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CASE STUDY

The First Case Report of an Idiopathic Systemic Capillary Leak Syndrome (Clarkson's Disease) in Morocco

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ABSTRACT

Background: **The idiopathic systemic capillary leak syndrome (ISCLS), also known as Clarkson disease, is an extremely infrequent and commonly misdiagnosed disease. This rare disorder is characterized by paroxysmal capillary hyperpermeability with diffuse severe oedema and hypovolemia, along with hemoconcentration and hypoalbuminemia.**

Case Summary: **A 60-year-old Moroccan man was admitted to our hospital, presenting with a severe hypovolemic shock associated with diffuse edematous syndrome following an emotional shock. Laboratory tests showed hemoconcentration, hypoalbuminemia, and a monoclonal gammopathy in the electrophoresis of proteins, while all other laboratory tests were normal. During hospitalization, the patient was conditioned and monitored with careful volume expansion using synthetic colloids and an ascites puncture was performed. After excluding other pathologies, the clinical presentation was consistent with the diagnosis of ISCLS. Recurrent episodes were reported before the patient's death.**

Conclusion: **The idiopathic systemic capillary leak syndrome is a potentially life-threatening disease with a high mortality. The pathophysiology of this condition remains unclear despite all previous attempts at clarification. Knowledge of the limited treatment options is crucial for patients' prognosis and overall survival. This report aims to raise awareness of ISCLS.**

Keywords: Capillary leak syndrome, Clarkson.

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1. Introduction

Idiopathic systemic capillary leak syndrome (ISCLS), first described by Clarkson *et al*. [1], is a rare and potentially fatal disorder characterized by recurrent shock with a pathognomonic profile of hypotension, hemoconcentration and paradoxical hypoproteinemia. Since 1960, there have been less than 500 cases and 32 paediatric cases of ISCLS in the literature, confirming this disorder's rare nature [2]. Subjects are most often adults of European origin during their fifth decade. Monoclonal gammopathy, mostly IgG kappa, can guide the diagnosis of ISCLS and is common among patients (65% to 85%) [3]. Patients are usually managed in the intensive care unit because of the severe acute hypovolemia attacks. This management is mainly supportive, and no treatment has proven effective. In severe forms, compartment syndrome and rhabdomyolysis are characteristic complications. This condition is often fatal, with a mortality estimated between 25% and 34% due to circulatory collapse in general. Clarkson's disease is mainly described as an acute form, but a chronic form associated with non-specific symptoms is also mentioned. The stereotypical acute form is divided into 3 phases: a prodromal phase, a leaking phase and a recruitment phase. This form is the most complex to differentiate from other diseases such as septic, toxic and anaphylaxis shock, nephrotic syndrome and drug reactions [4], [5].

ISCLS can present a variety of manifestations and is difficult to differentiate from other disorders. Therefore, the ISCLS is a commonly misdiagnosed disease, and its pathophysiology remains unknown. Increasing awareness and recognition is, therefore, vital to improving the outcome of patients [6], [7].

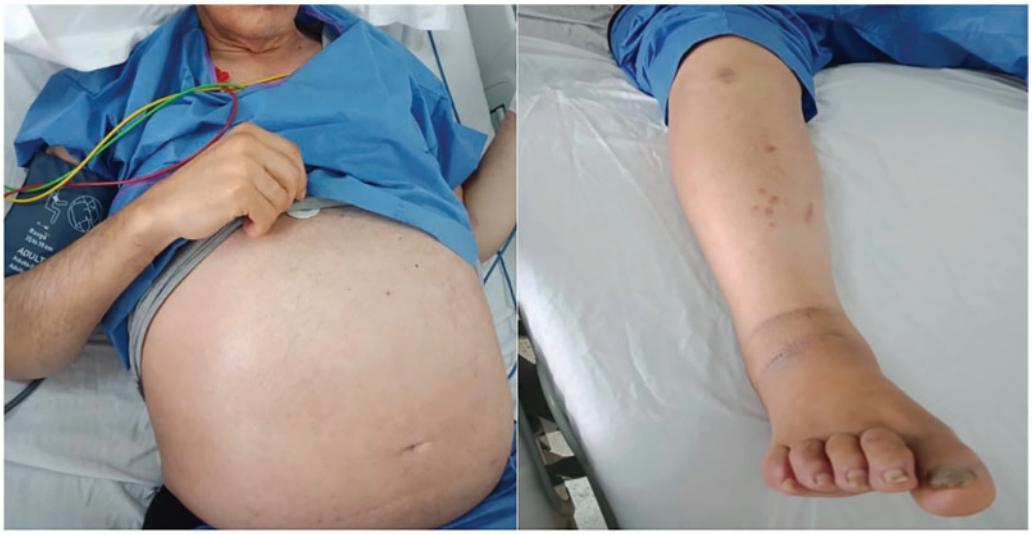

Fig. 1. Patient's ascites and oedemas.

We report the first African case of ISCLS of a 60-year-old Moroccan patient.

2. Case Presentation

2.1. Clinical History and Initial Laboratory Data

A 60-year-old patient was admitted to our department after presenting with acute hypotension complicated by respiratory discomfort with diffuse edematous syndrome following an emotional shock. He reported a coronary heart disease and stent replacement with current use of clopidogrel and acetylsalicylic acid and no allergies.

The patient declared that he started suffering from lipothymia and progressive worsening exertional dyspnea a few months ago. Moreover, he reported sudden asthenia with intense thirst, polydipsia and oliguria.

2.2. Clinical Course

On admission, the patient's body temperature was normal, blood pressure was 80/60 mm Hg, heart rate was 105 beats/min, and respiratory rate was 20 breaths/min. The examination revealed edemas of the face and lower limbs, and the abdominal examination revealed a shifting dullness. A chest X-ray, an abdominal ultrasound, and a cardiac ultrasound were performed, and the results showed pleural bilateral effusion, pericardial effusion, and abundant ascites.

During his hospitalization, the patient was conditioned and monitored, had ascites punctured (6 L in 48 h), and underwent very cautious volume expansion with synthetic colloid (1 L/24 h). Urine analysis was normal with no albuminuria, and the diuresis was 450 mL/24 h. Laboratory tests were prescribed and revealed multiple abnormalities, including anaemia with haemoglobin of 9 g/dL, hemoconcentration with a hematocrit of 55%, hypoalbuminemia with a serum albumin level of 24 g/L, low total protein of 52 g/L, a normal renal function and the 24 h proteinuria was negative. Serum protein electrophoresis showed a monoclonal peak in Beta 2 (Fig. 2 and Table I) and the serum immunofixation showed a monoclonal IgG lambda immunoglobulin. All other tests were normal.

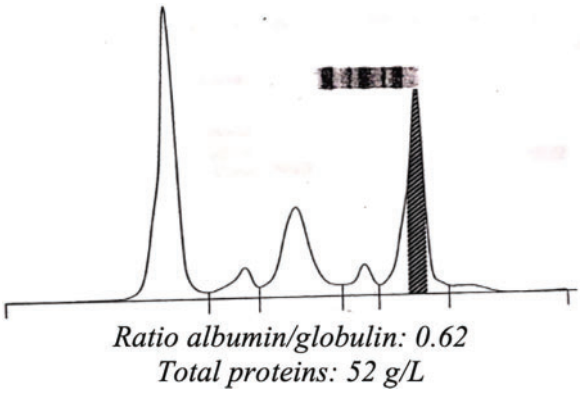

Fig. 2. Serum protein electrophoresis on capillary electrophosis Sebia technique showing a monoclonal peak in Beta 2.

TABLE I: Serum proteins electrophoresis on capillary electrophosis Sebia technique of our patient

Name	%	Normal values %	g/L	Normal values g/L
Albumin	38.1	55.8–66.1	19.8<	40.2–47.6
Alpha 1	5.2	2.9–4.9	2.7>	2.1–3.5
Alpha 2	20.5	7.1–11.8	10.7>	5.1–8.5
Beta 1	4.3	4.7–7.2	2.2<	3.4–5.2
Beta 2	29.9	3.2–6.5	15.5>	2.3–4.7
Gamma	2.0	11.1–18.8	1.0<	8.0–13.5

2.3. Follow-Up and Additional Admissions

After initial stabilization, the common generalized oedema causes were excluded, such as congestive heart failure, nephrotic syndrome, septicemia, acute liver failure and anaphylaxis choc. After 48 hours of hospitalization, the hemodynamic parameters stabilized, and the respiratory signs improved with progressive regression of the oedemas.

A diagnosis of ISCLS was established based on hypoalbuminemia without albuminuria, hypovolemic shock, generalized oedema and monoclonal gammopathy (Fig. 1). During the same year, the patient was admitted on three other occasions because of recurrent episodes of ISCLS with the same symptoms (ascites punctures were also performed), and the patient died at the end of the same year.

3. Discussion

Our patient represents a rare case of severe ISCLS. Idiopathic systemic capillary leak syndrome (ISCLS) is a rare systemic disease characterized by recurrent episodes of hypotension, hypoalbuminemia, and hemoconcentration. It can affect the entire vascular system and shift fluid and protein from the intravascular space to the interstitial space [8].

The clinical presentation of our patient matches the typical characteristics of ISCLS, which typically involve acute hypovolemia, respiratory distress and generalized oedema. A triggering factor is usually found, such as a viral infection, post-partum, exertion or intense emotions, such as in our case [4].

The patient, in this case, experienced a first episode of hypovolemic shock associated with hypoalbuminemia and hemoconcentration and three other attacks during the same year, the last one being fatal.

Our examination and the initial laboratory results allowed us to exclude all other possible causes of shock, like sepsis and anaphylaxis and allowed us to make the diagnosis. Additionally, despite hypoalbuminemia, the absence of albuminuria is a key diagnostic distinguishing ISCLS from other causes of generalized oedema.

To this day, there is still no curative treatment for ISCLS. The management of the hypotension and hypovolemia from the capillary leak phase is mainly supportive and depends on fluid resuscitation. It consists of correcting intravascular volume depletion, maintaining organ perfusion and avoiding severe metabolic complications. We used crystalloids to maintain this hemodynamic stability, but protein solutions could also be used. Fluid administration must be cautiously performed to prevent compartment syndrome and oedema from worsening. In this case, the patient received meticulous volume expansion with synthetic colloids to address hypovolemia, and ascites puncture to relieve fluid accumulation and monitor hemodynamic stability. In some cases, during the recovery phase, oliguria and edemas are improved by diuretics and in some severe cases, hemodialysis may be necessary. To reduce the occurrence of triggers, vaccinations are recommended to eliminate infectious outbreaks.

Besides these conventional treatments, various preventive measures have been explored. Although the pathophysiology of ISCLS is unsure, some cases report that beta-2-stimulants like terbutaline and isoprenaline help inhibit macromolecular leakage triggered by stimuli such as histamine or bradykinin [6]. Some case reports also tried theophylline, vascular endothelial growth factor (VEGF), TNFα and Thalidomide [9], [10]. Additionally, studies have indicated that intravenous immunoglobulin therapy (IVIG) is more effective than β2-agonists. It should be noted that IVIG is recommended as a preventive treatment only because its effect can be deleterious in the acute phase. Therefore, IVIG has become the first-line prophylactic therapy in ISCLS at a dose of 2 g/kg once a month [11]. In the present case, we could not prescribe IVIG because it was very difficult to obtain and expensive. In addition, the four episodes in the same year were close, which made it difficult to institute a prophylactic treatment. Despite the intensive care, the patient experienced recurrent episodes of ISCLS, highlighting the challenges in successfully managing this condition. Therefore, current management primarily focuses on symptom relief and preventing complications, given the absence of established treatments for ISCLS.

The pathophysiology of Clarkson's disease remains poorly understood and is believed to result from endothelial dysfunction caused by endothelial contraction, apoptosis or injury and immune dysregulation. The latest studies showed that dysfunction in endothelial glycocalyx markers contributes to clinical symptoms of acute ISCLS [12]. It has also been suggested that there are exaggerated microvascular endothelial responses to surges of inflammatory mediators. Elevated levels of cytokines have also been observed in acute ISCLS such as CXCL10, CCL2, IL-1β, IL-6, IL-8, IL-12 and tumour necrosis factor α (TNFα) [3], [5]. Moreover, the exact relationship between ISCLS and the monoclonal gammopathy often associated remains unclear. This lack of knowledge about the pathogenesis contributes to the non-existence of targeted therapeutics. Further understanding of the mechanisms is crucial for developing targeted therapies and improving the prognosis.

Various studies associated with ISCLS reported a monoclonal gammopathy of undetermined significance and multiple myeloma. Some reports even showed progression to multiple myeloma after diagnosis [5]. In our case, serum protein electrophoresis showed a monoclonal peak in Beta 2 (Fig. 2), and the serum immunofixation showed a monoclonal IgG lambda immunoglobulin, which comforts the diagnosis.

Clinical challenges are common for patients suffering from ISCLS, and the heterogeneous presentation mainly justifies them. As a result, ISCLS is associated with high morbidity and mortality with fatal outcomes like in the present case. Recurrent attacks, as observed in our case, contribute to the poor prognosis. Concerning complications, various case reports have reported some in association with ISCLS.

Our patient did not experience a kidney complication; however, it is reported that kidney injury is the most common complication. Chronic idiopathic systemic capillary leak syndrome usually leads to acute kidney injury and, therefore, requires daily hemodialysis [10]. Moreover, kidney injury may also result from hypovolemia and cytokine-induced injury, leading to acute tubular necrosis [13].

In the present case, the patient also presented diffuse edemas of the face and lower limbs, and paraclinical examinations showed pleural bilateral effusion, pericardial effusion, and abundant ascites. These edemas are complications of the capillary leak and can even develop into compartment syndrome, as described in some case reports [14].

4. Conclusion

In conclusion, we reported a case of a patient with ISCLS who experienced four severe episodes of this disorder, the last being fatal. ISCLS remains a very rare and severe disease to stumble for an emergency doctor or any

other physician because of its various presentations and symptoms. It can take a considerable delay from the onset of symptoms or many acute attacks before establishing the diagnosis, which can become fatal for the patient. This condition is easily misdiagnosed and probably underdiagnosed due to the lack of awareness. Before assessing this disease, all other causes must be excluded. Clarkson's disease can compromise the patient's quality of life, and the acute attacks are life-threatening. To prevent the recurrence of the attacks and the development of complications, a prophylactic treatment needs to be instituted, IVIG being the most recommended in the first line. Prompt recognition of the disorder and the institution of preventive therapy could reduce morbidity and improve the overall survival of patients.

This report is, therefore, meant to enhance awareness of ISCLS and make clinicians aware of some clinical characteristics and treatment options.

Author Contributions

MB contributed to conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing original drafts, writing review and editing. YT contributed to formal analysis, investigation, methodology, visualization and writing of the original draft. LB contributed to formal analysis, investigation, methodology, visualization and writing of the original draft. A. Morjan contributed to validation. A. Mounir contributed to supervision and validation. RC contributed to validation. CE contributed to validation. NK contributed to validation. LB contributed to validation.

Informed Consent

Written informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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