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## Case Report

## Successful treatment of a 3-year-old boy with hepatitis-associated aplastic anemia with combination of auto-umbilical cord blood transplantation and immunosuppressive therapy

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## ABSTRACT

In this work we describe a 3-year-old boy with hepatitis-associated aplastic anemia (HAAA) treated successfully with autologous cord blood transplantation combined with immunosuppressive therapy. There is little previous experience in the utility of autologous cord blood transplantation in the treatment of HAAA. Nowadays, for patients born after 1980, an HLA matched sibling donor is not usually available because of the family planning policy in our country. So more and more parents choose to preserve the umbilical cord blood for their children. We consider it a new effective choice for the treatment of HAAA, especially for the pediatric patients.

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A 3-year-old boy presented to the department of gastroenterology with nausea, vomiting, deep jaundice and dark urine in May 2013. There was no history of fever, weight loss, previous blood transfusion or exposure to drugs or toxins. He had severely damaged liver function with a bilirubin level of 370  $\mu\text{mol/L}$  and alanine aminotransferase (ALT) level of 1700 U/L. The serologic markers of hepatitis A, B, C, D and E were all negative, and the blood cell counts were normal at that time. He was diagnosed with acute icterohepatitis. The disease progressed rapidly and deteriorated to hepatic coma in a few days. Then he received treatment with an artificial liver support system (ALSS). His liver function gradually returned to the normal range in the

following one and a half months and the boy was getting better. But two weeks later, he suffered from spontaneous skin and mucosal bleeding and was admitted to our hospital.

Lab results revealed abnormal blood cell counts. He was pancytopenic with a hemoglobin level of 91 g/L, WBC  $3.13 \times 10^9/\text{L}$ , neutrophils  $0.38 \times 10^9/\text{L}$ , and a platelet count of  $25 \times 10^9/\text{L}$ . Two weeks later the blood cell counts went down further, the WBC was  $1.09 \times 10^9/\text{L}$  with a neutrophil count of  $0.15 \times 10^9/\text{L}$ . Erythrocyte and platelet transfusions were performed for the patient. A blood smear showed leucopenia and thrombocytopenia with normal morphology. The bone marrow aspirate and biopsy showed that the marrow was severely hypocellular with no signs of fibrosis or malignancy, consistent with the criteria for aplastic anemia. Bone marrow cytogenetic study revealed a normal male karyotype. A Mitomycin-C (MMC)-induced chromosomal breakage study was also performed and showed normal results. Therefore, Fanconi's anemia was excluded. In addition, there was no evidence of paroxysmal nocturnal hemoglobinuria and hemolytic anemia.

Anti-HBV surface antibody (HBsAb), anti-HBV core antibody (HBcAb) and anti-HBV e antibody (HBeAb) were

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positive, but the HBV surface antigen (HBsAg) and HBV-DNA were negative. Other serologic marks associated with hepatitis A, C, D and E were all negative. Anti cytomegalovirus (CMV)-IgM and CMV-DNA were negative, and Epstein-Barr virus and parvovirus B19 were not found in the serum. The liver function tests showed a bilirubin level of 17.1  $\mu\text{mol/L}$ , ALT of 70 U/L, aspartate aminotransferase (AST) of 60.2 U/L and  $\gamma$ -glutamyl transferase (GGT) of 102.6 U/L.

Based on the medical history and lab results, the patient was diagnosed with hepatitis-associated aplastic anemia (HAAA). After admission in our hospital, he suffered from recurrent fever, persistent fatigue and lethargy. Blood culture showed positive results for *Staphylococcus epidermidis*. After combinations of anti-infective therapy and intermittent blood transfusions, an auto-umbilical cord blood (UCB) transplantation was performed in this patient in September 2013. His own UCB with the total mononuclear cell (MNC) number of  $5.88 \times 10^8$  was preserved at birth. At the time of transplantation, the MNC number had been  $3.16 \times 10^7/\text{kg}$  and the number of CD34 positive cells was  $2.23 \times 10^6/\text{kg}$ . The conditioning regimen included antilymphocyte globulin (ATG) 2 mg/kg/d for 4 days and cyclophosphamide 40 mg/kg/d for 2 days. The cyclosporine A (CSA) therapy was initiated 1 day prior to stem cell transplantation and continued thereafter. Engraftment of neutrophils and platelets was achieved on day +16 and day +31 respectively. Forty days after transplantation, his full blood counts were completely normalized. The bone marrow aspiration showed active proliferation of hematopoietic cells. He remained well at 1 year after transplantation.

## 1. Discussion

HAAA is a syndrome of bone marrow failure following an episode of acute hepatitis. Clinically apparent hepatitis precedes aplasia by a period of weeks to months. The clinical course of hepatitis can be benign, severe, or even fulminant, and the subsequent bone marrow failure is usually fatal if not treated. HAAA has been reported in 2–5% cases of aplastic anemia (AA) in Western countries, and the incidence is higher in the East [1]. Furthermore, HAAA most often affects adolescent boys and young males. In a retrospective study, 56 patients who underwent liver transplantation for fulminant liver failure were assessed and the incidence of post-hepatitis AA was up to 33% in children and 5% in adults [2].

The etiology of HAAA remains unknown. Several possibilities have been discussed such as viral infections, autoimmune diseases or the liver transplantation procedure. Clinical features and experimental results suggest a central role for an immune-mediated pathogenesis. The existence of a specific antigen such as a viral pathogen was emphasized from the biopsied liver samples of the patients and the T-cell mediated suppression of bone marrow may be associated with liver infiltration by activated CD8 cells [3]. The hepatitis was clinically indistinguishable from a typical viral hepatitis. Several hepatitis viruses such as Hepatitis A, B, C and E have been anticipated to be associated with this set of syndrome. But, in no study has a specific virus been identified. Because most cases with HAAA are seronegative for known hepatitis viruses, HAAA

is commonly known as the non-A and non-B hepatitis-associated AA, which has been reported in more than 80% of the total HAAA [4]. HGV and TTV have been suspected as the cause of hepatitis that leads to HAAA, but no study has confirmed this relationship [5].

In our case, the child developed a fulminant hepatitis preceding AA, but was seronegative for the HBV markers at the onset of hepatitis. However, when AA occurred, the laboratory tests showed positive results for HBsAb, HBeAb and HBcAb, but negative results for HBsAg and HBV-DNA. It is still unclear whether HBV infection was a causative factor in this case. Through the process of transplantation and treatment of CSA, lamivudine was given to the patient, but no changes had been detected for the HBV serologic markers and HBV-DNA was negative throughout the follow-up period.

Since HAAA represents a life-threatening condition, its therapeutic approach should be considered as a medical emergency. The first-line treatment is allogeneic bone marrow transplantation from HLA-matched siblings [6]. Immunosuppressive therapy (IST) including ATG and CSA is recommended for patients without a sibling donor. Patients who fail immunosuppressive therapy are candidates for unrelated donor stem cell transplantation. The survival rate of the patients receiving hematopoietic stem cell transplantation and the response rate to immunosuppressive therapy were found to be 85% and 70% respectively [7]. Children responded better than adults to BMT and the survival rate of HAAA with BMT from HLA-matched donors was found to be similar to that for non-hepatitis associated AA [5]. The predictors of survival include younger age and interval between diagnosis and transplant [8]. Although IST has shown satisfactory results for AA patients, the normalization of peripheral blood cell counts was usually achieved 8 weeks later. In most studies, the response rate and quality of response were analyzed every 3 months after IST and only 40–60% of the patients achieved CR/PR at the first 3 months [9]. Therefore, for the IST, the factors ensuring disease remission were effective immunosuppression and the sufficient dose of residual hematopoietic stem cells in the bone marrow of the patients. In this case, with the transfusion of healthy stem cells from his own UCB, the child received a rapid hematopoietic engraftment and had no GVHD complications.

Autologous HCT for aplastic anemia utilizing cord blood has been only rarely reported [10–12]. In most cases, the conditioning regimen consisted of ATG. In another case, for a boy who had failed immunosuppressive therapy before transplantation, an immunoablative conditioning regimen including fludarabine and cyclophosphamide was applied [13]. In our case, the conditioning regimen included ATG and cyclophosphamide; post-transplantation immunosuppressive therapy with CSA was also utilized. The patient had a complete response to therapy and recovered quickly.

Nowadays, for patients born after 1980, an HLA matched sibling donor is not usually available because of the family planning policy in our country. Therefore, more and more parents choose to preserve the umbilical cord blood for their children. In this case, the result is quite encouraging. Given its convenience and lack of GVHD, we consider it a good choice for young patients. Otherwise, the patient may have to wait for a long time to find an unrelated donor, or the

treatment may be delayed because of severe infection and other unexpected complications. The prognosis may be totally different for the patient.

In summary, we report a case of a 3-year-old boy with HAAA who showed rapid, complete and persistent clinical and hematological remission after auto-UCB transplantation combined with immunosuppressive therapy. Although this treatment strategy may have some limitations in clinical use, we consider it a new effective choice for the treatment of HAAA, especially for pediatric patients.

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