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CE - LETTER TO THE EDITOR

Systemic capillary leak syndrome or Clarkson's disease: a case report

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Systemic capillary leak syndrome (SCLS) is a rare but devastating clinical condition first described by Clarkson et al. [1] in 1960. The last review of this syndrome in 2006 analyzed 75 cases, but only 50 had complete clinical data [2]. Clinically, the syndrome is characterized by hypotension, hypoalbuminemia and hemoconcentration, and is caused by the shift of fluid and protein from the intravascular space to the interstitial space as a result of capillary hyperpermeability. The purpose of this report is to enhance awareness of this syndrome that may be frequently underdiagnosed because of its rarity and wide range of presentation.

In November 2004, the patient, a 46-year-old man in prior good health, was admitted acutely to the hospital for severe hypotension (systemic arterial pressure 70/50 mmHg, heart rate 110 beats per min) generalized edema, cyanosis and altered consciousness. The prior day, he had experienced fever, abdominal pain, dizziness and forearm swelling. Selected laboratory data revealed: red blood cell count 6.17×10^6/μl, hemoglobin 18.4 g/dl, hematocrit 53%, leukocyte cell count 35.00×10^3/μl, blood urea nitrogen 70 mg/dl, creatinine level 3 mg/dl, total protein 4.2 g/dl, albumin 2.2 g/dl; urinalysis for proteinuria was negative. The body temperature was 39°C, the D-dimer was 847 ng/ml. During the acute phase, ampicillin plus sulbactam, steroids (40 mg methylprednisolone each day), albumin and intravenous fluid therapy (10 L of fluid during 72 h) were administered. After 24 h there was an improvement of symptoms with polyuria and edema resolution. Common causes of generalized edema accompanied by hypoproteinemia were excluded such as the nephrotic syndrome, liver dysfunction, congestive heart failure and gastrointestinal protein losing enteropathy. A chest radiograph revealed a slight pleural effusion without any abnormal shadows of the lungs. The pericardial effusion was demonstrable on an echocardiogram. Ascites was also present. During the hospitalization, tests for antinuclear antibodies and antibodies to DNA were negative. Adrenal and thyroid hormones were at the upper level of the normal ranges. A small amount of monoclonal IgG-k protein in the serum was evident. A bone morrow aspiration was performed and was normal. After 10 days, the patient was discharged with a diagnosis of viral polyserositis with acute glomerulonephritis, without further therapy. In January 2005, the patient suffered a second episode of hypovolemic shock (systemic arterial pressure 60/30 mmHg), with tachycardia (heart rate 120 beats per min), hemoconcentration (red blood cell count 8.22×10^6/μl, total leukocyte cell count 49.00×10^3/μl, hematocrit 62.3%), oliguria, peripheral vasoconstriction and derangement in hemostasis (aPTT 57 s, INR 5.88, platelets count 70,000/mm^3 and fibrinogen 114 mg/dl). Further laboratory values were: albumin 1.5 g/dl, total protein 2.9 g/dl, creatinine 3.2 mg/dl, blood urea 102 mg/dl. Arterial blood gas analysis showed the following values: pH 7.28, paO_2 65 mmHg, $paCO_2$ 32 mmHg, HCO_3^- 15 mEq/l. During 48 h an aggressive fluid support was given in the form of plasma plus plasma expanders, normal saline infusion (glucose 5%), associated with methylprednisolone, antibiotics (teicoplanine and ceftazidime). A clinical improvement was seen after 24–36 h. The diagnosis at discharge was hypovolemic shock with coagulopathy and renal

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insufficiency. No therapy to prevent episodes was suggested. During the following 2 years the patient experienced about eight episodes characterized by forearm swelling, dizziness, fatigue and mild hypotension; intravenous hydrocortisone was used with slight recovery from the symptoms.

Finally in December 2007, the patient was admitted to our Department of Internal Medicine. All laboratory and diagnostic tests were negative except for the presence of monoclonal IgGk protein. On the bases of the clinical history, we made the diagnosis of idiopathic SCLS. Therefore, prophylaxis with β_2 agonists (clembuterol 0.02 mg twice daily) and theophylline (200 mg twice daily) was started. No acute episode has been documented or prodromal symptoms requiring intravenous hydrocortisone have been reported during a 12-month follow-up.

The clinical presentation of SCLS is currently divided into two stages: the initial capillary leak phase and the recruitment phase. Prodromal symptoms include myalgias, fatigue, abdominal pain, nausea, and in some cases, polydipsia and dizziness. The capillary leak phase may last from 1 to 4 days, and is a phase of acute hypovolemia with capillary high-permeability and marked extravasation of intravascular fluids and macromolecules. Laboratory findings reveal hemoconcentration, leukocytosis, increase in IgM, decrease in albumin and decrease in IgG. At peak of an SCLS episode, the clinical features include generalized edema, interstitial edema, ascites, pleural and pericardial effusions. A compartment syndrome caused by massive swelling of muscular compartments sometimes requiring fasciotomy, is an uncommon complication as well as is rhabdomyolysis. Renal failure can result from acute tubular necrosis due to hypotensive shock and rhabdomyolysis.

The recruitment phase follows the capillary leak phase and involves the normalization of the vascular leak. During this phase, the interstitial fluid, native and supplemental, returns to the intravascular space, and may result in intravascular fluid overload. Although the patient's kidneys may function normally, pulmonary edema may result. In between episodes, patients are asymptomatic except for monoclonal gammopathy (70% of patients) without any evidence of multiple myeloma or amyloidosis. In some cases, a progression to multiple myeloma has been described [3].

The therapy of the acute phase consists of intravenous fluids (crystalloids and colloids), with most episodes resolving with this therapy [4]. Additionally, the aggressive fluid infusion in the leaking phase can result in pulmonary edema during recovery. In some patients, inotropes, mechanical ventilation and ultradiafiltration have been utilized. Intravenous steroid therapy may have a role in the acute leaking phase, where cytokine-mediated endothelial damage is prominent.

Many drugs have been tried to prevent future episodes. Terbutaline and theophylline reduce the increment of the capillary permeability induced by bradykinin by producing an increase of cyclic adenosine monophosphate [5]. Since 1981 a combination of aminophylline or theophylline plus terbutaline has been used at the Mayo Clinic Center to treat the recurrence of SCLS. With this regimen, a number of episodes of SCLS are completely prevented in some patients, and decreased in incidence and severity in others. Other agents used are intravenous immunoglobulins, prednisone, verapamil, leukotrienes modifiers and plasmapheresis. Although morbidity and mortality rates are still high, the prognosis seems improved in part due to careful monitoring of fluid volume and aggressive intensive care during attacks as well as treatment during the chronic phase.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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