Idiopathic Capillary Leak Syndrome (ISCLS) (Clarkson's Disease): First Reported Case in Oman

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Abstract

Idiopathic Capillary leak syndrome is a rare cause of hypovolemic shock that the physician need to be aware of. It is characterized by a state of hypovolemia with features of widespread fluid third spacing, resulting in a challenging diagnostic and therapeutic dilemma. Here we present a challenging case of a 36 year old women who presents with recurrent episodes of widespread edema with features of hypovolemic shock suggestive of capillary leak syndrome. The resuscitative and therapeutic measures will be discussed.

Keywords: Capillary leak syndrome, Clarkson's syndrome, Capillary leak, Hypovolemia shock

Introduction

Idiopathic Systemic capillary leak syndrome (ISCLS) is a midlife rare disease characterized by recurrent episodic hypotension, severe hypoalbuminemia and hemoconcentration caused by the sudden onset leak of plasma and protein into the interstitial compartment.[1,2] Attacks vary in severity between mild, self-limiting to severe requiring critical care admission. The acute onset of the disease is preceded by non-specific symptoms of fatigue, flu-like symptoms and dizziness as reported in previous studies[1.]

The first case of ISCLS was reported by Clarkson in 1960.[1] Worldwide, around 150 cases of ISCLS have been reported from different countries.[2] To our knowledge, there are no previous cases reported in Oman with Clarkson disease.

Case Report

A 36-year-old woman with a known history of Raynaud's phenomenon presented with a two days history of worsening abdominal pain, generalized body edema, and fever. She had similar presentations in the last three years, which resolved spontaneously within one week. At the time of admission, the patient had generalized pitting edema associated with facial swelling. She looked lethargic, her blood pressure was 77/40 mmHg, heart rate 110/min, SpO_2 was 98% on room air and she was afebrile. On chest examination, she had bilateral fine crackles at the lung bases. There was generalized abdominal tenderness with no rebound tenderness on abdominal examination. Her JVP was not raised.

Her laboratory investigations showed severe hemoconcentration with an initial hemoglobin of 19.1 g/dl (11.0-14.5) and neutrophilic leukocytosis of 32 (1.0-4.8). She had evidence of acute kidney injury with potassium level 5.3 (3-3.5), creatinine 171, eGFR 29 (>90) and bicarbonate of 7. Her chest X ray showed features of pulmonary edema. CT abdomen was done and showed mild ascites and subcutaneous edema. She was initially resuscitated with IV fluids,

a total of 4 L and subsequently was started on vasopressors. She was admitted to the intensive care unit. The cause of her shock was unclear at that point.

Point of care ultrasound was done which showed hyperdynamic left ventricle, underfilled right ventricle and a collapsed inferior vena cava, all of which suggested hypovolemic shock. Due to the constellation of signs and recurrent nature of the disease, capillary leak syndrome was suspected. She was started on intravenous aminophylline, nebulized salbutamol and intravenous human globulin (IVIG) 1g/kg for 3 days to abort the episode. Also, strict input and output was maintained. Improvement was noted on day two with discontinuation of vasopressors and improvement in renal failure. At that point, she had signs of overload for which she was started on furosemide.

On day 6 of admission, repeat investigations showed Hb 13.4 g/dl (11.0-14.5), WCC 6.2 (2.4-9.5), ANC 3.8(1.0-4.8). Her kidney function normalized. The generalized edema had subsided, and the patient returned to her normal weight. The decision was to administer IVIG every 3 months to prevent further episodes. Investigations to look for secondary capillary leak including, rheumatoid factor, ANA, Anti-dsDNA and other autoimmune work-up were all negative. Also, urine and plasma electrophoresis as well as free light chains were negative. Given the above and the recurrent nature of the disease a diagnosis of idiopathic capillary leak syndrome was concluded.

Discussion

We report the first case of Clarkson syndrome identified in Oman. Her presentation and the subsequent course follow the previously reported cases in the literature. A typical episode has three phases; non-specific prodromal phase, the capillary leak phase with hypovolemic shock and generalized edema, and then recovery phase of symptoms, with a period of fluid overload.[3,4] The presence of serum M protein is considered the only laboratory findings detected between each attack.

The patient presented with a typical episode of idiopathic leak syndrome that was previously reported. After the initial prodrome, the episode starts with a state of capillary leak that is characterized with relative hypovolemia secondary to decrease in effective circulatory volume. The patient had generalized massive edema secondary to widespread capillary leak, during which complications arise due to both hypovolemia, as well as tissue edema. Such complications include shock, acute kidney injury, abdominal compartment syndrome and muscular compartment syndrome for which active monitoring is required. This phase lasts for 2-3 days, followed by a state of overload as the capillary leak subsides. At this stage, the patient might develop acute pulmonary edema resulting in respiratory failure and diuresis should be initiated.

Capillary leak occurs in several other conditions that need to be kept in the differential diagnosis. These include septic shock, ovarian hyperstimulation syndrome, engraftment syndrome, hemophagocytic lymphohistiocytosis and viral haemorrhagic fever. However, in these conditions there are other associated features, and the episode is not recurrent.[5]

The pathophysiology of Clarkson syndrome is unclear. Interleukins, angiotensin 2 and vascular growth factors were found to be elevated in the acute phase.[5] Interestingly, acute sera from patients were found to induce microvascular capillary endothelial disruptions and increase permeability in molecular studies.[6]

Treatment strategies for the acute episode are based on observational data rather than controlled trials because of the disease infrequency. Patients presenting with hypotension and hemoconcentration consistent with acute SCLS should be treated in an intensive care setting with intravenous fluids sufficient to counteract intravascular volume depletion, maintain organ perfusion, and avoid severe metabolic acidosis. Despite receiving a large volume of isotonic saline for resuscitation, our patient remained hypotensive requiring vasopressor support. Fluid resuscitation needs to be balanced between maintaining tissue perfusion while monitoring for complications from leak and fluid overload. Early use of vasopressors might be helpful to achieve those goals.[7]

Our patient dramatically improved following administration of salbutamol, aminophylline infusion and IVIG of 1g/kg/d for 3 days. On day 2 of therapy, we observed marked improvement in clinical status of the patient and gradual complete recovery of laboratory markers on day 8 of hospital admission. This course of therapy was followed by IVIG

monthly infusion for a total of 6 cycles. The Patient remains in clinical remission for the last 2 years. IVIG in the acute attack has been used and showed rapid improvement in case reports.[8,9] Salbutamol and theophylline both increase intracellular cAMP that can decrease capillary leak in the acute episode and are also used in prevention.[9]

The long-term use of aminophylline combined with oral terbutaline therapy was utilized in previous case reports to decrease severity and recurrence of acute attacks of SCLS.[10] Intravenous immunoglobulins have been reported to successfully treat severe refractory cases of ISCLS in different case reports of patients of various ages, resulting in clinical remission for up to 3 years.[11] Steroids have failed to demonstrate effect on acute manifestation of ISCLS, thus it is not considered a treatment option in the acute attack or for prevention of subsequent episodes.[1]

The overall mortality reported is 23% in the acute episodes.[2] The attacks are usually self-limiting. Prophylactic B2 agonists, methylxanthines and IVIG may reduce mortality.[2] During the attack, it is important to provide supportive care based on the understanding of the pathophysiology of the disease in order to prevent acute complications, which can be life threatening.[7]

Conclusion

Physicians need to be aware of unusual causes of hypovolemic shock including idiopathic capillary leak syndrome that has a recurrent nature. Episodes are associated with multiorgan failure and increase mortality. The focus should be on acute resuscitation and abortive therapy however, it is important to prevent the attacks by instituting IVIG therapy as a prophylaxis.

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