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Case Report

Successful Allogenic Hematopoietic Stem Cell Transplantation for Infantile Osteopetrosis: A Case Report

Raed Alzyoud[1]*, Mohammad Wahadneh[2], Omar Wahadneh[2], Motasem AlSuweiti[1], Hiba Maitah[1], Boshra Adayleh[1], Mohammed Alnoubani[1] and Adel Alwahadneh[1]

[1]Immunology, Allergy, and Bone Marrow Transplantation Unit for Primary Immunodeficiency Disorders, Queen Rania Children's Hospital, Amman, Jordan

[2]Externship Physician, Queen Rania Children's Hospital, Amman, Jordan

***Corresponding Author:** Raed Alzyoud, Chief of Pediatric Immunology, Allergy, and Rheumatology Division at Queen Rania Children's Hospital, Amman, Jordan.

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Abstract

Osteopetrosis is an inherited bone disease, has different types of inheritance with variable phenotypes, characterized by increased bone mass and defective bone resorption can affect the bone marrow activity leading to suppressed hematopoiesis presenting in the form of anemia and reduced platelet numbers and white blood cells thus increasing risk of bleeding and immunodeficiency. Severe infantile form is presenting at birth or in the first few months, is usually fatal and the infants rarely survive beyond the second year of life, due to bone marrow failure and recurrent infections, this form can be cured by Hematopoietic stem cell transplantation (HSCT). We report an infant who had diagnosed during infancy and underwent HSCT, describing transplant details, complications and challenges.

Keywords: *Hematopoietic Stem Cell Transplantation (HSCT); Osteopetrosis; Bone Resorption*

Introduction

Osteopetrosis is a group of inherited bone diseases that are characterized by increased bone mass and defective bone resorption [1,2]. This is usually results in macrocephaly, altered craniofacial bones, susceptibility to fracture and osteomyelitis [3]. Other tissues can be affected mainly bone marrow and the nervous system [3]. There are several major types of osteopetrosis that are usually categorized by their inheritance; autosomal dominant, autosomal recessive, or X-linked. These types vary in the severity of disease presentation [1,3].

Autosomal dominant form is also known as Albers-Schönberg disease, is usually mild in presentation and may be asymptomatic and often diagnosed accidently on x-ray investigation [4]. In this group of patient's symptoms vary from bone fractures, scoliosis, hip joint arthritis and osteomyelitis [5].

Autosomal recessive form appears early in life and usually presents as a severe form of the disease [3]. It is usually presenting in the form of abnormal dense skull bones affecting the cranial nerves that leads to loss of vision, hearing and facial muscle paralysis [3,6,7]. Dense bones can affect the bone marrow activity leading to suppressed hematopoiesis presenting in the form of anemia and reduced platelet numbers and white blood cells thus increasing risk of bleeding and immunodeficiency [8]. These symptoms present themselves early in life and can be fatal. Other features of this category include short stature, dental abnormalities, hepatosplenomegaly and intellectual disability [8].

X-linked form is rarely seen and is characterized by lymphedema and anhidrotic ectodermal dysplasia affecting skin, hair, teeth and sweat glands [9]. Patients with X-lined form usually suffer from severe immunodeficiency [9].

Autosomal dominant osteopetrosis is usually seen later in life and presents itself with milder disease manifestations. In autosomal recessive form, on the other hand presents itself early in life and can be life threatening. Hematopoietic stem cell transplantation (HSCT) is the main rescue for those patients [1,10].

Case Report

A 15 months old male patient, first presentation at the age of 3 months with pancytopenia, hepatosplenomegaly and transfusion dependent anemia and Negative family history. Patient was diagnosed as osteopetrosis based on radiological and clinical findings, when a matched family donor was found for him (his mother) he was prepared for hematopoietic stem cell transplant (HSCT) as it's the only curative option when a matched donor is available. Pre-transplant assessment included cardiac, ophthalmic, neurological and hearing assessment, he was found to have craniosynostosis, right eye papilooedemea, normal cardiac and hearing assessment he had generalized radiological increase in bone density but he had no pathological fracture. Initial laboratory findings included macrocytic anemia, reticulocytopenia and thrombocytopenia, kidney function and liver function was normal.

Conditioning and transplant

Myeloablative conditioning was used (Busulfan 16 mg/kg, ATG 10 mg/kg, fludarabine 160 mg/kg), patient received bone marrow stem cells at a dose of CD34+ (7.6 x 10^6/kg). Cyclosporine as anti-GVHD and defibrotide from day 0 as prophylaxis until day +30. He was kept on prophylaxis: Micafungin, acyclovir, septrin and Intravenous immunoglobulin (IVIG) during BMT unit stay till B cell recovery.

Complications

The most challenging risk was delayed engraftment, patient neutrophil engraftment was at +18 day, but he had delayed platelet engraftment till +32 day for which he required multiple platelet transfusion with no serious bleeding. Around the time of increase of absolute neutrophil count (was between +17 up to +34) he had manifestations of stage-I hepatic Veno-occlusive disease (VOD), with high liver enzymes and elevated bilirubin but fortunately was responsive to defibrotide therapeutic dose along with medication and intravenous fluid infusion adjustment.

Patient was discharged at +50 day of transplant, presented at +65 with skin erythema involving 35% of his body surface area (BSA), was managed as acute skin GVHD (stage II) with intravenous steroid which settled by +72 day.

	WBC Cells/uL	Platelets/uL	PCV %
Day -1	5 x 10^3	66,000	20
Day +5	1 x 10^3	22,000	22
Day +50	8 x 10^3	188,000	31

Table 1: *WBC, Platelets and PCV readings for the patient before, during and after HSCT.*

Challenges

With platelet and neutrophil engraftment and recovered osteoclast function, patient was closely observed for possible hypercalcemia, at around +120 (Table 2) he had high creatinine, normal serum calcium level but he had nephrocalcinosis, and was managed with hydration, low calcium diet and thiazide diuretic. At one year after transplant patient still under observation for craniosynostosis, patient is still not indicated for surgical intervention with normal developmental assessment and normal optic disk.

	Serum calcium Mg/dl	Urine Ca/Cr
Pre-transplant	8.5 - 9.1	0.02 - 0.08
Day 0 to +30 day	8.2 - 9.6	0.08 - 0.1
+30 day to +100	8.6 - 9.7	0.06 - 0.2
+100 day to 180	9.2 - 10.9	0.6 - 0.9
+180 to +360	9.2 - 10.2	0.05 - 0.3

Table 2: *Serum calcium levels and urine Calcium/Creatinine ratio (Ca/Cr). Normal serum calcium 8.5 - 10.5 mg/dL. Normal value for Ca/Cr < 0.8.*

Discussion

Osteopetrosis is a rare disease, affecting osteoclast differentiation and function. So far, hematopoietic stem cell transplantation (HSCT) is the only available treatment for the infantile form [11-13]. Osteoclasts are known to be originating from the pluripotent hematopoietic stem cells [14]. Thus, HSCT is the way to correct the defective osteoclasts. Our patient suffered severe disease and HSCT was offered to reduce his suffering. It helped correcting the disease and the major laboratory problems including macrocytic anemia, and thrombocytopenia. Skin GVHD developed (stage II) at +120 days post-transplant and was managed with steroid. One of the major complications post HSCT is hypercalcemia [15]. In our patient this was transient and was back to normal. In patients with osteopetrosis, hypercalcemia post HSCT is relatively common (10 - 40%) [16-18]. Hypercalcemia was found to develop within approximately a month post HSCT or within two weeks of engraftment [17,19,20]. Hypercalcemia risk was associated with age, the younger the patient the lower the risk. Patients younger than two years old were at low risk of hypercalcemia [16,18]. Our patient is less than two years of age and we believe this is the explanation for his calcium status. We will still closely monitor his blood calcium and other indicators.

Conclusion

Although HSCT as treatment option in osteopetrosis is still challenging, but it is the only hope to cure severe infantile type. Early diagnosis based on clinical and radiological features, using defibrotide prophylaxis and long-term monitoring for posttransplant hypercalcemia, all are factors would improve HSCT outcome.

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