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Systemic Capillary Leak Syndrome Secondary to Viral Hemorrhagic Fever

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ABSTRACT

Idiopathic Systemic capillary leak syndrome is an unusual clinical presentation with recurrent episodes of shock due to leakage of plasma together with hemoconcentration, hypoalbuminemia and generalized edema. It is also called Clarkson disease and was first described 45 years ago. Fewer than 500 cases of SCLS were reported due to the nonspecific symptoms and high mortality rates. The pathophysiology involves the leakage of fluids and proteins from intravascular to interstitial spaces, leading to generalized edema and shock. Prophylactic treatment with intravenous fluids, immunoglobulins and steroids helped reduce the severity of attacks and improved patient survival in Idiopathic SCLS(Clarkson's). There are two types of SCLS- Idiopathic(Clarkson's) and secondary. The diagnosis of SCLS becomes difficult unless a high degree of suspicion is made, with different causes being ruled out. Here we present a case of a young female who presented with fever, cold/cough and generalized weakness eventually led to shock, later diagnosed as SCLS secondary to viral infection. The secondary form of SCLS is treated according to the underlying etiology with IV crystalloids, steroids, diuretics and other supportive medications. The sole purpose of this article is to emphasize the importance of diagnostic parameters in ruling out various forms of SCLS and to never diagnose a patient based on a single criterion.

Keywords

SCLS, Clarkson Disease, Shock, Generalized Edema, Hemoconcentration, hypoalbuminemia, Intravenous Immunoglobulins, Diuretics, Steroids, Intravenous Crystalloids.

Introduction

Idiopathic Systemic Capillary Leak Syndrome is a rare connective tissue disorder with a high mortality rate. It was first described by Clarkson in the year 1960, after whom the disease was named as Clarkson's Disease. So far, 300 cases have been reported worldwide [1]. It is characterized by increased capillary permeability, leading to generalized edema and hypovolemia. The triad of SCLS includes hemoconcentration, hypoalbuminemia, and hypotension due to the shift of intravascular fluid/proteins to the extravascular space [2]. The diagnosis is by exclusion, most patients develop shock and edema following a prodrome of weakness, myalgias and fatigue. SCLS is often mistreated as a case of Sepsis with SIRS guidelines-aggressive fluid resuscitation and inotrope support leading to compartment syndrome and recurrent flash pulmonary edema in majority of cases due to volume overload [3]. The mortality rate among patients have been reported to be as high as 18 to 36% [4]. According to Gouseff et al., 75% of deaths in sepsis patients were directly related to SCLS, which makes it a rare and fatal disease [5].

Case Presentation

This is the case of a 35Year-old-female presented to the ER with complaints of fever, cold/cough, generalized weakness, myalgias, headache, loss of appetite, and low back pain radiating to bilateral lower limbs for 3-4 days. She was initially managed at a local clinic for URTI infection with IV antibiotics, anti-emetics, antipyretics, antitussives and other supportive medications. Outside lab investigations showed thrombocytopenia and hemoconcentration. However, the symptoms persisted and she was referred to our tertiary care health centre. On evaluation, temperature 37.8^{o} C, blood pressure 80/50mmHg, heart rate 130bpm, respiratory rate

24cpm. Systemic examination showed facial puffiness, mildly decreased breath sounds in bilateral lower zones, restricted ROM, low back ache radiating to bilateral lower limbs and bilateral grade-I pedal edema. Investigations showed thrombocytopenia (1.09lacs), Elevated LDH (990U/L), albuminuria, rhabdomyolysis (CK-NAC-15310U/L) and hemoconcentration (Hb-17mg/dl/PCV-50.3%). Coagulation panel was within normal limits (PT/INR- 11.4sec/0.9). Blood and Urine cultures showed no growth. Hepatitis panel, Dengue/typhi/scrub typhus/Leptospira IgM, and malaria serology were negative. ECG showed sinus tachycardia. 2D Echo showed Good LV function. Troponin-T was negative. There was blunting of bilateral costophrenic angles on chest X-ray. USG abdomen showed mild bilateral pleural effusions with increased periportal hepatogenicity. The pertinent positives in this case are fever, thrombocytopenia, albuminuria and hemoconcentration. She was treated with IV Crystalloids, Albumin, diuretics, Terbutaline, Acebrophylline,

There were no autoimmune features present, however her ANA profile was borderline positive for SS-A. A rheumatologist cross-consultation was taken to rule out any underlying autoimmune conditions. The condition was conservatively managed. Venous Doppler of the Bilateral lower limbs showed mild cellulitis of the left mid-thigh. She had a normal nerve conduction study(NCS) on Bilateral lower limbs. After ruling out all the possible causes of her condition, she was diagnosed with systemic capillary leak syndrome secondary to viral hemorrhagic fever. After hemodynamic stabilization, she was initially managed with fluid restriction followed by loop diuretics for prevention of noncardiogenic pulmonary edema. She improved symptomatically and hence was discharged. At follow-up, she had normal lab parameters with no ongoing symptoms.

Discussion

The term "Capillary Leak Syndrome" is given to a subset of diseases with increased capillary permeability due to protein loss from the intravascular to interstitial space, resulting in generalized edema and shock [6]. Capillary leak is manifested by hypotension, hemoconcentration and hypoalbuminemia. SCLS can be complicated by compartment syndrome and multi-organ failure in severe forms due to shock and hypoperfusion [7]. Two different forms of SCLS have been diagnosed so far-Idiopathic and secondary SCLS [8]. Idiopathic SCLS is associated with monoclonal gammopathy (Clarkson disease), a rare and extreme form of ISCLS. It is effectively managed with monthly intravenous immunoglobulins according to Chamburan et al. [9]. The secondary form of SCLS is associated with underlying causes like sepsis, shock, OHSS, systemic infections, drugs/toxins like snake envenomation and hematologic disorders. Capillary leak is abrupt in secondary SCLS causing significant hemoconcentration [10]. This indicates CLS severity. The pathophysiology includes the leakage of plasma-rich proteinaceous fluid into the interstitial space, leading to generalized edema. The increase in cytokines causes vascular permeability. Subsequent volume depletion causes hypotension and decreased perfusion to the kidneys causing acute kidney injury. Accumulation of protein-rich fluid in the interstitial space causes pitting edema of legs, pleural/pericardial effusions, abdominal compartment syndrome, muscle edema leading to rhabdomyolysis, noncardiogenic pulmonary edema and ARDS.

Acute kidney injury is commonly seen in these diseases due to cytokine release [1]. An active urine sediment develops early in the disease course due to mild glomerular injury in patients with VHF. This form of SCLS does not recur once the underlying cause is cured or the offending agent is discontinued. Thus, distinguishing the two entities is crucial for quick diagnosis and positive outcomes. Until recent years, capillary leak cases were misdiagnosed as sepsis or other causes of hypoalbuminemia [11]. There are various causes for secondary SCLS, the most common being infections. Viral hemorrhagic fever can cause capillary leak together with shock, thrombocytopenia, and coagulopathy. Renal syndrome is the most common complication seen in VHF due to a persistent decrease in BP and plasma protein concentration [12].

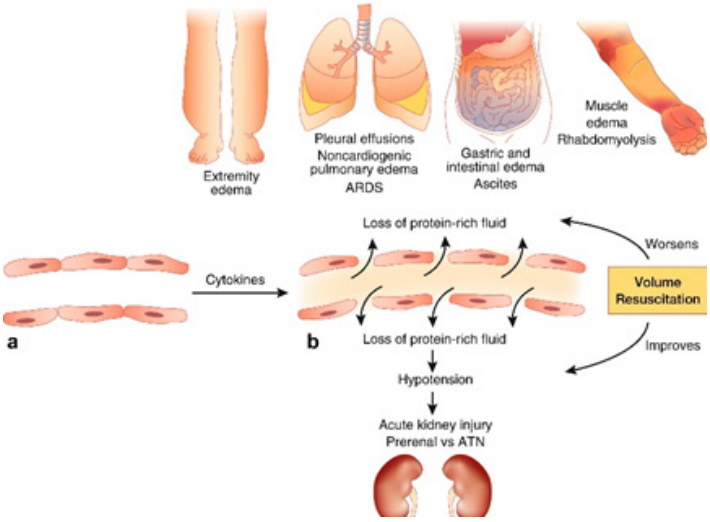

Figure 1: Clinical Manifestations of Systemic Capillary Leak Syndrome, excess fluid resuscitation worsens the edematous phase.

AKI incidence varies among types of viral hemorrhagic fevers-dengue being the least common and hantavirus being the most common [13]. Proteinuria and hematuria are significantly seen along with acute interstitial nephritis even in the absence of glomerular abnormalities [14]. Most patients recover from AKI through conservative management. Fluid resuscitation is most crucial in the management of SCLS. Crystalloids, albumin, immunoglobulins, steroids and diuretics are important in the treatment of patients with capillary leak syndrome [15]. Excess fluid resuscitation (Figure 1) leads to volume overload states, leading to effusions, compartment syndromes and ARDS [16]. Hence, hemodynamics must always be monitored in such cases and timely interventions need to be taken. Although limited data and guidelines exist, the promising therapy for the primary form of SCLS is Immunoglobulins. The most commonly given dose of IVIG for the treatment of Clarkson's disease is 1g/kg/day [17].

However, this patient presented with shock and thrombocytopenia with no underlying kidney injury. She was subsequently treated with IV Crystalloids, vasopressors and other supportive medications. After ruling out all the other causes of SCLS, she was diagnosed with SCLS secondary to VHF.

Conclusion

Capillary Leak Syndrome can be caused by a diverse set of diseases. Increased vascular permeability due to hypercytokinemia is the common pathophysiologic abnormality. Fluid losses can result in hypovolemia and prerenal azotemia, leading to shock and AKI in severe cases. Initial treatment for capillary leak is fluid resuscitation. However, all the other causes must be excluded before a diagnosis is made. Keeping in mind the possible complications of fluid overload, such as pulmonary edema and acute respiratory distress syndrome, fluid restriction must be achieved immediately after hemodynamic stabilization. SCLS is a diagnosis of exclusion, which is missed easily. Hence, proper investigations and timely interventions are needed for guarded prognosis. Its incidence may vary from the commonest of diseases to rare entities, such as this patient who presented with a viral profile but was later diagnosed as a case of SCLS.

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