Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 4 Article 21

2022

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Recommended Citation

Malla, Shelina; Pawar, Tushar; Tharu, Biswaraj; Basnet, Sijan; Rettew, Andrew C; and Forman, Daniel A (2022) "A Rare Case of Idiopathic Systemic Capillary Leak Syndrome," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 12: Iss. 4, Article 21.
DOI: 10.55729/2000-9666.1083
Available at: https://scholarlycommons.gbmc.org/jchimp/vol12/iss4/21

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CASE REPORT

A Rare Case of Idiopathic Systemic Capillary Leak Syndrome

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Abstract

Idiopathic systemic capillary leak syndrome (SCLS) is characterized by an increased capillary hyperpermeability with subsequent hemoconcentration, hypoproteinemia, and hypovolemia. Patients present with diffuse swelling, weight gain, low blood pressure, and shock. We present our case of idiopathic SCLS in a 50-year-old man presenting with prodromal flu-like illness associated with shock that was complicated by compartment syndrome requiring four limb fasciotomies, disseminated intravascular coagulation, acute kidney injury requiring dialysis, and cardiac arrest.

Keywords: Systemic capillary leak syndrome, Clarkson's disease, Capillary hyperpermeability, Polycythemia, Hemoconcentration

1. Introduction

Systemic capillary leak syndrome (SCLS), also known as Clarkson's disease or spontaneous periodic edema,[1] was first described by Clarkson et al., in 1960 in a 34-year old lady who presented with recurrent, idiopathic episodes of hypovolemic shock until she finally succumbed to it.[2] SCLS is a rare condition of unexplained cyclic capillary hyperpermeability with resulting third-spacing of intravascular fluid leading to hypovolemia, hypoproteinemia without albuminuria, and hemoconcentration. This leads to recurrent episodes of generalized edema, hypotension, and hypovolemic shock.[3,4] SCLS has been associated with various cancers, infections, drugs, and surgery. They are labeled idiopathic if no obvious etiology is noted.[4] We present a case of an idiopathic SCLS in our patient who presented with prodromal symptoms in the setting of a recent tick bite. We will also discuss about how we arrived at the diagnosis and rule out other possible differentials.

2. Case presentation

Our patient is a 50-year-old man who was transferred to our intensive care unit from an outside institution for management of suspected septic shock and ventilator-dependent respiratory failure. The patient was at a boy scout camp in western Pennsylvania and reported being bit on his right leg by a tick. A week later, the patient had generalized myalgias, lethargy, and dizziness. His past medical history was significant for mitral valve prolapse, chronic anxiety, and hyperlipidemia. At the outside hospital, he had a recorded peak temperature of 101.5 °F with a systolic blood pressure of 80 mm Hg. His white blood cell (WBC) count at the outside hospital was 23.6 10E3/μL (reference range: 4.8–10.8 10E3/uL), hemoglobin was 21.3 g/dL (reference range: 14.0–17.5 g/dL), hematocrit was 63.4% (reference range), erythrocyte sedimentation rate (ESR) was 1 mm/h (reference range: 0–20 mm/h). Venous doppler with compressible veins without findings of deep vein thrombosis. Computed tomography of the chest with contrast did not show

Received 20 February 2022; revised 5 April 2022; accepted 15 April 2022.
Available online 4 July 2022

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https://doi.org/10.55729/2000-9666.1083

pulmonary embolism or pneumonia. Transthoracic echocardiogram showed an ejection fraction of 56.4%. Electrocardiogram (EKG) showed normal sinus rhythm. Lyme titer was negative. He was admitted to the medical intensive care unit at the outside hospital for presumed septic shock. He was empirically started on intravenous (IV) aztreonam, vancomycin, and levofloxacin for broad-spectrum coverage. The patient was transferred to our facility for further medical management. On his way to our emergency department, the patient had a pulseless electrical activity (PEA) arrest and had to be intubated. He achieved a return of spontaneous circulation after 2 min of advanced cardiac life support.

At the time of admission, he was noted to have extensive dusky mottling of all distal extremities that were cool to touch. His extremities were full and firm. Lower extremity pulses were appreciated with Doppler ultrasound. His capillary refill time was more than 3 s. He had a right-sided leg lesion that was concerning for necrosis/vasculopathy related to suspected tick-borne illness. He was started on IV vancomycin, tazobactam-piperacillin, and doxycycline. He was noted to be hypotensive requiring norepinephrine and vasopressin drips. His hemoglobin was 22.4 g/dL, hematocrit 65.1%, WBC count was 34.5 10E3/μL, platelets was 167 10E3/μL (reference range: 130–400 10E3/μL), lactic acid was 7.5 mEq/L (reference range: 0.6–1.4 mEq/L), creatinine was 2.49 mg/dL. He had some evidence of liver injury due to shock with aspartate aminotransferase (AST) of 433 IU/L (reference range: 130–400 10E3/μL), alanine aminotransferase (ALT) of 477 IU/L (reference range: 130–400 10E3/μL), alkaline phosphatase of 26 IU/L (reference range: 130–400 10E3/μL), total bilirubin of 0.4 mg/dL (reference range: 0.3–1.0 mg/dL), and direct bilirubin 0.0 mg/dL (reference range: 0.0–0.2 mg/dL). His serum albumin was <1.5 g/dL (reference range: 3.5–5.7 g/dL) for which he received multiple albumin infusions. His serum calcium was 5.1 mg/dL (reference range: 8.6–10.3 mg/dL) likely due to hypoalbuminemia but he was also given intravenous calcium supplementation. His fibrinogen was 118 mg/dL (reference range: 193–488 mg/dL), d-dimer was 16.17 μg/ml (reference range: < 0.50 μg/ml), and fibrin split products was >40 μg/ml (reference range: < 10 μg/ml) suggestive of disseminated intravascular coagulation. The next day, the patient was noted to have worsening diffuse edema of his extremities. The ankle-brachial index could not be done as the technician was unable to hear pulses due to edema. Arterial doppler of bilateral lower extremities was able to visualize only the proximal tibial vessels on the left and the posterior tibial artery on the right which were normal. The following day, the patient was taken for a four-compartment right lower extremity fasciotomy, right lateral thigh fasciotomy, right forearm fasciotomy with an application of vacuum-assisted closures (VAC)s to all extremities for compartment syndrome of the bilateral lower legs, bilateral lateral thighs, and bilateral forearms. Unfortunately, the patient had to undergo a below-knee amputation of the right lower extremity a week later for a necrotic limb. He underwent multiple wound VAC changes throughout his stay with the eventual closure of his wounds a month later. The patient's creatine phosphokinase (CPK) at the outside hospital and on admission were 735 IU/L (reference range: 30–223 IU/L) and 1360 IU/L. It peaked at 33786 IU/L the next day and gradually trended downwards over days. Patient's creatinine was 1.2 mg/dL (reference range: 0.60–1.30 mg/dL) at the outside hospital. He presented with a creatinine of 2.5 mg/dL that worsened progressively to 6.61 mg/dL following which the patient was initiated on renal replacement therapy. Acute kidney injury was thought to be due to rhabdomyolysis and acute tubular necrosis (ATN) in the setting of septic shock and hypotension. The patient was placed on continuous renal replacement therapy for diuresis and then transitioned to intermittent hemodialysis over 2 weeks. His renal function recovered over the same time after which dialysis was halted. He was then placed on a furosemide drip for more third-space fluid removal. His creatinine had come down to 1.03 mg/dL by then.

Further workup did not reveal an underlying etiology. Infectious workup including initial blood cultures, blood parasite smear, *Ehrlichia chaffeensis* IgG antibody, *Anaplasma phagocytophilum* IgG antibody, rocky mountain spotted fever IgG, total Brucella antibody, and human immunodeficiency virus antibody-antigen screen were negative. Complements, C3 was 31.4 mg/dL (reference range: 59.0–152.0 mg/dL) and C4 was 5.5 mg/dL (reference range: 12.0–38.0 mg/dL) were low in the setting of shock. After a few days, C3 and C4 levels normalized at 62.4 mg/dL and 14.6 mg/dL, respectively. Serum immunoglobulin G (IgG) (148 mg/dL, reference range: 768–1632 mg/dL), immunoglobulin A (IgA) (32 mg/dL, reference range: 68–408 mg/dL), and immunoglobulin M (IgM) (19 mg/dL, reference range: 35–263 mg/dL) were all low but they normalized with clinical improvement. Serum protein electrophoresis was done on the day after admission and a month and 2 years later showed a slight restriction of protein migration in the gamma region. Immunofluorescence showed a faint band in

Table 1. Serum protein electrophoresis with immunofixation done on day 2 of admission and a month and 2 years after admission.

	Reference ranges	Day 2 of admission	1 month after discharge	2 years after discharge
Total protein electrophoresis	6.00–8.30 g/dL	3.8	7.2	7.6
Albumin	3.75–5.01 g/dL	2.63	4.46	4.61
Alpha 1 globulin	0.19–0.46 g/dL	0.36	0.30	0.31
Alpha 2 globulin	0.48–1.05 g/dL	0.40	0.66	0.74
Beta globulin	0.48–1.10 g/dL	0.24	0.82	0.93
Gamma	0.62–1.51 g/dL	0.17	0.96	1.01
Kappa quantitative free light chains	0.33–1.94 mg/dL	N/A	0.97	10.35
Lambda quantitative free light chains	0.57–2.63 mg/dL	N/A	0.96	9.75
Kappa/Lambda quantitative free light chain ratio	0.26–1.65	N/A	1.01	1.06

IgG kappa suggestive of an early monoclonal protein with normal kappa and lambda free light chain and kappa/lambda ratio. The patient was diagnosed with monoclonal gammopathy of unknown significance (MGUS) based on these findings (Table 1). Anti-nuclear antibody (ANA) titer was 1:640 (reference range: < 1:40) but workup for connective tissue disorders including anti-double stranded DNA antibody, cardiolipin IgG antibody, cardiolipin IgM antibody, myeloperoxidase IgG antibody, anti-proteinase 3 IgG antibody, and rheumatoid factor antibody were all negative. His hemoglobin and hematocrit down trended to 8.5 g/dL and 26.7% respectively on the day of discharge. Later during his hospital stay, the patient developed fungemia with *Candida albicans* for which he was treated with a 2-week course of IV micafungin. The rest of his hospital stay was uneventful, and the patient was discharged to an acute rehab.

With findings of four extremity compartment syndrome, hemoconcentration, hypoalbuminemia, acute renal failure, rhabdomyolysis, associated MGUS, and a negative workup for possible etiology, the patient was diagnosed with idiopathic SCLS. He is not on any prophylactic therapy.

3. Discussion

As per Seong et al., only 260 cases of idiopathic SCLS had been reported till 2017.[4] It was mostly seen in healthy middle-aged adults with men and women being equally affected.[3,5,6] There is no clear familial association in these cases.[1,3] Idiopathic SCLS has been commonly associated with monoclonal gammopathy of unknown significance (MGUS).[3] Kawabe et al. and Chambrun et al. respectively reported that 82% and 68% of their patients had an MGUS of IgG kappa.[3,7] Although MGUS is frequently associated, it is unclear if this contributes to presentation.[6] The exact pathogenesis of SCLS is unclear. Many of these patients have a preceding flu-like illness[3] which made Clarkson et al. suspect if SCLS is a hypersensitivity reaction to a viral antigen of the respiratory tract. However, not every attack of the index case was preceded by symptoms.[2]

Striking clinical features in these patients are weight gain and generalized swelling. They may gain up to 5 kg in less than a day.[2] Patients commonly present with myalgias, fatigue, hypotension along with generalized edema, and weight gain but may have a skin rash, nausea, vomiting, diarrhea, oliguria, and shortness of breath.[1,4] This has been termed as the "leak phase" as patients' symptoms are due to massive extravasation of fluids. This is followed by a "post-leak phase" which is accompanied by shifting of fluid back to the vasculature. Patients may go into arrest due to volume overload especially if they have been given a large amount of fluid to maintain blood pressures during the leak phase.[6] In severe cases, patients may have acute kidney injury (AKI), rhabdomyolysis, compartment syndrome, cardiac arrest, disseminated intravascular coagulation (DIC), ischemic stroke, and pulmonary edema.[1,4] Our patient presented with a prodromal illness and generalized edema that was complicated by AKI, DIC, rhabdomyolysis, compartment syndrome requiring fasciotomy, and cardiac arrest due to PEA. SCLS is a clinical diagnosis and should be considered in any patient presenting with hypotension or shock that gets worse with fluid resuscitation.[6] SCLS may initially be confused with hypovolemic or septic shock, angioedema, or polycythemia vera.[4] Hemoconcentration and hypoalbuminemia help support the diagnosis.[6]

The efficacy of different treatment agents is still controversial.[3] Vasopressors in conjunction with colloid, mostly albumin boluses are preferred over crystalloids to maintain blood pressures in the leak phase. Central venous pressure monitoring while treating shock to avoid overload may help prevent compartment syndrome and eventual cardiac overload during the post-leak phase. Loop diuretics can be used in the post-leak phase to volume overload and pulmonary edema.[5] Recurrence is common in

patients with SCLS.[3] Terbutaline, theophylline, polyclonal immunoglobulins, and steroids have been effectively used as prophylaxis in these patients.[3–6]

SCLS is often fatal despite early recognition, appropriate treatment, and prophylactic measures.[3] Seong et al. reported that around 78.4% of patients with SCLS died of SCLS itself.[4] Druey et al. reported a median survival of 15 years in patients that died of SCLS.[6]

4. Conclusion

Idiopathic SCLS is a rare clinical condition that is frequently fatal. Awareness of its presentation and early diagnosis with judicious intravenous fluid resuscitation especially with colloids may improve outcomes and prevent complications like volume overload and compartment syndrome. Also, educating these patients to seek professional help with initial prodromal symptoms can be helpful.

Financial statement

This research did not receive specific funding and was not performed as part of the employment of the authors.

Conflicts of interest

None.

Acknowledgments

None.

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