other triggers which have been suggested include influenza, West Nile virus, and intense physical exertion.[3]

Due to plasma extravasation, the complications of an acute attack are hypoperfusion, sometimes leading to acute kidney injury and shock, hypercoagulability due to increased serum viscosity, in turn causing thrombosis or pulmonary embolism. The hypovolaemic shock can be profound in Clarkson's disease and cause cardiac arrest (6). Massive peripheral oedema secondary to fluid extravasation coupled with aggressive fluid resuscitation can lead to compartment syndrome and consequent fasciotomies.[3,7]

Review of our patient's initial cardiothoracic intensive care admission revealed that despite good flow through his coronary vessels following stenting, he suffered a period of 'cardiogenic shock' just a few hours after stent insertion. He was cannulated for extra corporeal membrane oxygenation (ECMO) but recovered with fluid resuscitation and albumin. It is worth noting that the aetiology of his compartment syndrome was noted as unclear at the time and his haemoglobin was high. With hindsight, it is possible to speculate that the shock following the myocardial infarction was in fact his first documented presentation of Clarkson's disease. The haemoconcentration may have contributed to coronary arterial occlusion and the cannulation of large vessels may have exacerbated limb oedema and contributed to his compartment syndrome.

Treatment of Clarkson's disease involves initial supportive therapy with intravenous fluids. However, a recent multicentre study of patients with flares of Clarkson's Disease showed that treatment with high-volumes of intravenous fluids was independently associated with poorer outcomes.[7] Prophylactic IVIG reduces the severity and frequency of attacks and is significantly associated with improved survival in a multivariate analysis with a five-year survival rate of approximately 78%.[5,8,9] However, its role in acute flare management has not been established.[7] Prophylactic dosing of 1-2g/kg/month is thus currently recommended. Whilst the mechanism of action at such high a dose in not known, it has been suggested that there is neutralisation of proinflammatory cytokines involved in the flare phase of the disease.[3]

Conclusions

This is the first description of ISCLS or Clarkson's disease locally. Given the unique nature of this case, we have a number of significant learning points given the presentation with common masquerading symptoms. These are summarised below:

1. Multiple episodes of localised oedema with increased haematocrit are associated with ISCLS or Clarkson's Disease
2. The disease may present with recurrent episodes of syncope, chest pain and fatigue and may have a viral-like prodrome. These may progress to a shock-like presentation including hypotension with end-organ damage/failure requiring Critical Care
3. It is frequently associated with the presence of a paraprotein
4. High-dose prophylactic IVIG (1-2g/kg/month) is the current treatment of choice.
5. Prompt recognition and treatment with intravenous fluids is essential with careful monitoring for compartment syndrome.

Declaration of interests

The authors declare they have no competing interests.

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