

Successful combined umbilical cord blood and bone marrow transplantation from an HLA-matched sibling for MPS VI: a case report

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Abstract

Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux–Lamy syndrome, polydystrophic dwarfism, and arysulfatase B (ASB) deficiency, is a lysosomal storage disorder with autosomal recessive inheritance characterized by progressive multisystem involvement that causes many tissues and organs to enlarge and become inflamed. Skeletal deformities are common that progress and worsen in varying degrees thus affecting quality of life and life expectancy. Many studies have shown that allogeneic hematopoietic stem cell transplantation can reduce morbidity and enhance the survival and quality of life in such patients. We present a case of a 6-year-old girl diagnosed with MPS VI at the age of 3 years. Thereafter the patient developed various complications of the disease causing morbidity. She was then treated with combined umbilical cord blood (UCB) and bone marrow (BM) transplantation from complete human leukocyte antigen–matched (6/6) donor which was her younger sibling. The transplant was successful without any serious adverse effects. No additional treatments such as enzyme replacement therapy (ERT) were required. The transplantation of UCB along with BM can be considered as an effective treatment approach for this rare disease.

Plain language summary

Case of MPS VI treated with stem cell transplantation

This article reports a case of a 6-year-old girl who was diagnosed with mucopolysaccharidosis type VI also known as MPS VI, an autosomal recessive disorder that caused her arysulfatase B (ASB) deficiency. This disorder affects growth velocity, gives coarse facial features, gives rise to skeletal deformities, frequent upper-airway infections, enlarged liver and spleen, hearing loss, and joint stiffness. However, very few studies have reported definitive ways to treat or cure MPS VI. To help her combat this disorder, combined umbilical cord blood and bone marrow transplantation was done. This transplant alleviated her symptoms, and the patient did not need any further treatment. Follow-up, 4 years after transplantation, shows normal enzyme level, no complications, and improved quality of life.

Keywords: cord blood transplantation, hematopoietic stem cell transplant, lysosomal storage disorder, Maroteaux-Lamy syndrome, metabolic diseases, mucopolysaccharidosis type VI

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Introduction

Mucopolysaccharidoses (MPS) or lysosomal storage disorders (LSD) are a cluster of rare, progressive, inherited disorders characterized by defects in the glycosaminoglycan (GAG) catabolism that leads to the accumulation of partially degraded GAG within the lysosomes.¹ Its incidence is 1:250,000 to 600,000.² Epidemiological studies of MPS are limited to publications describing birth prevalence, whereas no studies describing the population prevalence are available. The rapidly progressive forms have their onset since birth, with death being reported before the second or third decades, whereas the mildly progressive forms have a later onset with death in the fourth or fifth decades.³ One such MPS disorder is MPS VI or Maroteaux–Lamy syndrome (253200), which is an autosomal recessive disorder caused by the deficiency of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB; EC 3.1.6.12).⁴ The arylsulfatase B (ASB) catalyzes breakdown of dermatan sulfate, which is present particularly in the skin but is also found in tendons, blood vessels, airways, and heart valves. Diagnosis is generally accepted by the confirmation in an accredited laboratory of ASB enzyme activity in cultured fibroblasts or isolated leukocytes of <10% of the lower limit of normal and demonstration of two disease-causing mutations.³

Symptoms of MPS VI include decreased growth velocity, coarse facial features, skeletal deformities, frequent upper-airway infections, enlarged liver and spleen, hearing loss, joint stiffness, and coarse hair.³ The available therapeutic options comprise symptomatic treatment, enzyme replacement therapy (ERT), and hematopoietic stem cell transplantation (HSCT).⁴ Recently, gene therapy is increasingly being investigated for treatment of MPS VI.⁵ Compared with bone marrow (BM), the use of umbilical cord blood (UCB) is rising as an alternative source of hematopoietic stem cells for transplantation due to the ease of procurement, accessibility for immediate use, reduced risk of donor morbidity, and severe graft-*versus*-host disease (GVHD) in recipients. However, MPS is a rare disease and only few studies or case reports have been published that have reported using UCB as a source of definitive ERT. Here, we present a case of a girl who was diagnosed with MPS VI at the age of 3 years. The CAse REport (CARE) guidelines were followed when preparing this case report.

Case report

The patient was first diagnosed with MPS VI at the age of 3 years in 2013 using an enzyme analysis, which showed reduced activity (~97.1%) of ASB in cultured skin fibroblasts [38.8 nmoL/h/mg (reference range: 379–980)] and in leukocytes [2.5 nmoL/h/mg (reference range: 84–452)]. The normal activity of α -iduronidase in leukocytes ruled out the possibility of Hurler (MPS I). She was apparently active at home and at school and displayed no behavioral abnormalities. However, she had impaired vision and hearing. Furthermore, there was an enlargement of the optic cup, out-pouching around the belly-button, and abnormal development of bones in the limbs, which were suggestive of abnormal growth and development. The patient's parents were thoroughly explained about all the available treatment options for MPS VI, including ERT. However, the parents did not agree for ERT due to financial constraints.

The parents had a second child and decided to store his UCB at Biocell® (cord blood bank of Regrow Biosciences Pvt. Ltd). The second baby, a male child, was born in June 2014 by Cesarean section. Approximately 100 ml of UCB was collected in a cord blood collection bag containing an anticoagulant under sterile aseptic conditions. The collected UCB was sent to the processing laboratory where the UCB sample was processed within 72 h from the time of collection using the double sedimentation method and was successfully cryopreserved after it was tested negative for transfusion transmissible disease (TTD) and bacterial contamination. Patient was decided to be treated by HSC transplantation. In order to attain adequate CD34⁺ cell dose, UCB was combined with BM [donor for both was complete human leukocyte antigen (HLA)-matched younger sibling] for transplantation.

Transplantation of UCB and BM

Preparatory steps. The processed UCB was analyzed for hematology [total nucleated cell count (TNCC) = 5.9×10^8 nucleated cells/unit; total CD34⁺ stem cell count = 18.7×10^5 nucleated cells/unit, viability (97.97%), microbial sterility (negative), and colony-forming capability of cells (granulocyte macrophage = 3.39×10^5 cells per colony and erythrocyte = 6.05×10^5 cells per colony)]. The UCB sample was verified to be free from infectious agents.

The BM was extracted from the same sibling. Cell count and potency were tested before transplant.

Pre-transplant assessment. As required for a transplant, HLA testing and matching were performed in-house on 21 June 2014. The HLA testing was initially done at low resolution (HLA-A, B and DRB1) by polymerase chain reaction (PCR) with sequence-specific primers (PCR-SSP). Results showed a complete 6/6 match between the siblings, that is, donor (younger brother) and recipient (elder sister). HLA typing was also confirmed at high resolution using sequence-based typing method from Applied Biosystems by Life Technologies, USA, a laboratory accredited by the National Accreditation Board for hospital and healthcare providers. High-resolution HLA testing of patient and sibling was done on 21 November 2015 at Jeevan Blood Bank and Research Centre, Chennai. The results from the high-resolution assessment also showed a complete 10/10 match of both alleles of 5 loci for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 between the donor and the recipient.

Based on the HLA matching report, the transplant physician requested retrieval of the donor's cryopreserved UCB for allogeneic HSCT to the recipient. Also, MPS VI is an indication for UCB-HSCT that is recognized as a medical procedure under the Indian Council of Medical Research (ICMR) guidelines. Parents' consent was taken for both retrieval and release of the stored UCB for the transplant.

Conditioning regimen and transplantation procedure. Before initiating the transplant procedure, the patient was placed in a high-efficiency, particulate air-filtered room in the BM transplantation unit of the Apollo Specialty Hospital, Chennai, Tamil Nadu, India. The preparative regimens consisted of Thiotepa 8 mg/kg (Day 7), Treosulphan 14 gm/m²/day (Days 4, 5, and 6), and Fludarabine 40 mg/m²/day (Days 3, 4, 5, and 6). Tacrolimus and short-course methotrexate were given as a prophylaxis for GVHD.

The UCB retrieved from 'Biocell®' was transplanted in the patient along with the BM from the same donor (the brother), simultaneously on 19 January 2016. The UCB unit consisted of 4.08×10^8 nucleated cells/unit after thawing with

gentle agitation in a 37°C water bath prior to infusion into the patient. The stem cell dose from BM that was infused was a CD34⁺ dose of 13.1×10^6 /kg recipient body weight.

Supportive care and post-transplantation follow-up. Prophylactic antivirals, antifungals, and antibiotics for febrile neutropenia were given. Post transplantation, she had mild GVHD in the form of grade-2 mucositis in the neutropenic period and had febrile neutropenia. Her blood cultures were sterile. She received intravenous antibiotics. Packed red blood cells (PRBCs) and apheresed platelets were given to maintain the hemoglobin and platelet counts.

We also used PedsQL™ for stem cell transplant module version 1.0 to evaluate clinical outcomes after treatment (Table 1).⁶ It has excellent psychometric properties and was accepted by patient and parents, as it is easy to use and internationally recognized. Furthermore, it is applicable across a wide range of ages: children from the age of 2 years, as well as for adolescents up to an age of 18 years.

Treatment outcomes

No severe adverse events were observed in the patient post-transplantation. A Chimerism test was performed at Day 100 by Short Tandem Repeat-polymerase chain reaction (STR-PCR) method. The transplant was engrafted in time with 100% chimerism that was persistent till the final follow-up. Absolute neutrophil count first exceeded >500 around Day 14 (range, 14–25 days), and the patient became red cell-independent and platelet-independent around Day 22. No signs of primary graft rejection were seen. Hypertension and mild grade-1 skin and gut GVHD were seen, which were resolved by steroids. No other related adverse events occurred at any point during follow-up visits.

Furthermore, 18 months post-transplant showed enzyme levels within normal range (ASB level 24 nmol/h/mg in leukocytes). Post-transplant the patient did not suffer from symptoms like impaired vision and hearing. Four years post-transplant, the patient was 10 years old, going to school, and had no difficulties in studying or with friends. She had shown normal growth and skeletal development including increase in height,

Table 1. PedsQL™ for stem cell transplant module score.⁶

Questions	Scale score	Transform score
Pain and hurt (problem with . . .)		100
I ache or hurt in my muscles and joints	0	
I ache or hurt		
Fatigue and sleep (problem with . . .)		100
I feel too tired to do things that I like to do	0	
I have to sleep a lot	0	
I feel physically weak	0	
Nausea (problem with . . .)		100
I become sick to my stomach when I have medical treatments	0	
I become sick to my stomach when I think of medical treatments	–	
Some foods and smells make me sick to my stomach	0	
Worry (problem with . . .)		100
I worry about whether I can return smoothly into normal life	0	
I worry about whether other people do not want me because of my disease	0	
Nutrition (problem with . . .)		62.5
Food does not taste very good to me	3	
I have to drink a lot when chewing food	0	
Thinking (problem with . . .)		50
It is hard for me to remember things that I have heard	2	
Communication (problem with . . .)		100
It is hard for me to ask the doctors or nurses questions	0	
Other complaints (problem with . . .)		100
I have dry or burning eyes	0	
I have a dry mouth, pruritus	0	
I feel lonely	0	
I have painful skin infections	0	
Total score	–	92.19
Scale score: 0 = never; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always. Transformed score: 0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0.		

without the need of medical care. She was doing fairly well. The PedsQL™ stem cell transplant score of 92 also indicates better quality of life and clinical condition of patient post treatment.

Discussion

This is a case of a successful combined transplantation of allogenic UCB along with BM in a 6-year-old diagnosed with MPS VI at the age of 3 years. The patient received UCB and BM from her younger sibling after HLA matching. No post-transplant severe adverse events were observed up to 4 years after transplantation. The patient is reported to be doing well in her day-to-day life with good PedsQL™ score post-transplant.

The first HSCT was performed in 1982 and the principle is based on the concept of cross-correction of the metabolic defects with the help of transferable enzyme.⁷ It has been shown that there has been an alleviation in the somatic features along with stabilization of cardiac function and improvement in the quality of life.^{8,9} There has been a decline in the transplant risks for MPS patients due to the collaborative efforts put by the transplant community.²

As patients with these disorders have no or very low residual enzyme activity, the normal active protein infused by ERT is perceived as foreign and thus most MPS patients receiving ERT develop antibodies.¹⁰ Treatment using ERT is also a prolonged and chronic treatment method, making it more expensive, time-consuming, and the need for continuous follow-ups. On the other side, those who have received transplantation from UCB have often achieved full donor chimerism and eventually normal enzyme levels.¹¹ The UCB-derived hematopoietic stem cells are easy to procure, donor is at no risk during collection, and stem cells present in the cord blood sample can be further processed, tested, and stored for future use.^{12–14} The average occurrence of acute GVHD was found higher after peripheral blood progenitor cells when compared with UCB transplantation, whereas chronic GVHD was higher in case of 8/8 matched BM transplantation compared with UCB transplantation.¹⁵ UCB-derived stem cells of HLA-matched siblings were used for transplant in 44 patients, in this transplant mismatch had at 0 or 1 HLA locus was observed. Eighty-five percent of engraftment was observed

after 50 days of transplant, while the rate of grade II–IV acute graft *versus* host disease was very low (3%), and after 1.6 years, the survival rate was about 72%.¹⁶ This justifies that the UCB are more suitable and better treatment of choice. Although UCB transplantation has been performed for the last four decades, it has been rarely reported and the existing literature is limited to single case reports owing to the rarity of the disease. It is noteworthy that Lee *et al.*¹⁷ reported successful recovery of the BM and enzymatic functions after UCB was transplanted from a 5-year-old Maroteaux–Lamy syndrome patient's unaffected HLA-identical brother. In this case, 6.08×10^7 /kg of nucleated cells and 2.92×10^5 /kg of CD34+ cells were transplanted with neutrophil engraftment and were achieved on Day 26. However, there was no evidence of acute and chronic GVHD. Thus, limited literature demands further research to identify minimum cell dose requirement and risk identification for GVHD.

Conclusion

UCB and BM transplantation was found to alleviate symptoms and improve quality of life. This corrected the enzyme deficiency in this patient with Maroteaux–Lamy syndrome, avoiding the need for ERT or other medications post transplantation even up to 4 years. However, continued follow-up will be needed to evaluate long-term outcome.

Declarations

Ethics approval and consent to participate

Institutional Committee for Stem Cell Research of Regrow Biosciences Pvt. Ltd. gave the approval (Letter no: REG/IC-SCR/2015/001; Dated: 19 November 2015) for the planned Hematopoietic stem cell Transplantation for the treatment of Mucopolysaccharidosis type VI (MPS VI) using HLA-matched Umbilical cord blood stem cell (related sibling) and was also communicated to the National Apex Committee for Stem Cell Research and Therapy on the same day. This report is original and written by the author. It has not been previously published and has only been submitted to this journal. The report has been referenced appropriately and does not infringe on any rights of others, including privacy rights and intellectual property rights. The case report data is true, not manipulated.

Consent for publication

The written informed consent to publish this case was obtained from the parents of the patient and donor (as the patient and donor are minors).

Author contributions

Pankti Haria: Conceptualization; Data curation; Investigation; Writing – review & editing.

Vinayak Kedage: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.

Pradnya Dalvi: Investigation; Methodology; Writing – review & editing.

Satyen Sanghavi: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Parvathi Chandran: Data curation; Methodology; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: V.K., P.D., S.S., and P.C. are employees of Regrow Biosciences Pvt. Ltd.

Availability of data and materials


Raw data were generated. Derived data supporting the findings of this study are available from the corresponding author on request.

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