Mild Autosomal Recessive Osteopetrosis: Successful Treatment With Bone Marrow Transplant

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SUMMARY

We describe a 5 ½ year old boy who was diagnosed with mild autosomal recessive osteopetrosis based on the presence of bony sclerosis, extramedullary haematopoeisis, leukoerythroblastosis and visual impairment who had an allogeneic bone marrow transplant from a matched sibling donor. Conditioning regime was busulphan 16 mg/kg and cyclophosphamide 200 mg/kg. Apart from transient hypercalcaemia, there were no major post transplant complications. Four years post transplant, the extramedullary haematopoeisis has resolved completely with normal blood counts. Apart from a fracture after a trivial fall two months after transplant, he has not suffered any fracture related limb deformities.

KEY WORDS:
Osteopetrosis, Transplant, outcome

INTRODUCTION

Osteopetrosis (also known as Albers- Schönberg disease or marble bone disease) comprises a rare group of heterogeneous disease affecting osteoclast function, leading to decreased bone resorption. There are four types described: i) autosomal recessive infantile 'malignant' osteopetrosis, ii) autosomal recessive 'mild' osteopetrosis iii) autosomal dominant osteopetrosis and iv) osteopetrosis due to carbonic anhydrase deficiency. Based on the clinical presentation and family history, this patient fits into the mild autosomal recessive form.

CASE REPORT

A 5 ½ year old boy was referred to us for assessment for a bone marrow transplant. He was the youngest of six siblings from a non consanguineous marriage. His eldest brother, 20 years old was bed ridden due to multiple fracture - related limb deformities and blindness in both eyes. Three brothers, a sister and both parents were phenotypically normal. There was no similar phenotype in any of his first degree relatives. A 17 year old HLA identical phenotypically normal brother had been identified as a potential bone marrow donor.

He had a ventriculo-peritoneal shunt inserted when he first presented at the age of two with hydrocephalus, bilateral proptosis and right optic atrophy. He was lost to follow up until the age of five, when a chest radiograph done for bronchopneumonia at another hospital showed sclerotic ribs. He was also noted to have anaemia and hepatosplenomegaly. A diagnosis of osteopetrosis was made on clinical grounds, supported by radiographic findings. At this point, a trial of calcitriol (1,25 (OH)2D3 or 1,25 dihydroxycholecalciferol,) was commenced with no apparent clinical improvement.

Development was slightly delayed, likely related to the visual loss. At five, he could ride a tricycle and climb up and down stairs, one foot at a time. He spoke in short sentences, sang simple songs and dictated short stories. He was dry by day and night but needed help with buttons and shoes.

He had only been transfused once for symptomatic anaemia when he was admitted for pneumonia. During follow up, his haemoglobin ranged around 6 – 7 grams/dL and platelets around 60 – 90,000 / Ìlitre. Peripheral blood film examination revealed normochromic normocytic anaemia with leukoerythroblastosis, consistent with the underlying disease.

When seen at our unit, he had bilateral proptosis, marked frontal bossing and a functioning ventriculo-peritoneal shunt. His height and weight were within the 10th to 25th centile for age while the head circumference was 53cm, well beyond the 95th centile for age. His liver was 3cm and spleen 4cm palpable below the right and left subcostal margin respectively.

A pre transplant skeletal radiograph showed increased density of all bones (Figure 1). There were old fractures of the 4th, 5th, 6th, 8th ribs on the right side and distal third of the left ulna. The vertebrae and the bones in the hands and feet showed "bone in bone" appearance. Cardiac and renal functions were normal. Urine pH and blood gases excluded renal tubular acidosis. Cranial tomogram done earlier did not demonstrate any calcifications. Ophthalmologic assessment revealed total blindness in the right eye and only perception to light in the left eye. Play audiometry showed mild hearing loss in the right ear while the left was normal.

He received an allogeneic HLA (human leukocyte antigen) identical sibling bone marrow transplant with minor ABO mismatch. Conditioning was with busulphan 16 mg/kg over four days and cyclophosphamide 200 mg/kg over four days. The nucleated cell and CD34 cell doses were 9.64 X 10^8/kg and 6.48 X 10^6/kg respectively. Short courses of methotrexate and cyclosporin were given as graft versus host disease prophylaxis. Successful neutrophil engraftment occurred on day 12 post transplant. Post transplant complications were minor. Of note is the occurrence of asymptomatic hypercalcaemia, highest being 3.15 mmol/L occurring on day

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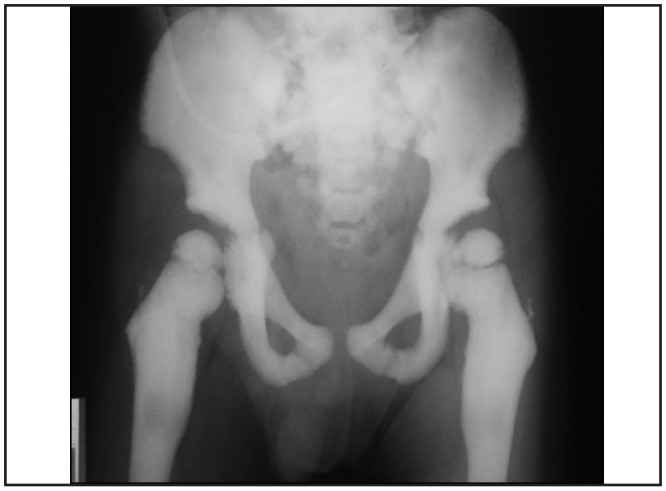

Fig. 1: Pre Transplant – The upper femur is sclerotic and abnormally shaped

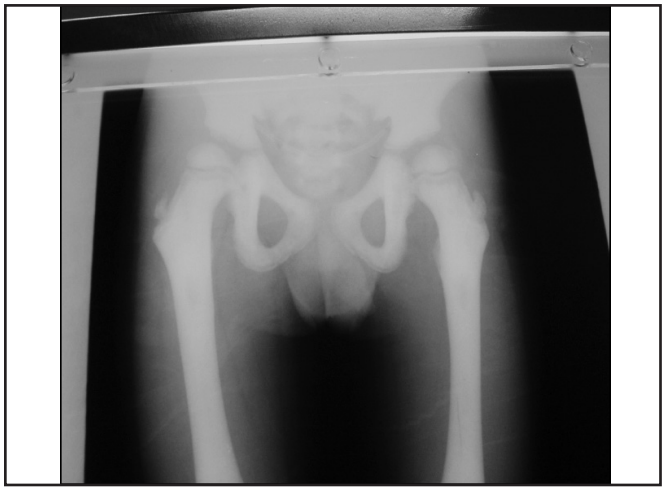

Fig. 2: One Year Post Transplant – The upper femur is still sclerotic, but shows some remodeling in the shape compared with pre transplant

29 of transplant. He was treated with vigorous hydration and loop diuretics and the calcium normalized by day 53. The liver and spleen size were 2cm and 1cm respectively by day 50 of transplant.

He sustained a pathological fracture of his left tibia and fibula after a trivial fall two months after transplant, and this was treated conservatively with immobilization. One year post transplant, his haematological parameters gradually improved. His haemoglobin level ranged from 9 – 10 g/dL with normal platelet counts. His liver was one cm below the right costal margin while the spleen was not palpable. Although the proptosis had resolved, there was no visual improvement. Skeletal radiographs showed some improvements in bone remodeling and density although the bones still remain abnormal in shape and density (Figure 2). At four years post transplant, his phenotypic features continued to improve.

DISCUSSION

Reports of successful transplantations for autosomal recessive infantile malignant osteopetrosis are widely published[3]. However, due to its rarity as well as limited availability of a matched sibling donor; very few cases of mild autosomal recessive osteopetrosis have been transplanted. Hongeng *et al* reported a successful transplant in a five year old Thai boy with osteopetrosis and similar phenotype to our patient[1]. Dini *et al* reported two children, aged five and six with similar features who had severe visual impairment pre transplant[2]. In both reports, remodeling of the skeletal abnormalities was observed after a year of transplant although the preexisting visual impairment was permanent.

Mild autosomal recessive osteopetrosis differs from the infantile malignant form because in the latter, the signs and symptoms appear shortly after birth. These infants have bulging fontanelles, extramedullary haematopoeisis with vision and neurologic impairment appearing within three months of life. At present, the only definitive cure for infantile malignant osteopetrosis is bone marrow transplantation.

Mild autosomal recessive osteopetrosis has a later onset, is slowly progressive and patients are only diagnosed once the extramedullary haematopoeisis and its complications become apparent. They are often diagnosed when there is macrocephaly, hydrocephalus or malocclusions. Being rare, diagnosis is often not made until visual loss due to optic atrophy become manifest. It is important to diagnose these patients early so that definitive treatment can be offered at an early age before irreversible damage occurs.

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