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CASE REPORT

Idiopathic Systemic Capillary Leak Syndrome: A Rare Cause of Refractory Shock Following Influenza B Infection

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Abstract

A 68-year-old man presented to the Emergency Department with undifferentiated shock. During the three days prior, he experienced a non-specific viral-like illness. On examination his blood pressure was 70/40 mm Hg with cool, clammy, and mottled extremities and flat neck veins. Laboratory investigations revealed a positive influenza B screen alongside elevated hemoglobin and hematocrit. Following aggressive fluid resuscitation his blood pressure had marginally improved and he was transferred to the intensive care unit (ICU). Vasopressor support with cautious fluid resuscitation continued and at 7- and 10-h following presentation, serum albumin levels were extremely low. Idiopathic systemic capillary leak syndrome triggered by influenza B infection was diagnosed. Following a 9-day ICU stay the patient made a complete recovery and remains stable on intravenous immunoglobulin therapy. This case highlights the importance judicious fluid resuscitation and serum albumin levels when confronted with refractory shock.

Keywords: Idiopathic systemic capillary leak syndrome, Influenza B, Shock, Resuscitation

1. Introduction

Idiopathic Systemic Capillary Leak Syndrome (ISCLS) or Clarkson's Disease, is extremely rare with the hallmark of spontaneous sudden episodes of generalized edema alongside the triad of hypotension, hemoconcentration, and hypoalbuminemia without albuminuria.[1] Fewer than 260 cases have been reported in the literature.[2] The classic presentation is an attack of refractory distributive shock. Attacks of ISCLS are characterized by three phases: a prodromal phase, a leak phase with increased capillary permeability, rapid extravasation of plasma and proteins, and subsequently massive "third-spacing", and a post-leak or recovery phase.[2,3] The causes of ISCLS remain unknown but it has been associated with monoclonal gammopathy of unknown significance (MGUS).[3] ISCLS diagnosis is challenging, therefore a high degree of clinical suspicion is warranted.[4] Severe presentation, and delays in appropriate therapy are associated with increased mortality.[4] We herein report a case of a 68-year-old patient who was admitted to our intensive care unit (ICU) with an extreme refractory vasodilatory shock following influenza B infection.

2. Case description

A 68-year-old male presented to the Emergency Department (ED) with undifferentiated shock and hypotension. He complained of a 3-day history of generalized weakness, scratchy throat,

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lightheadedness, and headache. In addition to vague chest discomfort, he reported diffuse abdominal pain and nausea without vomiting. He had intermittent back pain in the weeks prior and denied any other symptoms. He was a former smoker with a medical history of COPD, peptic ulcer disease with perforation, and two admissions in the preceding two years for low blood pressure (BP) and polycythemia attributed to dehydration. His only daily medication was a multivitamin. On clinical examination in the ED he was afebrile, eupneic, tachycardiac, and hypotensive (58/26 mm Hg) with a normal oxygen saturation. His neck veins were flat, and his extremities were cold, clammy, and mottled.

Blood and urine specimens were sent for cultures and respiratory virus nucleic acid testing (NAT) was ordered. Aggressive fluid resuscitation with crystalloids was initiated alongside broad-spectrum antibiotics. Electrocardiogram revealed sinus tachycardia. Contrast-enhanced computed tomography scan of the Thorax, Abdomen and Pelvis was unrevealing. Urinalysis was normal. Stat laboratory examination revealed lactic acidosis (3.3 mmol/L), neutrophilic leukocytosis (19,300 cell/ml), elevated hemoglobin (14.09 mmol/L) and hematocrit (68.3%), and a normal platelet count. Electrolytes were unremarkable other than low serum bicarbonate (15 mmol/L) and calcium (1.62 mmol/L). Blood urea nitrogen and serum creatinine were slightly elevated (10.71 mmol/L and 168 μmoL/l, respectively) as was serum cortisol (1241.55 nmol/L). Coagulation panel and liver function tests were normal; serum albumin was not sent. Serum tryptase level was normal. After the initial hour of fluid resuscitation with 6 L normal saline, his BP remained low and norepinephrine was commenced. NAT resulted positive for influenza B and he was transferred to the ICU.

Upon arrival to the ICU, he remained hypotensive (BP 82/60 mm Hg) and oliguric. Focused bedside echocardiogram showed a small pericardial effusion, hyperdynamic ventricles with normal ejection fraction, and a >50% collapsible inferior vena cava. Additional crystalloid resuscitation with 4 L of lactated ringer's was performed over the next several hours. Despite adequate fluid resuscitation, increasing norepinephrine requirements necessitated the addition of vasopressin.

Owing to refractory hypotension the differential diagnosis at this time included undifferentiated shock, and adrenal insufficiency; in addition, leukocytosis and hemoconcentration gave credence to systemic mastocytosis, stress-induced secondary polycythemia (Gaisbock's syndrome) or a myeloproliferative disorder. During a prior admission for hypotension JAK2 mutation testing was negative, ruling out polycythemia vera. Over the subsequent hours repeat testing resulted in consistently elevated hemoglobin and a progressive lactic acidosis (6.3 mmol/L). We had a high clinical suspicion for ISCLS, and therefore we checked serum albumin at hours 7 and 10 after ICU admission and found it to be extremely low (7 g/L and 4 g/L, respectively). This confirmed the diagnosis of ISCLS.

Late during the first evening of ICU stay a chest x-ray was ordered due to worsening hypoxia and revealed bilateral pleural effusions. The patient was intubated and mechanically ventilated. On day 2, the patient's serum albumin had increased (30 g/L), hypotension had resolved, and vasopressor support was withdrawn. Cultures reported negative and antibiotics were discontinued. The following day Hematology was consulted and montelukast was given, alongside a recommendation for maintenance therapy with intravenous immunoglobin (IVIG) following discharge. Bilateral chest tubes were placed to aid in resolution of pleural effusions.

Over the following week the patient developed acute kidney injury due to a combination of prolonged hypotension, mild rhabdomyolysis and contrast nephropathy, however renal replacement therapy was not required. A tracheostomy tube was placed on day 9 of hospitalization and the patient was transferred to a rehabilitation unit for eventual ventilator weaning. He was decannulated as an outpatient and continues to do well on low-dose monthly IVIG therapy 8 years after this presentation (Fig. 1).

3. Discussion

Idiopathic Systemic Capillary Leak Syndrome is a rare condition. According to the latest literature,[2–5] fewer than 260 cases of ISCLS have been reported since the original description by Clarkson et al., in 1960.[1] The syndrome typically affects patients older than 50 years, and has a slight male-to-female predominance of 1.4:1.[6,7] ISCLS is defined as the cyclic triad of hypotension, hemoconcentration, and hypoalbuminemia without albuminuria in the absence of a secondary cause, and progresses through three phases: prodromal, leak, and post-leak or recovery phase.[1,3–5] The prodromal phase has non-specific symptoms mimicking a viral illness and lasts between 1 and 5 days.[2] Nearly 90% of patients report fatigue, 50% complain of myalgia and flulike symptoms, and 30% have a scratchy throat.[4] The leak phase begins and progresses abruptly to refractory shock over the course of hours

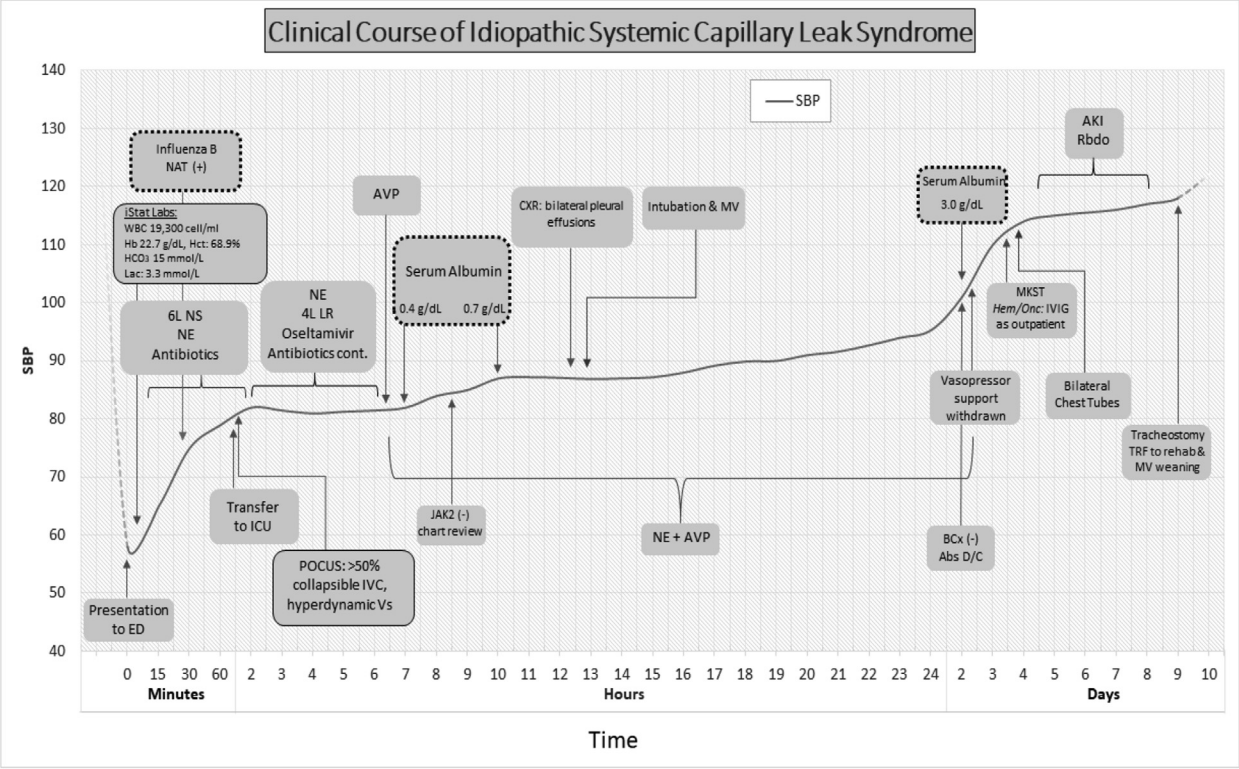

Fig. 1. The clinical course of our patient who presented to the emergency department at the beginning of the leak phase. Abbreviations: Abs; antibiotics, AKI; acute kidney injury, AVP; vasopressin, BCx; bacterial cultures, CXR; chest x-ray, D/C; discontinued, ED; emergency department, Hb; hemoglobin, Hct; hematocrit, Hem/Onc; hematology consult, ICU; intensive care unit, IVIG; intravenous immunoglobulin, JAK2; Janus Kinase 2, Lac; lactate, LR; lactated ringers, MKST; montelukast, MV; mechanical ventilation, NAT; nucleic acid test, NE; norepinephrine, NS; normal saline, POCUS; point-of-care ultrasound, Rbdo; rhabdomyolysis, SBP; systolic blood pressure, TRF; transfer, WBC; white blood cells.

and lasts 24–72 h.[3] Extravasation of up to 70% of total plasma volume causes profound distributive shock.[3,8] This phase is characterized by the classic diagnostic triad of the "3 Hs": hypotension (<90 mmHg systolic), hemoconcentration (hematocrit >49% in males and >43% in females), and hypoalbuminemia (<3.0 g/dL) without albuminuria.[5] Additional laboratory findings, seen in over 85% of patients, include leukocytosis and polycythemia.[2] Edema, although seen in more than 50% of patients during the recovery phase, may be mild initially, and is often not useful for diagnosis.[2,5] Between 68 and 76% of adult patients may have an underlying MGUS, most commonly immunoglobulin kappa.[2,4,5] Our patient did not have MGUS, and in the absence of a pathognomonic biomarker, ISCLS remains a clinical diagnosis. Such a constellation of findings during the leak phase makes diagnosing an initial ISCLS attack challenging. Indeed, the most common misdiagnoses include hypovolemic septic shock, polycythemia vera, and angioedema.[2] Anaphylaxis should also be definitively ruled out with serum tryptase levels.[3] The leak phase may be complicated by compartment syndrome, rhabdomyolysis, and acute renal failure in 20%, 36%, and 57% of cases, respectively.[4] The post-leak or recovery phase begins with the rapid remobilization of fluids back into circulation and diuresis, and lasts from 48 h to more than one week.[3] Alongside the resolution of shock, this phase may be complicated by severe pulmonary edema and cardiovascular overload.[3] Most fatal outcomes from ISCLS occur during this phase due to overzealous initial fluid resuscitation.[3,6,9] Overall the condition remains underrecognized and is fatal in 30–75% of cases.[3,10]

Our patient presented at the verge of the leak phase, just after a typical course of prodromal symptoms. The mainstay of treatment during this phase is supportive care and judicious fluid replacement in the ICU. Fluid overload should be avoided as it is associated with a higher mortality during the recovery phase.[6,9] The choice of fluids remains somewhat controversial. Owning to profound hypoalbuminemia, colloid solutions have been proposed in addition to crystalloids.[3] Proteins like albumin, which has a molecular weight <200 kDa extravasate into the interstitial space during the leak phase of ISCLS and may not be effective.[11] As we did not have a definitive diagnosis

during the leak phase, our patient was initially stabilized using crystalloids without colloids. According to a report in two ISCLS patients, hemodynamic stabilization can be achieved during the leak phase with 10% pentastarch infusion, due to its greater molecular weight.[12] Disease specific treatment remains elusive. Pharmacologic agents targeted at reducing capillary permeability and histamine release such as terbutaline, theophylline, and montelukast have demonstrated sporadic success.[4,13] Our therapeutic decisions were anchored to the presumed pathogenesis of ISCLS, namely leukotriene enhanced capillary leakage coupled with immune-complex mediated cytokine release and complement activation.[14,15] Indeed, the initiation of montelukast followed by maintenance IVIG has been shown to be beneficial in previous reports.[16]

The trigger of an ISCLS attack is important for the clinician to recognize as it may hint towards the diagnosis during the initial resuscitation. Triggers may include surgical interventions, malignancies, medications, and viral infections.[3,17–19] Influenza A is perhaps the most common viral ISCLS trigger, yet less than a handful of cases have been reported.[20–22] To the best of our knowledge this is the first report of influenza B precipitating an ISCLS attack. The exact mechanisms remain ill-defined; however, it is suggested that T-cell activation in response to influenza and other viruses increases the production of pro-inflammatory cytokines and complement activating proteins, which, coupled to an MGUS paraprotein induce immunopathological damage of the endothelial barrier. Which influenza epitopes trigger ISCLS are yet to be determined as so few cases have been reported.[21] Although it may be presumed that our patient had milder attacks in the two years prior to this presentation, it is unproven that influenza B was the trigger in those instances. A single report of ISCLS attack following seasonal influenza vaccination has been published,[23] and this may also be an explanation for our patient's prior episodes. The protective effects of IVIG wean once it is discontinued leading to ISCLS flares.[24] Scattered reports have determined that low-dose (0.4–2 g/kg) monthly IVIG decreases the incidence of such attacks by as much as 89%, and has thus become the standard of care.[25] Furthermore, as the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also been reported as a trigger,[19,26] and it remains unclear whether vaccines against this virus may also induce ISCLS, there is no plan to stop monthly IVIG therapy in our patient. Indeed, our patient was advised and received both influenza and SARS-CoV-2 vaccines without adverse events.

4. Conclusion

This case highlights the importance of obtaining serum albumin levels when initially confronted with refractory distributive shock. When albumin is unavailable, maintaining a high degree of clinical suspicion for ISCLS with possible triggers in mind, may help to guide a judicious fluid resuscitation.

Consent

Patient has consented for the publication of this case report. Signed consent form is attached.

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Not Applicable.

Conflict of Interest

The authors have no competing interests to declare.

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