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Case Report Open Access

Life-threatening Capillary Leak Syndrome in an Adult with Refractory Acute Myeloid Leukemia during Allogeneic Transplantation: a Case Report and Review of Literature

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Abstract

Background: Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers the possibility of cure for hematological malignancies, various complications have been described. Capillary leak syndrome (CLS) has been previously observed in HSCT patients. CLS is a rare disease characterized by recurrent episodes of generalized edema and severe hypotension along with hypoproteinemia. Case Report: A 27-year-old Chinese man, diagnosed with refractory acute myeloid leukemia, was treated with a haploidentical stem cell transplant combined with an unrelated umbilical cord blood unit. The patient developed fatal CLS during the 9th day of the conditioning therapy.

Conclusion: Since it is difficult to distinguish between CLS and other early complications during allo-HSCT, our report highlights the need for rigorous investigation of identifying CLS and the increasing need of insightful diagnosis to manage any incidence of CLS.

Keywords: Acute myeloid leukemia; Allogeneic transplantation; Capillary leak syndrome; Endothelial damage; Early complications

Introduction

CLS is one of the life-threatening early complications which usually occur during hematopoietic stem cell infusion or hematopoietic reconstruction process in addition to graft-versus-host-disease (GVHD) and infection [1]. It is characterized by unexplained episodic capillary hyperpermeability, which causes the shift of fluid and protein from the intravascular space to the interstitial space [2]. However, since the nonspecific signs and symptoms of CLS and the overlapping manifestations of early complications after transplantation, CLS tends to be easily confused with other early complications for clinicians. In this case, we report an adult with refractory acute myeloid leukemia who developed fatal CLS during allo-HSCT with review of the literature.

Case Report

A 27-year-old male was first admitted to our hospital in August 2014 with complaints of chills and fever. He exhibited obvious pain and swelling of gastrocnemius and activity abstacle. Peripheral blood counts revealed white cell counts of 29.9×10^9/L, hemoglobin lever of 89g/L, platelet counts of 179×10^9/L. Bone marrow was hypercellular exhibiting infiltration with 30% blast cells comprising myeloblasts and promonocytes. Immunophenotype analysis showed 54% abnormal cells which were positive for CD13, HLA-DR, CD11b, CD11c, CD33, CD14, CD64 and CD15, and weakly positive for CD34 and MPO. The overall findings were consistent with acute myeloid leukemia. G-banding revealed 46, XY. Moreover, genetic testing revealed positive for dupMLL fusion. He did not respond to "HA"(HHT 4 mg/d × 7d, Ara-c 0.2 g/d × 7d) and subsequent "IA" (IDA 30 mg d1, 20 mg d2-3, Ara-c 0.2 g/d × 7d) induction chemotherapy.

Salvage therapy consisted of DAC (decitabine) (20 mg/m^2/d × 5d), Ara-c (cytarabine) (10 mg/m^2/d × 2d) and Ara-c (10 mg/m^2 every 12 h × 3d) was planned. Because no full HLA-matched donor was readily available, a combination of a haploidentical stem cell graft and an unrelated umbilical cord blood unit was scheduled. The BU/CY-based conditioning regimen consisted of Me-CCNU 250 mg/m^2 (day -10), Ara-c 4 g/m^2/day (days -9 and -8), Bu 4mg/kg/day (days -7 to -5), CTX 1.8 g/m^2/day (days -4 and -3) and r-ATG (rabbit antithymocyte globulin) 2.5mg/kg (days -5 to -2).

The number of infused nucleated cells and CD34+/CD45+ cells were 21.75×10^8/kg and 2.33×10^6/kg for haploidentical transplantation and 0.184×10^8/kg and 1.35×10^5/kg for cord blood transplantation.

On the ninth day of the conditioning therapy, he developed palpitation, breathlessness, oliguria and progressive edema of his face and four limbs. But his blood urea nitrogen (BUN 5.77 mmol/L) and creatinine (55.3 μmol/L) were in normal ranges. The following day at 8:00 AM, he developed generalized edema and BUN and creatinine levels began to rise (BUN 15.38 mmol/L and creatinine 87.9 μmol/L) accompanied with hypoalbuminemia (total protein/albumin 45.5/25.1 g/L). On physical examination, his temperature was 37.4°C, blood pressure (BP) was low (70/45 mmHg), central venous pressure was only 3 cm/H_2O, heart beats were 140 beats/min and oxygen saturation decreased to 80%. The electrocardiogram (ECG) showed sinus tachycardia.

He had no painful hepatomegaly and ascites suggesting veno-occlusive disease. As these findings pointed out CLS, the patient was resuscitated with fluid infusion under intensive care and appropriate diuretic to relieve the edema. Prophylactic therapy with macromolecule hetastarch was done to improve colloid osmotic pressure. methylprednisolone was administered to improve the

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capillary permeability, relieve the capillary leak, and to ensure the perfusion of major organs. CVP was closely monitored. Clinically, the patient progressively improved. However, he redeveloped severe edema and anuria on day 30. BNP, liver enzymes and serum bilirubin lever continued to increase. Neutrophil engraftment was achieved on day 33. After sequential hemofiltration, he developed poor progress with deteriorating renal and liver function, resulting in death on day 42. A documented infectious cause was found in this episode. On the tenth day he developed a high fever but quickly controlled after empiric antibiotics (imipenem and vancomycin) were administered. His blood and catheter cultures were positive for Klebsiella pneumoniae.

Discussion

Allo-HSCT is a curative procedure for a subset of patients with hematologic malignancies. However, allo-HSCT is still associated with high treatment-related mortality due to severe infections and noninfectious complications. Especially during hematopoietic stem cell infusion or hematopoietic reconstruction process, a constellation of symptoms and signs including fever, erythrodermatous skin rash, and noncardiogenic pulmonary can be potentially fatal. CLS is a severe early complication of HSCT characterized by weight gain, generalized edema, hypotension, and hypoalbuminemia [2]. We present an allo-HSCT AML patient affected by fatal CLS during conditioning therapy with a short survival in which the crises have disappeared temporarily after treatment but eventually died of CLS recurrence.

CLS can be secondary to HSCT [3] including autograft, allograft and non-myeloablative transplantation, severe infections, trauma, post extracorporeal circulation [4] especially infants after extracorporeal circulation and some cytokines [5,6] such as IL-2, G-CSF and GM-CSF. The main CLS pathogenesis is injury of the capillary endothelium resulting in a loss of intravascular fluid into interstitial spaces [7]. Its mechanism is unknown, but in many studies vascular endothelial growth factor (VEGF) is the most suspected potent inducer of vascular permeability and may have a crucial role in the mechanism underlying CLS formation [8]. It is a serious condition and can be potentially fatal if not treated at the right time and with appropriate therapy. CLS after HSCT has been difficult to ameliorate. Treatment is limited to withdrawal of growth factors and systemic corticosteroids. The main aim of the treatment in the acute phase of CLS is to maintain tissue perfusion and to protect organs from the effect of the shock [2,9]. Yabe et al reported that bevacizumab may have a broad spectrum of efficacy against the life-threatening complication during HSCT [10]. In addition to the treatment for the acute phase, prevention of this is also important. Several prophylactic therapies such as Beta-2 stimulators (terbutaline or salbutamol) and theophylline have been tried, but their efficacy remains unclear [2].

The reported clinical presentation of CLS was varied primarily due to the lack of uniform diagnostic criteria. Currently, the diagnosis of CLS is still rely on clinical information, generally according to the following points 1) the cause of CLS, such as severe infection, chemotherapy drugs, CsA and cytokines such as interleukin-2, G-CSF and GM-CSF, 2) progressive systemic edema, weight gain, oliguria even anuria, dyspnea, drop of BP and CVP, severe edema after albumin supplementation and poor therapeutic efficacy after diuretic, 3) laboratory tests reveal that hypoalbuminemia, hypoxemia, creatinine and BUN increase progressively [11].

In our case, the patient was clinically diagnosed as CLS because of unexplained hypotension, diffuse edema, severe hypoalbuminemia, progressive oliguria and weight gain that occurred suddenly during the conditioning therapy. Infections and high-dose cytotoxic drugs rather than allograft were considered to be the common event due to the symptoms first appeared before allograft implanted. We treated our patient with intravenous fluid therapy (4 L/m^2) and albumin (1 g/kg). In addition to the fluid therapy, we also treated him with methylprednisolone (2 mg/kg/doses) and immunoglobulin (1 g/kg). His symptoms disappeared temporarily while he redeveloped severe edema and anuria on day 30. We speculated that the recurrence of CLS might be associated with the following factors. Firstly, he was a patient with refractory acute myeloid leukemia and did not achieve complete remission (CR) before allo-HSCT. Secondly, he received high-dose chemotherapy consisted of various cytotoxic drugs. Last but not least, he developed blood poisoning after CLS. All the disadvantages might accelerate the development of CLS. He finally died of multiple organ failure despite early recognition of the syndrome and prompt resuscitation.

Although acute GVHD is a major complication appear soon after allo-HSCT, patients often experience other serious non-infectious complications, such as hepatic veno-occlusive disease (VOD), transplant-associated microangiopathy (TAM), intestinal TAM (iTAM), engraftment syndrome (ES), hemophagocytic syndrome, idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), and CLS. All these non-infectious complications share the following characteristics: they have an early onset after HSCT, overlapping clinical manifestations, the absence of well-defined clinical criteria for diagnosis (and consequently an unknown true incidence), the absence of well-established treatments, and the tendency to evolve to an irreversible multiorgan dysfunction syndrome [12]. The similar presentation and management of CLS to ES, VOD or GVHD has therefore made their distinction difficult in allogeneic setting [13]. In our case, the symptoms first appeared was prior to engratment. In addition, the findings related to skin rash, pruritis, dyspnea, angioedema, painful hepatomegaly and liver damage were not present as the initial symptoms. Hence, we excluded ES, VOD and GVHD decisively.

Recent studies indicated that endothelial injury seems to be the initiating event in the cascade of events leading to their overlapping clinical manifestations of the early complications [14]. During HSCT, endothelial cells (ECs) are activated and damaged by several factors, including conditioning, cytokines released by damaged tissues, endotoxins translocated through damaged mucosa [15], drugs used in the procedure (such as G-CSF or calcineurin inhibitors) [16,17], the engraftment, and in the allogeneic setting-immunological reactions [18]. The different clinical syndromes that

occur could be determined by the predominant phenotypic change in the ECs and the location of this change (organ dependant or systemic) [19]. Several translational studies have provided evidence of this endothelial dysfunction on the basis of analysis of soluble markers, soluble forms of adhesion molecules, the enumeration of circulating ECs and microparticles, and morphologic and functional changes induced in cultured ECs [20]. Besides, Norihiro et al, [21] reported that the high ANG2 level at transplant was significantly associated with the increased incidence of the non-infectious complications and poor survival.

In conclusion, this report demonstrates fatal CLS can occur at each phase especially during hematopoietic stem cell infusion or hematopoietic reconstruction process. When sudden systematic edema and severe hypotension not reacting to hyperensort occur, evaluation and treatment are required to be performed with consideration of the

possibility of CLS. To identify CLS from other early complications during HSCT and find out optimal management of it should be future goals.

Patient Consent

Written informed consent was obtained from the patient's parents for publication of this case report.

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