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Case Report

Internal Medicine Section

Idiopathic Systemic Capillary Leak Syndrome: A Diagnostic Challenge and Its Management

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ABSTRACT

Idiopathic Systemic Capillary Leak Syndrome (ISCLS) is a fatal disorder characterised by recurrent episodes of hypotension, hypoalbuminemia and haemoconcentration. It is a rare disease, underreported partly because of unawareness of treating physician. Here is a description of a 30 year old male presenting with history of fever, generalized oedema progressing to hypovolemic shock and multi organ dysfunction. His laboratory studies showed haemoconcenration, hypoalbuminemia and monoclonal gammopathy with negative bacteriological cultures. After excluding other probable etiologies he was diagnosed to have ISCLS. He was managed successfully with intravenous methylprednisolone, theophylline and other supportive measures. He has been put on prophylactic oral theophylline for one year.

Keywords: Hypovolemic shock, Theophylline, Steroids

CASE REPORT

A 30-year-old indian male with nil premorbidities who was initially managed by a primary care physician for low grade fever and generalised oedema presented to the Emergency Department, hypotensive with a primary diagnosis of dengue shock syndrome. On examination patient was dyspneic at rest with room air saturation of 85 percent. He had a heart rate of 110 per minute with blood pressure of 90/60 mm of mercury. General examination showed pitting pedal oedema, tense distended abdomen, scrotal oedema and decreased breath sounds in bilateral basal.

The lab values included a raised hematocrit, hypoalbuminemia, raised creatinine and high potassium [Table/Fig-1]. A presumptive diagnosis of septic shock was made with multiorgan dysfunction and patient was started on prophylactic antibiotics and other supportive measures. Later in the day he was intubated in view of flash pulmonary oedema. Echocardiogram revealed trivial pericardial effusion, normal cardiac function with moderate pulmonary artery hypertension. D-dimer was done which turned out to be negative. He was treated with diuretics and made a gradual improvement and hence later extubated.

His blood cultures were sterile, screening for other tropical diseases which are commonly encountered in this part of country like dengue, scrub typhus, malaria, rickettsia, leptospirosis were unyielding. Diagnostic evaluation of fluid obtained through thoracocentesis and abdominal paracentesis revealed transudative fluid with normal cell count and its cultures were sterile.

He again worsened with generalized oedema, developed hypotension and he gained 10 kg over four days. He was meticulously treated with crystalloids and colloids. He was started on noradrenaline and reintubated. He had a cardiac arrest and was successfully resuscitated. He was started on high dose intravenous thiamine suspecting wet beriberi but his general condition did not improve. As patient had classic triad of hypotension, hypoalbuminemia, haemoconcentration after extensive literature search ISCLS was considered and monoclonal gammopathy workup was sent. Pending reports he was started on intravenous methylprednisolone and theophylline following which he improved. His monoclonal gammopathy workup turned out to be positive with M band on serum protein electrophoresis. Methylprednisolone was given at a dose of 1mg/kg/day and theophylline at a dose of 400 mg twice a day intravenously during acute episode and was later changed to oral theophylline 200 mg twice a day for prophylaxis. He is currently on follow up for one year without new episodes.

DISCUSSION

In 1960 Clarkson B et al., first described ISCLS or Clarkson's Syndrome as a syndrome of intermittent episodes of generalized oedema with an unknown etiology [1]. The disease is misdiagnosed probably because of its close resemblance to cardiogenic and septic shock leading to mismanagement from the start. Early recognition of the disease shifts the treatment paradigm towards use of steroid, theophylline and meticulous use of intravenous fluids which are otherwise detrimental in cardiogenic and septic shock respectively. Clinically, the course of ISCLS is understood to have three phases which include a prodromal phase, extravasation phase or leak phase and recovery phase. Prodromal phase is characterized

Test	Result	Normal Range
Haemogram		
Haemoglobin	17.6 g%	13-17 g%
White cell count	17,500/micro litre	4.0-10.0 /micro litre
Platelet count	145,000/ micro litre	150-400/ micro litre
ESR	78 mm/hr	0-20 mm/hr
C reactive protein	Negative	
Renal function tests		
Blood urea nitrogen	78 mg/dl	10-40 mg/dl
Creatinine	2.7 mg/dl	0.6-1.4 mg/dl
Na^+/K^+	123/ 5.3 mmol/l	
Liver function tests		
Total bilirubin	3.6 mg/dl	0.3-1.2 mg/dl
AST	39 iu/l	15-40 iu/l
Total protein	7.0 g/dl	6-8 g/dl
Albumin	2.6 g/dl	3.5-5 g/dl
PT	26.2 sec	15.9 sec
APTT	53 sec	32.3
Amylase	167u/l	
Lipase	426 u/l	

[Table/Fig-1]: The laboratory findings of the patient.

by coryzal symptoms. Leak phase, is characterized by loss of intravascular fluid into interstitial space which results in hypovolemic shock. Inotropes are used along with intravenous fluids to keep the blood pressure within normal range during this phase. Hypotension might induce variable degree of hypoxia in end organs such as the kidney, brain and liver which might result in acute kidney injury, encephalopathy and ischaemic hepatitis respectively. Then follows the recovery phase in which the fluid lost to third space is brought back into the intravascular compartment [2]. However, the return of this fluid is sudden and if the patient is receiving intravenous fluids as well, this creates a scenario of volume overload on the heart. This excess fluid might even cause pulmonary oedema and worsen the clinical picture of the patient. However, limiting the fluids and trying to reduce the endothelial inflammation can help the patient navigate safely out of this phase.

Several hypotheses have been proposed to explain the patho-physiology, but none seem to explain it entirely. However, it is known that the triad of haemoconcentration, hypovolemia and hypoalbuminemia should raise the clinical suspicion of ISCLS. Studies have shown a consistent association of the episodes with monoclonal gammopathy [3]. In our case, the patient was found to have monoclonal gammopathy on evaluation. Even though consistent association has been established, underlying pathophysiology has been not clearly described. Zhang W et al found that when healthy endothelial cells were exposed to paraprotiens invitro no detectable cytological effects were found [4]. However there were reports describing reduced frequency of attacks of ISCLS in multiple myeloma patients on polychemotherapy. In a normal hypovolemic shock, the play of hydrostatic forces leads to loss of fluids into third spaces. In ISCLS, however, the most accepted pathophysiology is that the apoptosis of endothelial cells but not the shrinking of endothelial cells resulting in escape of intravascular fluid into interstitial space. This has been proven by using serum of patients during an episode of ISCLS and letting it react with normal endothelial cells. It resulted in apoptosis of endothelial cells [5]. The other difference between ISCLS and a routinely observed hypovolemia is that it is not mediated by the regular modulators such as histamine, prostaglandins, complements or kinins. It has been showed that when recombinant interleukin 2 and interferon are used in therapy, they result in a clinical picture similar to ISCLS, thus pointing towards a probable role of cytokines in pathophysiology of ISCLS [6,7].

These evidences suggest an approach towards treating this reversible but fatal disease. Various approaches have been described for the management of acute phase of ISCLS which include intravenous immunoglobulin, corticosteroids, prostacyclin analogues[8] , bevacizumab[9,10] terbutaline and theophylline. Terbutaline and theophylline have been showed to antagonize the capillary hyper permeability and endothelial damage caused by probable cytokine involvement [11]. Terbutaline acts by increasing production of cAMP while theophylline acts by blocking its degradation, thus resulting in elevated circulating cAMP levels. This elevated cAMP levels inhibits the capillary leak. Dowden AM et al., described a successfully treated case series of ISCLS with intravenous theophylline and also showed the potential benefit of theophylline as a preventive measure [12]. Corticosteroids are also supposed to be beneficial during acute episode of ISCLS as cytokine mediated endothelial damage has been implicated in the pathophysiology of the disease [10,13,14]. In this case report, patient was managed successfully with intravenous corticosteroids, theophylline and other supportive measures during acute phase and was maintained on oral theophylline with no recurrent episodes during the follow up. Other approaches described for management of acute phase of ISCLS include, a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF). Little effect has been seen by using mephalan which was used on the rationale of the underlying gammopathy [15,16].

CONCLUSION

ISCLS must be considered a differential when one presents with triad of acute hypovolemia, hypoalbuminemia and raised haematocrit not responding to inotropes and fluids. In such a clinical scenario, a positive monoclonal gammopathy can aid in making this diagnosis. As ISCLS closely mimics cardiogenic shock and septic shock, treating physician should exercise a close watch for ISCLS because its management differs from the rest. More case series need to be published to the pool of literature to provide more insight into the disease.

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