Splenic infarction due to severe hemoconcentration in a case of systemic capillary leak syndrome (Clarkson's disease)

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Systemic capillary leak syndrome is a potentially fatal disorder characterised by transient but severe hypotension, resulting in vascular collapse and shock, in combination with extreme hemoconcentration and anasarca oedema accompanied by a monoclonal gammopathy of unknown significance. We describe a case of Clarkson's disease, complicated with severe hemoconcentration leading to splenic infarction and pulmonary oedema treated with ultrafiltration. The pathogenesis of systemic capillary leak syndrome remains unknown. We determined the serum concentration of soluble mediators erythropoietin and vascular endothelial growth factor, in order to attribute their role in the underlying pathophysiology of the disease.

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Introduction

Systemic capillary leak syndrome (SCLS, Clarkson's disease) is a potentially fatal disorder of unknown aetiology and pathogenesis, occurring in typical attacks of various intensity, characterised by transient but severe hypotension resulting in vascular collapse and shock, in combination with extreme hemoconcentration and anasarca oedema due to extravasation with consequent accumulation of fluids and macromolecules in interstitial tissues. A monoclonal gammopathy of unknown significance (MGUS), typically of the IgG kappa, is present in the majority of the patients. This suggests a contribution in the pathogenesis, but in reality the mechanisms of vascular hyperpermeability remain unclear.[1-4] SCLS is a rare disorder. Since 1960 only approximately 160 cases have been reported. In the past decade there has been an increase in publications, probably due to greater awareness and better knowledge of the disease. There doesn't seem to be a geographical or gender predomination.[1,2]

Case report

A 60-year-old woman presented to the emergency department with a one-day history of gastro-enteritis like symptoms of nausea and vomiting. She had been in follow-up for an MGUS since 25 years. She also had been suffering of recurrent viral infections with severe stomatitis. What struck us most in her medical history was the occurrence of two episodes of shock, complicated with rhabdomyolysis and compartment syndrome

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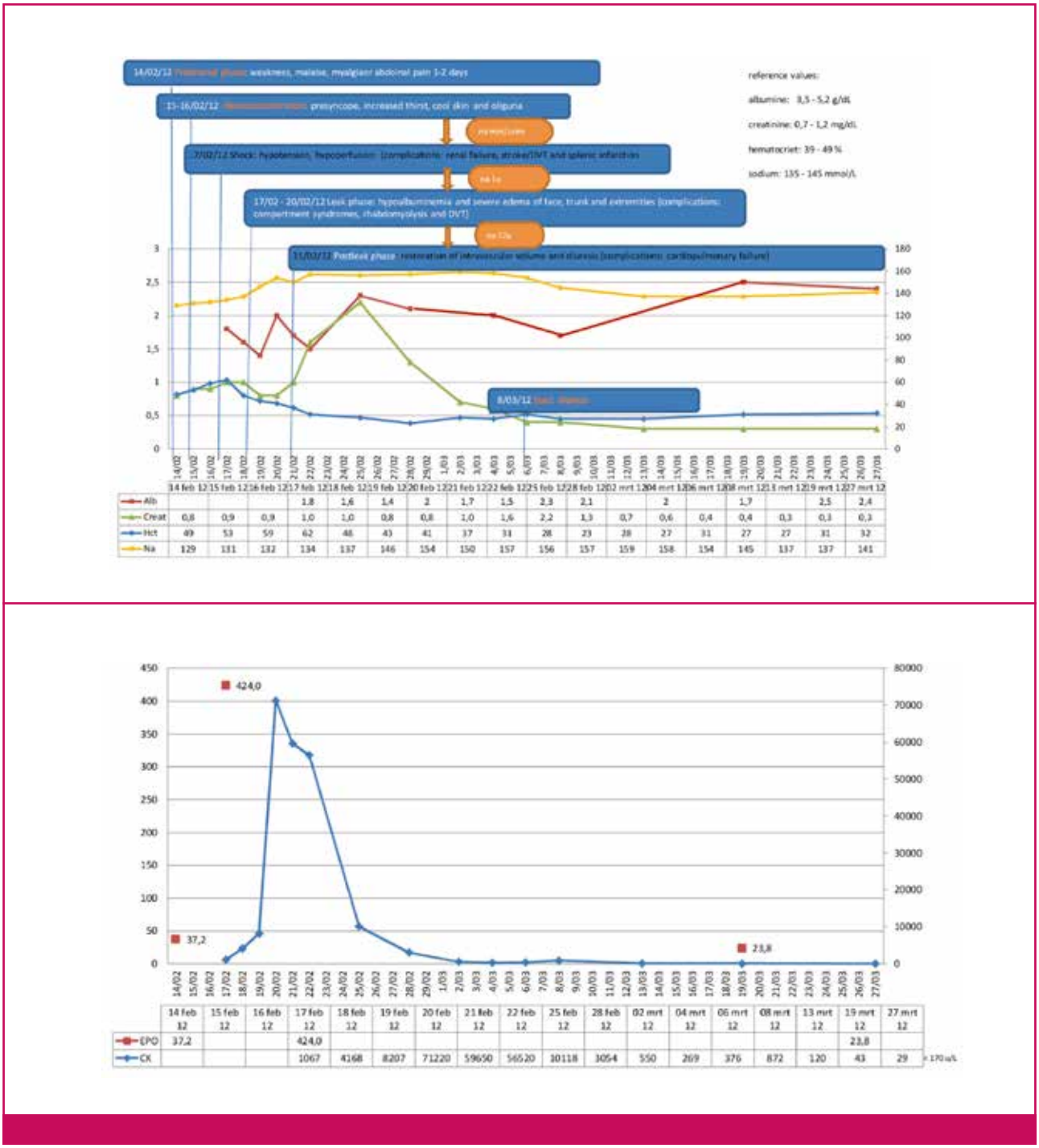

Figure 1. Part 1 and 2. Laboratory findings in relation with physical symptoms and different phases of the systemic capillary leak syndrome.

of the lower extremities. During her last admission in 2007, an iliac crest biopsy was performed to explore severe hemoconcentration, with normal results (bone marrow plasmacytosis of 2%). This examination together with a negative analysis for JAK2 mutation excluded polycythemia vera. This otherwise healthy woman did not take any medication. There was no known history of allergy.

Initial examination and findings

Clinical examination was reassuring. Vital signs were stable. Findings from auscultation of the heart, lungs and abdominal examinations were within normal limits. Initial laboratory findings only showed a mild hemoconcentration that was attributed to the dehydrated state of the patient.

Hospital course

Just one day after admission, although intravenous fluids were given, the hemodynamic status of the patient changed abruptly. Physical examination revealed severe hypotension, tachycardia, normal body temperature and tachypnea despite normal oxygen saturation. She developed peripheral vasoconstriction with cold, clammy and slightly cyanotic extremities and orbital oedema. She was immediately transferred to intensive care. *Figure 1* shows the laboratory findings in relation to these physical symptoms. The other laboratory findings were within normal limits.

In our differential diagnosis all causes of shock were withheld. Because there was a slight raise in body temperature one day after admission to the intensive care, septic shock was the most likely diagnosis at that time. This was however contradicted by the repetitive negative cultures and persistently low biochemical indicators of inflammation. Electrocardiography was normal. A transthoracic echocardiography showed neither signs of heart failure nor any other structural abnormalities, which, in combination with a blank cardiac history, made a cardiogenic shock less likely. A transesophageal echocardiography was not performed. Furthermore, there was no evidence for an anaphylactic reaction.

In theory, the hypovolemic state of our patient could have explained the severe hemoconcentration and hypernatremia. These findings however, are in contrast with the severe oedema and hypoproteinemia. Malnutrition, malabsorption, liver disease and renal disease (e.g. nephrotic syndrome) were excluded, given the normal serum creatinine value and normal liver tests at the moment of admission to the intensive care unit. There was no proteinuria. Malnutrition could be ruled out based on anamnesis and physical constitution. The level of creatine kinase (CK) in the blood was elevated so we excluded an intracompartmental syndrome by measuring a normal intracompartmental pressure in the lower legs. It was more likely due to rhabdomyolysis.

The CT scan of the abdomen, taken a few hours before admission to intensive care, showed hypoperfusion of the intra-abdominal organs and multiple splenic infarctions. Post hoc, we assumed that the rise in body temperature was due to these splenic infarctions.

The patient was sedated, intubated and artificially ventilated. Aggressive rehydration therapy with colloids was started along with administration of noradrenaline. A day later, the diagnosis of idiopathic capillary leak syndrome was made partly by linking hemoconcentration and generalised oedema to the MGUS. Therapy was started with intravenous immunoglobulins, theophylline and corticoids according to the scarce literature. Gradually the clinical picture changed to a hypervolemic state and pulmonary oedema (the post leak phase), requiring hemodynamic stabilisation, guided by central venous pressure. Diuretics were started but discontinued after the development of acute kidney failure, partly due to severe rhabdomyolysis as well, and due to the absence of clinical improvement. Dialysis with pure ultrafiltration was initiated and the oedema disappeared, so the outcome of this treatment was very successful. The kidney function and CK values normalised. The further course of the disease was complicated with bilateral deep venous thrombosis (although she was receiving prophylactic dose of low molecular weight heparins) and with critical illness polyneuropathy. Our patient survived, recovered completely and was discharged from the critical care unit 28 days after admission. Bone marrow aspiration at day 38 showed 4% plasmacytosis and a normal erythropoiesis. She left the hospital 67 days after admission with a maintenance therapy of corticosteroids, alternately two and four milligrams.

Table 1. VEGF serum values.

Day of admission to Intensive Care Unit	208
Day 2	257
Day 3	223
Day 8	526
Day 9	490
After three months	629

Systemic capillary leak syndrome (Clarkson's disease)

The pathophysiology and cause of SCLS remain unclear. Different hypotheses have been enlisted since the first reports. Most recent work suggests that the extravasation of fluids is not due to endothelial apoptosis but to transient endothelial contraction and disruption of endothelial structure (through remodelling of endothelial cell junctions). An important breakthrough role is reserved for non-immunoglobulin humoral factors, such as vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang2), that contribute to this mechanism, suggesting a molecular mechanism. In certain patients VEGF and Ang2 are elevated during an acute attack, in contrast to

Key messages for clinical practice

1. Systemic capillary leak syndrome is a potentially fatal disorder.
2. Monoclonal gammopathy of unknown significance is present in the majority of cases.
3. Attacks are characterised by transient but severe hypotension, shock, hemoconcentration and anasarca oedema.
4. There is a potential role of ultrafiltration.

normal serum concentration during quiescent periods. We measured the VEGF in serum, during two capillary leak attacks; both values were at the upper limit of the normal range. Possibly we missed the elevation of VEGF because of the time lapse between the prodromal phase (several days) and the apparent capillary leak phase.

Treatment

The cornerstone of the treatment during an acute attack is aggressive fluid resuscitation with the aid of colloids and albumin, in combination with vasopressors.[1] Next to this approach immunoglobulins and phosphodiesterase inhibitors are indicated.[1-3,5] In this case we were able to treat the pulmonary oedema in the post leak phase with ultrafiltration. This was previously never described. Theophylline and beta adrenergic agonists should be administered as maintenance therapy in dormant phases.[1-3] These are known to promote endothelial barrier function by stabilising VE-cadherin-mediated adhesive junctions.[4]

At discharge, the patient was kept on a low dose of steroids, which she is still taking.

Prognosis

The five-year survival rate is approximately 70-75%.[2,4]

Discussion

SCLS is a potentially fatal disorder with a serious rate of complications. It is characterised by transient but severe hypotension resulting in vascular collapse and shock, in combination with extreme hemoconcentration and anasarca oedema due to extravasation. The most remarkable complication in our patient was hypoperfusion leading to multiple splenic infarctions in the leak phase. In the post leak phase, pulmonary and anasarca oedema could be successfully reversed with ultrafiltration. This was never done before but may suggest a potential role of ultrafiltration in the treatment of the post leak phase of SCLS.

The pathogenesis of SCLS remains unclear. In our patient erythropoietin (EPO) serum concentration was determined as well as VEGF (*Table 1*), in order to illustrate a possible implication of the oxygen sensing pathway in this syndrome and to exclude possible causes of aberrant EPO production. Despite the severe hemoconcentration, the level of EPO was extremely high. VEGF levels were on the edge of the normal upper limit of the reference values. EPO and also VEGF gene expression is induced by hypoxic induced transcription factors (HIF) which are normally elevated in hypoxic conditions. Our patient however, was not in a hypoxic state due to rapid adequate ventilation. The suspicion was raised that another mechanism caused HIF to be elevated in our patient. Up till now, the pathophysiology and triggers are not well understood. Further investigation was superfluous.

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