

# Haploidentical Hematopoietic Stem Cell Transplantation in a 3-Year-Old Girl with Congenital Amegakaryocytic Thrombocytopenia: A Case Report

## Haploide hämatopoetische Stammzelltransplantation zur Behandlung der kongenitalen megalokalytischen Thrombozytopenie bei Mädchen



### Introduction

Congenital amegakaryocytic thrombocytopenia (CAMT) is an autosomal recessive disorder characterized by severe thrombocytopenia that presents soon after birth and is usually not accompanied by specific somatic malformations [Germeshausen M, Ballmaier M. *Best Pract Res Clin Haematol* 2021; 34: 101286]. CAMT is more prevalent in females than males [Ballmaier M, Germeshausen M. *Semin Thromb Hemost* 2011; 37: 673–681; Germeshausen M, Ballmaier M. *Haematologica* 2021; 106: 2439–2448], in contrast to other congenital bone marrow failure syndromes. Patients with CAMT also exhibit cardiac malformations, cerebellar hypoplasia, growth retardation, and a distinctive facial appearance [Yldrm A T, Güneş B T, Oymak Y, et al. *Blood Coagul Fibrinolysis* 2015; 26: 337–341], although it remains unknown whether these are related to CAMT. Mutations in the *MPL* gene, which encodes the thrombopoietin receptor, are the pathogenetic cause of CAMT [Germeshausen M, Ballmaier M. *Haematologica* 2021; 106: 2439–2448]. Since thrombopoietin is involved in the maintenance of hematopoietic stem cells and megakaryocyte development [Germeshausen M, Ballmaier M. *Best Pract Res Clin Haematol* 2021; 34: 101286], CAMT may eventually manifest as a hematopoietic failure. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only cure for CAMT. Human leukocyte antigen (HLA)-matched siblings are the first-choice donors for HSCT because transplantations from matched unrelated donors have a low success rate [King S, Germeshausen M, Strauss G, et al. *Br J Haematol* 2005; 131: 636–644]. Cancio et al. [Cancio M, Hebert K, Kim S, et al. *Transplant Cell Ther* 2022;

28: 101 e101–101 e106] reviewed 86 patients treated over 18 years and reported that although HLA-mismatched donors can extend the survival of CAMT patients, HLA-matched donors are preferred. The present report describes the successful treatment of a 3-year-old girl with CAMT using haploidentical allogeneic HSCT from the father, even though he harbored a mutant *MPL* gene.

### Case presentation

A 39-month-old girl was admitted to the hematology and oncology department of West China Second Hospital of Sichuan University with a > 3-year history of skin ecchymoses. The family denied consanguineous marriage or a history of blood diseases. After birth, the child developed recurrent bleeding spots and ecchymoses on the skin, and her platelet count was  $2 \times 10^9/L$ . She was diagnosed with immune thrombocytopenia and given platelet transfusions. However, the patient continued experiencing recurrent localized skin bleeding without other manifestations such as epistaxis, intracranial hemorrhage, or joint hematoma. The child gradually developed pallor when she was 2 years old, and routine blood investigations showed reductions in platelet count ( $5 \times 10^9/L$ ) and hemoglobin level (55 g/L). Platelet infusions (41 treatments at 9-day intervals) and leucodepletion with suspended red blood cells (18 units) were performed regularly.

She was admitted at the outpatient department of the pediatric hematology department when she was 39 months old. Physical examination revealed skin ecchymoses, and routine blood tests showed thrombocytopenia. The child had no obvi-

ous immune deficiency manifestations such as eczema and repeated infection in the past. Therefore, combined with the genetic test results, a diagnosis of Wiskott-Aldrich syndrome was not considered. The examinations were not suggestive of any autoimmune condition because every infusion of platelet was effective and reduced the occurrence of bleeding events. In addition, due to the young age, no clinical manifestations such as rash, photosensitivity, urination changes, joint pain, etc., were observed. The genetic screening revealed that the patient had an insertion mutation in exon 4 (exon4:c.417dupC:p.I139fs, acquired from the father) and a deletion in exon 3 (exon3:c.297delG:p.E99fs, acquired from the mother) in the *MPL* gene, and the patient was admitted with a diagnosis of CAMT.

The patient had no potential sibling donors, and no matched unrelated homozygous allogeneic healthy donors were identified. Both parents were carrying an *MPL* mutation, while the mother has an experience of pregnant and delivery, and might have an increasing risk of graft-versus-host disease (GVHD). Therefore, the patient received haploidentical HSCT from her father (matched for 5/10 HLA alleles) even though he carried an *MPL* gene mutation. A conditioning chemotherapy regimen was used before transplantation (busulfan 4 mg/kg/d on days -10 to -9; fludarabine phosphate 36 mg/m<sup>2</sup>/d on days -7 to -3; cyclophosphamide 45 mg/kg/d on days -5 to -2; and anti-human T cell rabbit immunoglobulin 7 mg/kg/d on days -4 to -2). HLA-7/10-matched unrelated umbilical cord blood stem cells were infused as adjuvant therapy ( $1.0 \times 10^5$  CD34+ cells and  $2.3 \times 10^7$  mononuclear cells per kg). The patient was in-

fused with 368 mL of related haploidentical allogeneic bone marrow stem cells on day 1 and 60 mL of related haploidentical allogeneic peripheral hematopoietic stem cells on day 2 (the number of CD34<sup>+</sup>, mononuclear and CD3<sup>+</sup> cells was  $5 \times 10^6$ /kg,  $9 \times 10^8$ /kg and  $13.69 \times 10^7$ /kg, respectively). Low-dose methotrexate (10 mg/m<sup>2</sup> on days +1, +3, +6 and +11), mycophenolate mofetil (40 mg/kg/d on days +1 to +45), cyclosporine (2.5–3.0 mg/kg/d injected on days -9 to +14 followed by 6 mg/kg/d orally tapered gradually over 1 year) and methylprednisolone (1–2 mg/kg/d on days +10 to +27 and then gradually decreased) were administered to prevent GVHD after transplantation. Recombinant human granulocyte colony-stimulating factor (10 µg/kg/d on days +3 to +15d) and recombinant human TPO (300 U/kg/d on days +6 to +20) were administered to promote hematopoietic reconstitution. Neutrophils and platelets were implanted on day 12 and day 20 after transplantation, respectively. The patient was discharged one month after transplantation and attended the outpatient department for follow-up and gamma-globulin injections (administered once weekly during months 1–6 and once every two weeks during months 7–12). Routine blood, electrolyte, liver function, and kidney function tests, measurement of drug concentrations, and tests for cytomegalovirus DNA and Epstein-Barr virus nucleic acid were performed once weekly during months 1–6 and once every two weeks during months 7–12. Gene chimerism conforming to the patient's father was assessed every month. The patient was then followed up every month from 1 year after transplantation. No acute or chronic GVHD, hepatic vein occlusion, Epstein-Barr virus infection, human cytomegalovirus infection, or other transplantation-related complications occurred during follow-up. There was no need for blood transfusion after hematopoietic reconstruction. The immunosuppressive regimen was given for a total of 10 months. B lymphocytes were fully normal 12 months after transplantation, and monitoring remained normal after immunoglobulin infusion was stopped. The patient was having a normal life for 4 years after transplantation, and no complication was recorded during follow up.

## Discussion

This case report describes a 39-month-old girl with CAMT who carried two *MPL* gene mutations inherited from her mother (exon3:c.297delG:p.E99fs) and her father (exon4:c.417dupC:p.I139fs). A unique feature of this case is that the patient was cured by haploidentical HSCT (with matching of 5/10 HLA alleles) despite the donor (her father) carrying an *MPL* mutant gene.

Type I CAMT arises from nonsense, deletion, or frameshift mutations that lead to the complete absence of thrombopoietin receptor function. Type I CAMT generally presents with severe clinical symptoms and is characterized by persistent, severe thrombocytopenia and rapid progression to bone marrow failure. Type II CAMT is often due to missense mutations that cause a partial absence of thrombopoietin receptor function. Hence, the presenting symptoms are generally mild. Patients with type II CAMT often have near-normal platelet levels during the first year of life and usually progress to bone marrow failure more slowly than patients with type I CAMT [King S, Germeshausen M, Strauss G, et al. *Br J Haematol* 2005; 131: 636–644; Germeshausen M, Ballmaier M, Welte K. *Hum Mutat* 2006; 27: 296]. However, severe clinical manifestations have been reported in some patients with type II mutations [Ok Bozkaya İ, Yaralı N, Işık P, et al. *Turk J Haematol* 2015; 32: 172–174]. Moreover, CAMT can manifest in the absence of *MPL* gene mutations [Kanaji S, Kanaji T, Migita M, et al. *Eur J Haematol* 2008; 80: 361–364], possibly due to defects in other genes involved in the thrombopoietin signaling pathway. The present case had an insertion in exon 4 (exon4:c.417 dupC:p.I139fs) and a deletion in exon 3 (exon3:c.297 delG:p.E99fs) of the *MPL* gene. CAMT manifested as skin ecchymoses and persistent severe thrombocytopenia soon after birth, followed by the rapid development of bone marrow failure, indicating that the patient had type I CAMT.

Thrombocytopenia in the neonatal period is often related to perinatal factors (hypoxia, placental insufficiency, or intrauterine growth retardation), infection (bacterial or TORCH-related), or neonatal alloimmune thrombocytopenia. Nevertheless, congenital thrombocytopenia should also be considered in a neonate with thrombocytopenia. CAMT should be suspected

when thrombocytopenia occurs immediately after birth in the absence of other physical deformities and lasts for >3 months [Germeshausen M, Ballmaier M, Welte K. *Hum Mutat* 2006; 27: 296; Rose M J, Nicol K K, Skeens M A, et al. *Pediatr Blood Cancer* 2008; 50: 1263–1265]. Bone marrow examination generally shows an absence of/severe decrease in megakaryocytes, while other lineages are normal [Ballmaier M, Germeshausen M. *Semin Thromb Hemost* 2011; 37: 673–681], although some children with CAMT initially exhibit little or no reduction in megakaryocytes [Rose M J, Nicol K K, Skeens M A, et al. *Pediatr Blood Cancer* 2008; 50: 1263–1265]. The patient in this report was diagnosed with immune thrombocytopenia during the early course of the disease, but the diagnosis was reconsidered when thrombocytopenia persisted following several platelet transfusions. CAMT was eventually diagnosed by genetic testing after the patient had developed progressive erythrocytopenia. This illustrates the importance of genetic testing to confirm the diagnosis of CAMT and identify whether there are homozygous or compound heterozygous mutations in the *MPL* gene.

Research into targeted therapies for *MPL* gene mutations is ongoing, but HSCT remains the only currently available cure for CAMT. Although HLA-matched siblings are the first choice as a donor [King S, Germeshausen M, Strauss G, et al. *Br J Haematol* 2005; 131: 636–644], success has also been achieved using matched unrelated allogeneic donor transplantation [Frangoul H, Keates-Baleeiro J, Calder C, et al. *Pediatr Transplant* 2010; 14: E42–45]. Since neither sibling donors nor matched unrelated healthy donors were available in the present case, and it was decided that haploidentical allogeneic HSCT should be performed with the father (matched for 5/10 HLA alleles) as the donor. This decision was made because the patient was already reliant on platelet and red blood cell transfusions, and the disease was likely to progress rapidly to bone marrow failure. Therefore, the father was chosen as the related donor for HSCT. This is the first report to describe stem cell transplantation from a haploidentical related donor carrying a mutant *MPL* gene. His wild-type allele was apparently enough to restore *MPL* gene function of this patient. HLA-7/10-matched unrelated um-

bilical cord blood stem cells were infused as adjuvant therapy to increase the likelihood of success and because cord blood stem cells are readily available [Ballen K K, Gluckman E, Broxmeyer H E. *Blood* 2013; 122: 491–498]. Related and unrelated cord blood transplants have high rates of success for a variety of hematologic and metabolic storage diseases in children [Ballen K K, Gluckman E, Broxmeyer H E. *Blood* 2013; 122: 491–498]. Cancio et al. [Cancio M, Herbert K, Kim S, et al. *Transplant Cell Ther* 2022; 28: 101 e101–101 e106] reviewed 86 patients and reported that HLA-mismatched donors could extend the survival of CAMT patients but that complication and mortality rates were higher than with HLA-matched donors. In the case presented here, an HLA-matched donor was not possible, and an HLA-mismatched donor still had better chances of good outcomes than no HSCT at all.

There is no current consensus on the optimal timing of transplantation for CAMT, although transplantation before bone marrow failure would reduce the patient's exposure to blood products and the risk of GVHD after transplantation. Therefore, the key to long-term disease-free survival may be early diagnosis by genetic testing followed by HSCT with an appropriate donor. Since studies of CAMT are limited, addition-

al case reports are needed to facilitate decision-making by clinicians.

In conclusion, the present case demonstrates that a haploidentical related donor carrying a mutant *MPL* gene could be considered for HSCT when HLA-matched sibling donors or unrelated healthy donors are not available.

## Contributor's Statement

Sisi wang and Yuan ai carried out the studies, participated in collecting data, and drafted the manuscript. Xue yang and Sisi wang performed the statistical analysis and participated in its design. Xue yang and Yiping zhu participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved the final manuscript.

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*Klin Padiatr* 2022; 234: 388–390

DOI 10.1055/a-1933-2583

ISSN 0300-8630

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