CASE REPORT

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

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ABSTRACT

Idiopathic capillary leak syndrome, also known as Clarkson's Disease, is a rare cause of hypovolemic shock that physicians should be aware of. It is characterized by a state of hypovolemia with features of widespread fluid third spacing and poses diagnostic and therapeutic challenges. Here, we present a challenging case of a 36-year-old woman who experienced recurrent episodes of widespread edema and hypovolemic shock symptoms suggestive of capillary leak syndrome. The resuscitative and therapeutic measures employed in managing this disease are described in this case report.

Idiopathic systemic capillary leak syndrome (ISCLS) is a rare disease that primarily affects individuals in midlife. It is characterized by recurrent episodic hypotension, severe hypoalbuminemia, and hemoconcentration resulting from a sudden leakage of plasma and proteins into the interstitial compartment.[1,2] The severity of attacks ranges from mild and self-limiting to severe, requiring critical care admission. Non-specific prodromal symptoms such as fatigue, flu-like symptoms, and dizziness have been 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 to date.[2] To the best of our knowledge, no cases of Clarkson's disease have been reported in Oman.

CASE REPORT

We present the case of a 36-year-old woman with a known history of Raynaud's phenomenon. She presented with worsening abdominal pain, generalized body edema, and fever that had been progressing for two days. Similar presentations had occurred in the past three years, with spontaneous resolution within one week. Upon admission, the patient exhibited generalized pitting edema and facial swelling. She appeared lethargic, with a blood pressure of 77/40 mmHg, heart rate of 110 beats/min, oxygen saturation of 98% on room air, and was afebrile. Bilateral fine crackles were auscultated at the lung bases, and abdominal examination revealed generalized tenderness without rebound tenderness. Jugular venous pressure was not elevated. Laboratory investigations revealed severe hemoconcentration, with an initial hemoglobin level of 19.1 g/dL (reference range: 11.0–14.5 g/dL) and neutrophilic leukocytosis of 32 × 10^9/L (reference range: 1.0–4.8 × 10^9/L). Acute kidney injury was evident, as indicated by a potassium level of 5.3 mmol/L (reference range: 3–3.5 mmol/L), creatinine of 171 µmol/L, estimated glomerular filtration rate of 29 mL/min/1.73 m^2 (reference range: > 90 mL/min/1.73 m^2), and bicarbonate level of 7 mmol/L. Chest X-ray revealed features consistent with pulmonary edema, while abdominal computed tomography showed mild ascites and subcutaneous edema. The patient received initial resuscitation with 4 L of intravenous (IV) fluids and was subsequently initiated on vasopressors. She was admitted to the intensive care unit, and the cause of her shock remained unclear at that point. Point-of-care ultrasound demonstrated a hyperdynamic left ventricle, an underfilled right ventricle, and a collapsed inferior vena cava, suggestive of hypovolemic shock. Given the constellation of signs and the recurrent nature of the disease, capillary leak syndrome was suspected. Treatment included intravenous aminophylline, nebulized salbutamol, and intravenous immunoglobulin (IVIG) at a dose of 1 g/kg for three days to stop the episode. Strict

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input and output monitoring was maintained, and on day two, improvement was observed with discontinuation of vasopressors and resolution of renal failure. At this stage, signs of fluid overload prompted the initiation of furosemide. On day six of admission, repeated investigations showed a hemoglobin level of 13.4 g/dL (11.0–14.5 g/dL), white cell count of 6.2 × 10^9/L (2.4–9.5 × 10^9/L), and absolute neutrophil count of 3.8 × 10^9/L (1.0–4.8 × 10^9/L). Kidney function had normalized, and the generalized edema had subsided, with the patient returning to her normal weight. As a preventative measure against further episodes, the decision was made to administer IVIG every three months. Investigations to look for secondary capillary leak including rheumatoid factor, antinuclear antibody, anti-dsDNA, and other autoimmune work-up, were all negative. Urine and plasma electrophoresis, as well as free light chains, were all negative. Considering the aforementioned findings and the recurrent nature of the disease, a diagnosis of ISCLS was concluded.

DISCUSSION

We report the first case of Clarkson's disease in Oman, which exhibited a clinical presentation and subsequent course consistent with previously reported cases in the literature. A typical episode of this syndrome involves three distinct phases; a non-specific prodromal phase, a capillary leak phase with hypovolemic shock and generalized edema, and a recovery phase marked by resolution of symptoms and 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. Following the prodromal phase, the episode started with a state of capillary leak characterized with relative hypovolemia secondary to decrease in effective circulatory volume. The patient had generalized massive edema secondary to widespread capillary leak, which can cause complications due to both hypovolemia and tissue edema. Such complications include shock, acute kidney injury, abdominal compartment syndrome, and muscular compartment syndrome for which vigilant monitoring is required. This phase lasts for two to three days, followed by a state of overload as the capillary leak subsides. At this stage, patients might develop acute pulmonary edema, potentially leading to respiratory failure, and requiring diuresis initiation.

It is important to consider several other conditions in the differential diagnosis of CLS. These include septic shock, ovarian hyperstimulation syndrome, engraftment syndrome, hemophagocytic lymphohistiocytosis, and viral hemorrhagic fever. However, these conditions exhibit distinct associated features and their episodes are not recurrent.[5]

The precise pathophysiology of Clarkson syndrome remains unclear. Studies have revealed elevated levels of interleukins, angiotensin 2, and vascular growth factors during the acute phase.[5] Intriguingly, molecular investigations have demonstrated that acute sera from affected patients induce microvascular capillary endothelial disruptions and increase permeability.[6]

Treatment strategies for the acute episode are based on observational data due to the rarity of the disease, and controlled trials are limited. Patients presenting with hypotension and hemoconcentration consistent with acute ISCLS should be treated in an intensive care setting. IV fluids should be administered sufficiently to counteract intravascular volume depletion, maintain organ perfusion, and prevent severe metabolic acidosis. In our case, 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 leaks and fluid overload. Early use of vasopressors might be helpful to achieve those goals.[7]

Our patient exhibited a remarkable improvement following treatment with salbutamol, aminophylline infusion, and IVIG at a dosage of 1 g/kg/day for three days. On day two of therapy, there was a significant improvement in the patient's clinical status and laboratory markers gradually returned to normal on day eight of hospital admission. This course of therapy was followed by IVIG monthly infusion for a total of six cycles. The patient has been in clinical remission for the last two years. The use of IVIG during acute attacks has been reported in case reports, demonstrating rapid improvement.[8,9] Salbutamol and theophylline, both of which increase intracellular cyclic adenosine monophosphate levels, have been utilized in the acute episode to decrease capillary leak and are also used in prevention.[9]

Long-term treatment with aminophylline in combination with oral terbutaline therapy has been reported in previous cases to reduce the severity and recurrence of acute attacks of ISCLS.[10] IVIGs have shown success in treating severe and refractory cases of ISCLS in various age groups, resulting in clinical remission for up to three years.[11] Steroids have not yet demonstrated efficacy in managing the acute manifestation of ISCLS and are not considered a treatment option in the acute attack or for prevention of subsequent episodes.[1]

The overall mortality reported for acute episodes of CLS is 23%.[2] The attacks are usually self-limiting. Prophylactic use of β2 agonists, methylxanthines, and IVIG may help reduce mortality rates.[2] During the attack, it is important to provide supportive care based on the understanding of the disease's pathophysiology to prevent potentially life-threatening acute complications.[7]

CONCLUSION

It is important for physicians to be aware of unusual causes of hypovolemic shock including ISCLS that has a recurrent nature. These episodes can lead to multiorgan failure and increased mortality rates. The management approach should prioritize acute resuscitation and abortive therapy. However, it is important to prevent attacks using IVIG therapy as a prophylactic intervention.

Disclosure

The authors declared no conflicts of interest. Informed consent was obtained from the patient.

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