EXCEPTIONAL CASE REPORT

blood advances

Hematopoietic cell transplantation for a child with OSTM1 osteopetrosis

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Key Points

- HCT prior to onset of neurologic symptoms in children with OSTM1 osteopetrosis does not halt neurologic progression.

Introduction

Osteopetrosis (OP) is a rare, heterogeneous genetic disease characterized by the dysfunction or deficiency of osteoclasts, with increased bone mineral density (BMD) secondary to absent bone reabsorption. Children with malignant infantile osteopetrosis (MIOP), the lethal form of OP, exhibit an array of symptoms including pancytopenia, defective bone metabolism, and neurologic abnormalities such as progressive blindness, seizures, and eventual death if untreated; symptoms are secondary to both bony overgrowth and direct neurotoxicity.[1-7] To date, mutations in 12 genes have been associated with the OP phenotype, most commonly in the *TCIRG1* (50%), *CLCN7* (15%),[8,9] and *OSTM1* (5%) genes.[2,3] Although the average lifespan for a patient with MIOP is 5 to 6 years of age, patients specifically with *OSTM1* mutations display a more severe, intrinsic neurodegenerative process, and death generally occurs earlier, between 0 and 2 years of age.[1,2,4,5,7,10]

Hematopoietic cell transplant (HCT) for the treatment of MIOP has become the standard of care since the first successful transplant in 1980; however, HCT has not been uniformly effective.[2,11] We now understand that the potential efficacy of transplant as a curative treatment depends on the specific genetic mutation and the presence or absence of neuropathic disease. Children with *TCIRG1* and some *CLCN7* mutations should be considered early for HCT; however, HCT in children with *OSTM1* and some *CLCN7* mutations have historically not abrogated the associated neuropathologic progression to death.[2-4,7,10]

Recent studies have focused on the characterization of the OSTM1 protein in an effort to identify an effective treatment. Although not completely elucidated, the protein has been shown to play a primary, autonomous role in neuronal homeostasis independent of the hematopoietic lineage, in addition to its critical role in osteoclast function.[10,12] Heraud et al have shown that, despite functional rescue of the hematopoietic defects in OSTM1-deficient mice after HCT, neurodegeneration continues, leading to local inflammation and eventual cell death. Although the hematopoietic and neurologic effects are seemingly discrete, it is unknown whether there can be cross-correction of the nervous system from transplanted hematopoietic cells if HCT is performed before neuronal damage, a concept previously reported in patients with metabolic conditions including purine nucleoside phosphorylase (PNP) deficiency,[13,14] α mannosidosis, Hurler syndrome, and cerebral X-linked adrenoleukodystrophy.[15]

Case description

In this report, we describe a 4-week-old male who presented with MIOP caused by compound heterozygous mutations in the *OSTM1* gene. He underwent HCT at 3 months of life, after discussion with family about the potential for cross-corrective benefit, as well as possible development of progressive neurologic disease.

Methods

Our patient was born at term via vaginal delivery to nonconsanguineous parents. Shortly after birth, he developed tachypnea and was treated for presumed bacterial pneumonia. After discharge, he had sustained tachypnea, shortness of breath with feeding, and episodes of perioral cyanosis. At 2 weeks of age, chest radiograph suggested reactive airway disease.

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At 4 weeks of age, as a result of sustained symptoms, he presented to a cardiology clinic, where echocardiogram showed normal anatomy and function. Otolaryngology evaluation demonstrated a normal airway, whereas repeat chest radiography showed increased bone density suggestive of osteopetrosis. Other than tachypnea, his physical examination was normal without other clinical stigmata: his weight was in the 10th percentile, length was in the 20th percentile, and head circumference was in the 5th percentile.

Laboratory evaluation showed macrocytic anemia (hemoglobin 6.8 g/dL; mean corpuscular volume 100 fL), reticulocytosis (19%), and thrombocytopenia (35×10^9/L). An elevated alkaline phosphatase (766 U/L) with normal calcium level (9.3 mg/dL) was consistent with abnormal bone metabolism. An autosomal recessive osteopetrosis gene panel (Connective Tissue Gene Tests) identified 2 heterozygous mutations in the *OSTM1* gene, a pathogenic frameshift, c.442delA, in exon 2, and a novel splicing mutation, c.402+5G>A, of unknown significance. The splicing variant was not found in available sequence databases, and the "G" at the +5 position was present in 84% of introns. The patient's mother carried only the splicing mutation, implying the mutations were in trans; testing on the father could not be performed. Because of uncertainty regarding the pathogenicity of the splicing variant, a bone marrow examination was performed at 6 weeks of age, which confirmed marrow space obliteration with hypocellular marrow, fibrosis, and thickened bone trabeculae, consistent with OP. Ophthalmologic examination showed mild pallor and poor foveal light reflex without signs of optic nerve atrophy and normal visually evoked potential. Electroencephalogram and auditory evaluations were normal.

Given the absence of obvious neurologic signs and symptoms, and after discussion about the possibility of an unclear outcome, the family decided to proceed with HCT with an HLA-matched sibling. The patient developed left facial nerve palsy one month before transplant, which was consistent with nerve compression in the foramina as a result of bony overgrowth and is commonly seen in patients with MIOP. He was evaluated with computed tomography of the head at the time, which was negative for hemorrhagic stroke, and brain magnetic resonance imaging, obtained 20 days before HCT, showed no abnormality. Development was otherwise appropriate for age.

At 3 months of age, the patient underwent myeloablative conditioning with busulfan targeted to pharmacokinetics (AUC 3600) and fludarabine (30 mg/m^2 per dose). He received tacrolimus and mycophenolate mofetil for graft-versus-host disease prophylaxis and ursodiol for vaso-occlusive disease prophylaxis. His transplant course was uneventful, attaining neutrophil engraftment on day 18, platelet engraftment on day 41, and erythrocyte engraftment on day 88. Chimerism analysis of peripheral blood on day 30 revealed that 90% of nucleated cells, 47% of CD3$^+$ cells, and 99% of CD33$^+$ cells were of donor origin. His facial nerve palsy had resolved by discharge (day 31), supporting our diagnosis of modest cranial nerve compression; however, 2 months after transplantation he developed seizurelike activity and the electroencephalogram pattern was consistent with infantile spasms. Brain magnetic resonance imaging at that time revealed diffuse cerebral atrophy, and ophthalmology evaluation revealed retinal dystrophy with abnormal visually evoked potential. He was started on vigabatrin for treatment of his spasms but eventually transitioned to clobazam, levetracitam, and zonisamide for control of his seizures. He has since had progression of neurologic disease, requiring gastrostomy tube placement for feeding difficulties and tracheostomy for airway support, and placement in hospice care, yet at 28 months of age, he has a normal BMD for his age (measured and radiographically estimated) and reconstituted hematopoiesis. He has not demonstrated any transplant-related complications and donor chimerism in peripheral blood collected at 1 year post-transplant showed 98% total nucleated cells, 94% CD3$^+$ cells, and 99% CD33$^+$ cells.

Results and discussion

HCT for patients with MIOP corrects the osteoclast defect, which restores physiologic bone remodeling but simply halts the progression of ongoing soft tissue and neurologic damage. Whether HCT for a child with an OSTM1 mutation before neurologic inflammation and damage could cross-correct affected neurons and halt neurologic symptoms is an open question. Our patient with OSTM1 osteopetrosis unfortunately progressed neurologically shortly after transplant despite early HCT, suggesting that that either cross-correction from the hematopoietic system seen in other metabolic disorders did not occur or did not occur fast enough to be clinically relevant. Although clinically his neurologic status was intact before transplant, it is reasonable that neurologic inflammation may have been ongoing, and it is difficult to predict effectiveness of HCT had this been performed earlier.

A common obstacle in studying rare diseases is the difficulty in drawing conclusions from examination of only a few patients. Although we now have a mouse model that allows us to further study disease pathogenesis, treatment decisions rely heavily on previously published patient experience. Our goal in treating this patient with HCT was with the intent of altering the natural course of the disease to a manageable chronic disease course with acceptable quality of life. In addition, we sought to evaluate for the possibility of neurologic cross-correction. By proceeding with transplant, we hoped to prolong lifespan and improve the quality of life of this child as opposed to the expected progression toward an early neurologic death.

The outcome of our patient suggests that early HCT in patients with an *OSTM1* mutation without clinical or global signs of neurologic findings does not prevent onset or progression of neurologic deterioration. Our patient is 28 months old at the time of this publication and, although he is transfusion independent, he continues to have neurologic progression. Longer follow-up is required to determine the impact on his duration of life.

Authorship

Contribution: K.M.O. participated in care of the child and prepared the manuscript; M.J.R., S.J., G.E.H., R.B., and R.A.-A. participated in care of the child and review of the manuscript; and H.G.R. and E.M.H. participated in care of the child and edited and finalized the manuscript.

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