

Case Report

Treatment of acute monocytic leukemia with concurrent systemic capillary leak syndrome: a case report and literature review

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Abstract: Systemic capillary leak syndrome (SCLS) is a rare and potentially fatal disorder which causes recurrent episodes of hypovolemic shock due to a markedly increased plasma shift into the interstitial space. Patients with SCLS have a characteristic triad of hypotensive shock, hypoalbuminemia and hemoconcentration. Treatment of the acute phase is supportive, focusing on adequate but not overzealous fluid resuscitation, because pulmonary edema usually occurs in the recruitment phase. We reported a case of treatment of acute monocytic leukemia with concurrent SCLS. A 51-year-old man was admitted to hospital for recurrent oral ulcer, hypodynamia and fever, an initial diagnosis of acute monocytic leukemia (M5b) was made. But he developed severe anasarca, seroperitoneum and hydrothorax after chemotherapy, as well as the progressive decrease of serum albumin (lowest to 10 g/L) led to a revision of diagnosis to SCLS. Treatment with hydroxyethyl starch, doxofylline and ulinastatin resulted in a gradual improvement in 3 weeks and a persistent remission after 5 weeks. The mechanism of SCLS remains uncertain for the rarity of the disease and its unpredictable course. All the treatments are lack of the basis of strictly evidence-based medicine. Physicians should be aware of this illness and provide timely therapy because of its poor prognosis.

Keywords: Systemic capillary leak syndrome, acute monocytic leukemia, treatment, diagnosis

Introduction

SCLS, firstly described by Clarkson in 1960 [1], is a rare disorder with episodes of hypotensive shock, hypoalbuminemia and hemoconcentration. The clinical presentation of SCLS shows no specificity, thus it's easy to be confused by severe infection, septic shock, etc. There is no proof that monoclonal immunoglobulin is the cause of SCLS even though studies find that most patients with SCLS have monoclonal immunoglobulin [2-4]. Hematopoietic system diseases such as lymphadenoma and hemophagocytic syndrome may cause SCLS, but up to now, we have found few reports about acute monocytic leukemia with concurrent SCLS. We describe a case that a man, who has been cured successfully, supervenes with SCLS after treatment of acute monocytic leukemia.

Case report

On 3 February 2015, a 51-year-old man was admitted to our hospital for recurrent oral ulcer,

hypodynamia and fever. He suffered from recurrent oral ulcer nearly one month. The patient had a feeling of fatigue but without headache and dizziness ten days ago. Two days ago, his trunk and limbs experienced interspersed protruded rash but without pruritus and blister. At the same time, he had chills, fever and his lower limbs had a lot of hemorrhagic spot. Admission check showed his temperature was 38.2°C, his blood pressure was 130/62 mmHg and his pulse rate was 112/min. He was sober, anemic without cutaneous or sclera icterus. There was no palpable cervical lymph node and tenderness in chest was not apparent. Examined by auscultation, his lung respiratory sound was coarse and there was no moist or dry rale sound. There was no pathologic murmur in all auscultatory valve areas. His abdomen was flat and soft, no tenderness or rebound tenderness. Subcostal liver and spleen were untouched. His trunk and limbs experienced interspersed congestive rash accompanied by haemorrhage but he didn't suffer from lower

limbs swelling. His nervous system was normal.

Routine blood test revealed leucocyte levels of $8.0 \times 10^9/L$, hemoglobin 70 g/L, erythrocyte $1.78 \times 10^{12}/L$, platelet $24 \times 10^9/L$, high sensitive C-reactive protein 16 mg/L, blast cell 16%, blood biochemical alanine aminotransferase (ALT) 15 U/L, aspartate aminotransferase (AST) 13 U/L, γ -glutamyltransferase (γ -GT) 22 U/L, alkaline phosphatase (ALP) 39 U/L, total protein 74.2 g/L, albumin 28.0 g/L, total bilirubin 5.4 $\mu\text{mol}/L$, conjugated bilirubin 2.2 $\mu\text{mol}/L$, indirect bilirubin 3.2 $\mu\text{mol}/L$, carbamide 3.32 mmol/L, creatinine 79 $\mu\text{mol}/L$, uric acid 291 $\mu\text{mol}/L$, creatine kinase 52 U/L, CK-MB 10 U/L, α -hydroxybutyrate dehydrogenase (α -HBD) 192 U/L, lactate dehydrogenase (LDH) 218 U/L. The laboratory test performed later showed that immunoglobulin G 34.200 g/L, immunoglobulin A 5.230 g/L, immunoglobulin M (IgM) 1.760 g/L, K light chain 26.80 g/L, L light chain 16.30 g/L, KAP/LAM 1.64. There was no monoclonal immunoglobulin M (IgM) showed on immunofixation electrophoresis. Bone marrow smear mainly showed monocytosis: 90% marrow blasts including promonocytes, and 63% marrow blasts. Flow cytometric detection of bone marrow showed that abnormal cells expressed CD117, CD123, CD34, CD33, CD15, HLA-DR, CD13 and CD38 and partial cells expressed CD71, CD64, CD14 and MPO. We diagnosed our patient with acute monocytic leukemia (M5b) in consideration of all these medical histories and clinical examination.

On 12 February 2015, he started the treatment with therapeutic regimen of IA: intravenous injection of 15 mg idarubicin on the first and second day and 10 mg idarubicin on the third day, intravenous drip of 100 mg cytosine arabinoside every 12 hours from the 1st day to the 7th day. On the first day after the chemotherapy, the patient had a fever accompanied by lacking of granulocyte. Thus, he successively took sulperazone, meropenem, teicoplanin and voriconazole. 4 days later, he began suffering from lower limbs swelling and his albumin level declined to 20 g/L. Levels of liver enzyme and bilirubin turned out to be normal. Tests on coagulation function showed PT 16.8 s, APTT 45.2 s and fibrinogen 1.66 g. Although the infusion of refrigerated plasma and human serum albumin could help supplement albumin (20 g~40 g every day) for the patient, blood tests

still showed progressive decrease of albumin, lowest to 10 g/L. His lower limbs swelling developed into severe anasarca, multiple blisters on lower limbs, moderate seroperitoneum and severe hydrothorax. During these days, all the results of urine protein detections were negative, which led to a further diagnostic confirmation of SCLS.

After the diagnosis of SCLS was made, 400 mg/kg low-dose corticosteroids combining with high-dose intravenous immunoglobulin were involved in the treatment for 5 days, but the level of blood albumin didn't increase. He experienced hypotension (86/50 mmHg) on the 8th day of chemotherapy. Meanwhile, he behaved worse on coagulation function: PT 18.2 s, APTT 90.2 s and fibrinogen 1.93 g. Results of tests on coagulation factor activity included 47% factor II, 21% factor VII, 74% factor VIII and 59% factor IX. Results of tests on serum cytokine included IL-6 18.6 pg/ml (0-3.4 pg/ml), TNF- α 24.2 pg/ml (0-8.1 pg/ml). And the concentration of IL-8, IL-10 and IL-1 β were normal. In order to improve capillary permeability, the treatment was judicious use of volume expansion, dopamine, prothrombin complex, hydroxyethyl starch, doxofylline and ulinastatin. He stopped taking pressor agent for his blood pressure was rising to normal on the 20th day after the chemotherapy. The edema began to subside, albumin level increased to 15 g/L and coagulation function were gradually improved in the next 5 days. On the 35th day after the chemotherapy, tests of bone marrow showed that the situation had markedly improved. Then, he successfully took twice treatment of IA and once of medium-dose cytosine arabinoside. The patient achieved a gradual improvement and a persistent remission up to now.

Discussion

We describe a 51-year-old man who suffers from acute monocytic leukemia with concurrent SCLS during the chemotherapy. SCLS is diagnosed clinically after exclusion of other diseases that cause systemic capillary leakage, including severe sepsis, toxic shock syndrome and anaphylaxis. SCLS was rare and fatal disease that there were less than 300 cases all over the world [5]. The crucial cause of SCLS is the increasing of capillary permeability that the components including albumin in blood vessel transfer from blood vessel to the interstitial

space. The molecular weight of extravasating macromolecule is less than 200 KD, but sometimes more than 900 KD [4, 6]. In our case, blood coagulation factor exsmosis and prominent hypoalbuminemia made the PT and APTT significantly extended. Coagulation factor activity detection indicates that the activity of plasma factor II, VII and IX decreased. The molecular weight of the coagulation factor is analogous or less than albumin's. Because huge amount of plasma composition is leaking into interstitial space, it leads to pulmonary interstitial edema. Lacking of effective circulating blood volume always leads to renal inadequacy. There was one case in which rhabdomyolysis occurred on that patient and it is a seriously complication [7]. The main reason for this is the increasing of interstitial pressure of bone fascia caused by liquid exsmosis. Meanwhile, the recovery of liquid aggravates fascia compartment pressure.

The etiology of SCLC is unknown, although the monoclonal immunoglobulin has been proposed to be one possible reason in SCLS [2-4]. However, monoclonal immunoglobulin may not be the direct reason of vascular endothelial barrier dysfunction. Xie and his colleagues found that VEGF and Ang2 were elevated in episodic SCLS sera while inflammatory mediators such as TNF- α , platelet activating factor (PAF), thrombin, histamine and IL-8 didn't increase. For our patient, level of IL-6 and TNF- α increased [8]. Studies report that SCLS may result from cytotoxic drugs such as gemcitabine and granulocyte colony-stimulating factor [9, 10]. Lymphoproliferative disorders such as lymphadenoma can also cause SCLS. Up to now, there exist 10 SCLS caused by lymphoproliferative disorders, of which prognosis was poor in patients. These patients could only live for several days to several months. These lymphoproliferative disorders include diffuse large B cell lymphoma, T-cell lymphoma and anaplastic large cell lymphoma [11]. Gousseff and his colleagues found that possible triggers for SCLS included infections (mostly upper respiratory tract infections), which was 74% of 28 patients. The cause of our patient's SCLS might be precipitating factor [2]. Our patient received treatment with IA after he achieved bone marrow remission, which was the same treatment as before. Granulocyte colony-stimulating factor was used for the patient in bone marrow

depression period, but he didn't get SCLS again. Therefore, medicine was not the cause of SCLS in our patient. On the other hand, his fever, which appeared after the treatment with IA, could be relieved by antibiotics. Besides, CRP increased slightly and procalcitonin level was not high. Thus, diagnosis of sepsis could not be made.

All the therapeutic measures of SCLS are based on observational data. Because capillary permeability increases, a lot of fluid and plasma proteins extravagate, resulting in hypotension and lacking of blood volume. Thus, it should be very careful when using crystalloid fluids and colloids [12]. A large amount of crystalloid fluid infusion would cause more fluid leaks into interstitial space, so SCLS should be taken into account when hypotensive shock is hard to be cured. It's controversial to supplement albumin because albumin can theoretically leak into interstitial space [12]. In our case, the supplement of albumin didn't increase the level of plasma albumin and resulted in more severe anasarca. Recent studies advise that hydroxyethyl starch should be the first choice when choosing colloid. The molecular weight of hydroxyethyl starch is about 100-200 KD which makes it impossible to leak into interstitial space. Therefore, hydroxyethyl starch can avoid capillary leak, control inflammatory reaction and improve tissue perfusion [13]. It can improve symptom and prevent SCLS by increasing CAMP such as terbutaline and theophylline in cells [14, 15]. A research based on small sample verified that intravenous immunoglobulin can prevent SCLS, especially patients with monoclonal gammopathy of unknown significance (MGUS) and acquired von Willebrand's disease (vWD). But intravenous immunoglobulin (IVIG) doesn't have effect on all patients [16]. Ulinastatin is an efficient hydrolase inhibitor. Ulinastatin can restrain TNF- α via restraining protein kinase C in mononuclear cells and signal transduction pathway between NF-KB. There already exists a case that a patient with SCLS was cured by TNF- α [17].

The mechanism of SCLS remains uncertain for the rarity of the disease and its unpredictable course. It can hardly be recognized at the very first time. This is the rare case report of the diagnosis and treatment of acute monocytic leukemia with concurrent SCLS. Since it hardly

happens that a patient may experience arrest of bone marrow, pancytopenia, pachyemia and increase of hematocrit after chemotherapy, hypotension can easily be misdiagnosed as infectious shock caused by lacking of granulocyte. We successfully diagnosed our patient and cured him by using different kinds of medicine including theophylline, hydroxyethyl starch and ulinastatin. In conclusion, awareness of this enigmatic syndrome is most important for improving the outcome because early diagnosis and immediate therapy are essential, more cases and in-depth researches are also needed to elucidate the potential mechanisms of SCLS.

Disclosure of conflict of interest

None.

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