The effect of tetrastarch solution for capillary leak syndrome following allogeneic hematopoietic stem cell transplantation: A report of 2 cases

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Abstract

Capillary leak syndrome (CLS) is a severe complication of allogeneic hematopoietic stem cell transplantation (HSCT) characterized by weight gain, generalized edema, hypotension, and hypoalbuminemia. The primary pathogenesis is injury of the capillary endothelium resulting in a loss of intravascular fluid into the interstitial space. Treatment is limited to vascular endothelial growth factor withdrawal and systemic corticosteroids. We report two cases with CLS where weight gain, ascites, and hypotension developed after neutrophil engraftment following allogeneic HSCT.

Case Report #1

A 14-year-old girl was admitted to our hospital in March 2016 with a 1-month history of pallor. Physical examination revealed cervical lymphadenopathies and marked hepatosplenomegaly. Peripheral blood counts revealed a white blood cell count of 250.4×10⁹/L with 94.0% blasts, hemoglobin level of 36 g/L, and platelet count of 21×10⁹/L. Bone marrow was hypercellular, exhibiting infiltration with 30% blast cells comprising myeloblasts and promonocytes. Immunophenotype analysis found 54% abnormal cells positive for CD19, CD10, CD34, and weakly positive for cytoplasmic Igμ and CD20, diagnosing acute lymphoblastic leukemia. The G-banding analysis revealed the karyotype 46,XX,add(10)(p13)[13]/47,XX,+X[13]. Three years after initial diagnosis, the bone marrow of the patient remained minimal residual disease (MRD)-positive by traditional leukemia-associated immunophenotype (LAIP)-gating at a level of 8.0×10⁻², whereas the central nervous system was free of blasts.

Due to the lack of response with standard treatment, allogeneic hematopoietic stem cell transplantation (HSCT) was proposed to the patient as a therapeutic option, to which she agreed. Pretransplant pulmonary function and echocardiography were within normal ranges. A human leukocyte antigen (HLA)-identical sibling donor was available, and transplantation was performed under myeloablative conditioning with total body irradiation and cyclophosphamide. The number of infused nucleated cells and CD34+ cells were 12.47×10⁹/kg and 5.77×10⁹/kg, respectively, for HLA-identical peripheral blood progenitor cell transplantation.

At day +12 post-transplant, the patient developed palpitation, breathlessness, oliguria, and progressive edema of her face and four limbs. Her blood urea nitrogen and creatinine levels began to rise, accompanied by hypoalbuminemia (plasma albumin <28 g/L). On physical examination, her temperature was 36.1°C, blood pressure was low...
(89/62 mmHg), heartbeats were 119 beats/min, and oxygen saturation decreased to 83%. The electrocardiogram showed sinus tachycardia. She had no painful hepatomegaly suggesting sinusoidal obstructive syndrome (SOS). Ultrasound (US) also excluded the diagnosis of SOS. CLS is a potentially life-threatening disorder characterized by distributive shock, hypoalbuminemia, and hemocoencentration. As these findings pointed out CLS, the patient was resuscitated with albumin plus diuretic therapy to relieve edema. Methylprednisolone was administered to improve capillary permeability and ensure the perfusion of major organs. However, the response to this combination of albumin and a diuretic has not been sufficient to produce the desired results. Volume therapy with 6% hydroxyethyl starch (HES) was infused to maintain colloid osmotic pressure. HES therapy started between day +19 and +29 post-transplant. Clinically, the patient progressively improved. She was subsequently discharged at day +33 post-transplant.

Case Report #2

The patient is a 3-year-old boy who was diagnosed prenatally with HB Zürich-Albsrieden and αα-thalassemia of SEA deletion (ααZA /--SEA ), which led to severe anemia. Evaluation of the fetus with anemia by fetal echocardiography demonstrated cardiomegaly and polyhydramnios. His parents declined to terminate the pregnancy but instead actively investigated potentially curative therapies for their child. He was delivered at 36 weeks by cesarean section, with Apgar scores of 2 and 6. His birth weight was 1,338 g, and his length was 39 cm. Total bilirubin at birth was 14.3 mg/dL (244.6 μmol/L). He was discharged home on the 40th day of life and required regular leukocyte-depleted red blood cells (RBC) transfusions after birth. A report from Tzu Chi Taiwan Marrow Donor Registry indicates an 8/8 HLA-matched adult unrelated donor is available.

At the pre-transplantation evaluation, the patient had received 12 units of RBC, and desferrioxamine had not been commenced. The serum ferritin level was 2,216 μg/L (normal, 6 □ 142). Pre-transplant echocardiography revealed a left ventricular ejection fraction of 72%. The preparative regimen consisted of busulfan 3.5 mg/kg/day (day –9 to –6), cyclophosphamide 50 mg/kg/day (day –5 to –2) and anti-thymocyte globulin (ATG) 30 mg/kg/day (day –4 to –1). Graft-versus-host disease (GVHD) prophylaxis comprised cyclosporin A from day –3 and short-term methotrexate. The number of infused nucleated cells was 16.05×10³/kg, and CD34 cells, 12×10⁶/kg. Neutrophil and platelet engraftment was successfully achieved on day 18 and 34, respectively.

Chimerism analysis at day +18 showed 98.6% of donor alleles; however, profuse ascites was identified 3 days later, and the US with Doppler showed no reversal of portal venous flow. The US features and clinical characteristics both indicate suspicious diagnosis of CLS. He was also treated with tetrastarch at a dose of 30 mL/hr for 20 days. The ascites resolved gradually within 3 weeks of commencing treatment. The patient was discharged in stable condition at day +49 post-transplant. He is now transfusion-independent without sequelae for 18 months.

Discussion and Conclusions

The diagnosis of CLS is based on clinical presentation, laboratory analysis, and sonographic results. Proper fluid management is crucial for managing critically ill patients. Because of its superior ability to remain in the intravascular space, colloid solution is theoretically advantageous to crystalloids.6 Maize derived 6% HES 130/0.4 (Volulyte®, Fresenius Kabi GmbH, Bad Homburg, Germany), commonly known as tetrastarch, has been routinely used to treat hypovolemia in patients undergoing cardiac surgery with cardiopulmonary bypass, as it is considered preferable for volume expansion compared with crystalloid solution.7 Application of HES solution is relatively limited due to its side effects, including renal toxicity and coagulopathy.8 This fluid consists of large-branched glucose molecules substituted with hydroxyethyl groups for increased solubility and intravascular persistence.

This case study aimed to describe the benefit of adjuvant therapy for CLS in the transplant setting. The complicated biological relationship among sepsis, GVHD, and CLS development regarding cytokine release and endothelial damage warrants validation by further studies.9 In the setting of inflammatory conditions, steroid-refractoriness is characterized by the presence of lymphocytes whose proliferation and cytokine production is not inhibited by corticosteroids. Fluid resuscitation is a critical part of the treatment of CLS; hypovolemia and hypotension can cause organ injury, whereas capillary leakage of administered fluid can worsen organ edema leading to progressive organ injury. The objective of this strategy is to highlight the diseases other than sepsis that produce capillary leak and review their collective pathophysiology and treatment.10

CLS had been challenging to ameliorate, and vascular endothelial damage plays a causal role in early complications of vascular origin after allogeneic HSCT, including sinusoidal obstruction syndrome and engraftment syndrome.11 Intravenous immunoglobulins and anti-IL6 antibody were validated in the treatment of CLS.12 Precise differential diagnostic categorization is essential, as CLS’s treatment and prognosis largely depend on its cause. Moreover, capillary leak due to engraftment syndrome responds to treatment with steroids,13,14

There is no deterministic algorithm was used to guide HES administration in the vast majority of previous trials assessing HES utilization in CLS patients. Moreover, the literature is mostly silent on the feasibility of this approach in children. The number of patients is too small to make determinations regarding the response and overall survival rates.

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