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Case Report

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Successful allogeneic hematopoietic stem cell transplantation in a child with transfusion-dependent pyridoxine refractory hereditary sideroblastic anaemia

Abstract

We report a case of pyridoxine refractory, hereditary sideroblastic anaemia (HSA) in a 23 months old girl who underwent bone marrow stem cell transplantation (BMSCT) from his 28-year-old HLA-identical maternal uncle.

By using short tandem repeat polymorphism, 95% donor cells were observed in peripheral blood on day +15, +30, +90 and until the present time; the patient did not develop any significant graft-versus-host disease or other transplant complications. One year after transplantation, the patient has a Lansky score[1] of 100, with a normal cell blood count (CBC).

Keywords: hematopoietic stem cell transplantation, hereditary sideroblastic anemia, unrelated donor

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Introduction

Sideroblastic anaemias are a heterogeneous group of inherited and acquired bone marrow disorders defined by pathological iron accumulation in the mitochondria of erythroid precursors leading to appearance of ring sideroblasts in bone marrow.[2] Hereditary sideroblastic anemia (HSA) is a rare genetic dyserythropoietic disorder caused by a mutation in the erythroid *δ*-aminolevulinic acid synthase.[3] The disease is characterized by hypoproliferative anemia and secondary hemochromatosis due to ineffective erythropoiesis and red-cell transfusions. These patients survival has seldom been beyond the second decade; however, allogeneic hematopoietic stem cell transplantation has emerged as a successfully curative treatment strategy for HSA in more than a few reported cases.[4]

Case report

The patient was admitted in hospital with severe anemia at 2 months of age. Thalassemia as a common anemia etiology in the region was ruled out by normal hemoglobin electrophoresis in the child and her parents. At 4 months of age, she was diagnosed with HSA due to observation of ringed sideroblasts using light microscopy in her bone marrow after Perl's stain. She did not respond to high dose pyridoxine and folic acid and became transfusion dependent since then. Her haemoglobin (Hb) values ranged between 7 and 9g/dL and she needed to receive at least monthly packed red blood cells. When she was one year old, SCT was proposed for her and she was referred to Hematology-Oncology and SCT Research Center (HORCSCT). However, she had only one sibling whose HLA did not match her. Her parents and close relatives were screened and fortunately, her 28-year-old maternal uncle's HLA fully matched her.

At the time of transplantation, she weighed 12 kg (between 50 and 85 percentile for age) and her length was 85 cm (between 15 and 50 percentile for age).

Her biological values were: Hb 9.1g/dL; mean cell volume (MCV) and mean cell haemoglobin (MCH) 71.6fl and 21.9pg respectively; leucocytes 10.8×10^9/ L; platelets 764×10^9/ L; serum ferritin 100 ng/ml. Hepatic function was normal (total serum bilirubin 0.6mg/dL, AST 33U/l, ALT 32U/ L, LDH 364U/ L, alkaline phosphatase 1089U/l).

A bone marrow examination showed marked erythroid hyperplasia and presence of many ring sideroblasts in iron stain with normal cytogenetics. Using Sanger sequencing, targeting the *SLC25A38* gene, disclosed a homozygous mutation and confirmed her diagnosis. Both parents were carriers (heterozygous) for the mutation. Consanguinity in the family was evident and the patient's parents were cousins. An abdominal ultrasonography showed hepatic (90mm) and splenic (65*42mm) enlargement.

The patient and the donor were both CMV-seronegative and both blood group was B positive. Conditioning regimen consisted of busulphan 3.5mg/kg/d for 4 days, from day −9 to day −6 (total dose 14mg/kg) and cyclophosphamide 50mg/kg once daily for 4 days, on days −5 to −2 (total dose 200mg/kg).

Anti-thymocyte globulin (ATG) was given i.v. at a dose of 2.5mg/kg on d −3 and −2 and cyclosporin (3mg/kg starting from on days −2

and, after that, the dose necessary to maintain blood levels between 150 and 300ng/ml). Graft-versus-host disease (GVHD) prophylaxis included methotrexate (10mg/m^2 on day +1 and 6mg/m^2 on days +3, +6 and +11).

The total number of infused bone marrow stem cells was 3.79×10^6/kg CD34$^+$ cells and 50.0×10^6/kg CD3$^+$ cells. The patient was isolated until engraftment and all administered blood products were leucocyte-filtered and irradiated.

Transplant was well tolerated except for stage 2 skin GVHD.

The neutrophil count reached >0·1×10^9/ L and >0·5×10^9/ L on days +9 and +12, respectively, and the platelet count reached >20×10^9/ L on day +12 and >50×10^9/L on day +14.

She was discharged from hospital on day +16 after allogeneic BMSCT. By using short tandem repeat polymorphism, 95% donor cells were observed in peripheral blood on day +15; the bone marrow examination confirmed trilineage engraftment with no evidence of ringed sideroblasts on day +30.

At the present time, a year after SCT, the patient has normal haemoglobin values (12-14g/dL) considering the normal range for her age[5] and is transfusion independent. The patient has not developed chronic GVHD so far.

Discussion

Sideroblastic anemia is identified by the unique presence of pathological erythroid precursors that contain iron-loaded mitochondria, which encircle the nucleus and form a Prussian blue-positive staining ring.[6] nherited sideroblastic anemia is a dyserythropoietic disorder that leads to transfusion dependency and subsequent iron overload. The responsible molecular defects reside in the pathways of heme synthesis, iron-sulfur cluster biogenesis, and mitochondrial protein translation. The most common HSA forms are X-linked sideroblastic anemia due to mutations upsetting the erythroid heme synthesis enzyme 5-aminolevulinate synthase 2 (ALAS2) and the autosomal recessive sideroblastic anemia due to mutations affecting the erythroid-specific mitochondrial inner membrane protein SLC25A38.[7] Most mutations are severe or complete loss-of-function mutations and lead to severe anemia, requiring lifelong transfusions and iron chelation. At present, definitive cure for HSA is proposed to be allogeneic HSCT.

To our knowledge, the first BMSCT in a case of HAS was reported by in 1992.[8] Later, Ayas et al. reported BMSCT from matched sibling donors in three children with CSA who were blood transfusion dependent.[9] González et al.[10] described peripheral blood SCT in a 19-year-old pyridoxine refractory HSA man from his HLA-identical brother.

The mentioned five patients, all received myeloablative conditioning with busulfan and cyclophosphamide +/− antithymocyte globulin (ATG) as the preparative regimen.

Medeiros et al. reported nonmyeloablative SCT for a 22-year-old male patient with CSA, who had contraindications to conventional allografting due to progressively worsening cardiomyopathy and frequent episodes of supraventricular tachyarrhythmia. Even though the patient experienced full engraftment, he yielded to GVHD on day +190.[11] BMSCT using reduced-intensity-conditioning (RIC) regimen (busulfan, fludarabine, and alemtuzumab) was also reported in a 4-year-old case of HSA from her full matched sibling, efficaciously.[12] Conversely, using RIC regimen in the SCT of a 17-year-old Japanese boy with ALAS2 R170L mutation from an HLA-identical unrelated donor led to secondary graft failure.[13] However, we were successful in transplanting from an unrelated donor using conventional regimen.

In conclusion, this case illustrates that myeloablative conditioning regimen is preferred for the HSCT from another relative donor in HSA. The extension of genetic knowledge in HSA may further benefit their SCT process toward achieving successful outcomes.

Acknowledgments

None.

Conflicts of interest

We declare that there is no conflict of interest in our article.

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