

Malignant Infantile Osteopetrosis in a Filipino Child

Mary Anne D. Chiong¹, Carmencita David-Padilla²,
Allan Robert Racho³, Ma. Assunta Hiquiana⁴

¹Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila;

²Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila;

³Department of Pediatrics, St. Lukes Medical Center; ⁴Department of Pediatrics, Dagupan Doctor's Villaflor Memorial Hospital

ABSTRACT

We present a female infant who presented with hematologic abnormalities, hepatosplenomegaly and eye problems and was initially considered to have a hematologic malignancy. Review of radiologic findings however, revealed a generalized increase in bone density, sclerosis of the skull and vertebra, and 'bone-in-bone' appearance. On the basis of the clinical history and the characteristic radiographic findings, she was diagnosed with malignant infantile osteopetrosis.

Key Words: autosomal recessive malignant osteopetrosis, "bone-in-bone" appearance, hepatosplenomegaly, bone marrow transplantation

Introduction

Albers-Shonberg first described osteopetrosis in 1904.¹ It results from a generalized accumulation of bone mass that is secondary to a defect in bone resorption. The defect prevents the normal development of marrow cavities, the normal tubulation of long bones and the enlargement of osseous foramina leading to osteosclerosis, hematologic abnormalities, extramedullary hematopoiesis and cranial nerve palsies.

Over 300 cases have been reported with an overall incidence of 1:100,000-500,000.² Among these, two principal types were distinguished. An autosomal dominant form was called the adult benign form because of the relatively few symptoms and the benign course which is compatible with a normal life span. At the other extreme is the clinically severe autosomal recessive form which has its onset in infancy and produces anemia, leukopenia, hepatomegaly, failure to thrive, cranial nerve symptoms and early death.¹

We report a case of a Filipino child with autosomal recessive malignant infantile osteopetrosis.

Clinical Report

G.P. was referred to a genetics clinic at 1 1/2 years old due to a finding of generalized osteosclerosis on chest X-ray. She was born full term to a 33 year old G3P2 (2002) mother after a pregnancy complicated by a urinary tract infection during the second trimester. She was delivered via caesarean section due to oligohydramnios with a birth length of 49 cm and a birth weight of 3.2 kg. She had good Apgar scores and the neonatal course was unremarkable.

She was apparently well until 2 months of age when an incidental finding of hepatosplenomegaly was noted during a bout of pneumonia. Complete blood count showed anemia, thrombocytopenia, leukocytosis with blast cells and promyelocytes and reticulocytosis. A diagnosis of congenital leukemia versus juvenile chronic myelogenous leukemia was considered. However, bone marrow aspiration biopsy showed anemia and normoblastemia. Hemoglobin electrophoresis revealed a high fetal hemoglobin. Presence of leukocyte alkaline phosphatase at 51% was noted on immunohistostaining which could pertain to a reaction to an infection. An impression of congenital hemolytic disease secondary to alpha thalassemia versus a congenital infection was then considered. Blood cultures, TORCH profile, ANA, Coomb's test, total bilirubin and cranial CT scan were all normal. The patient was then lost to follow up for almost a year.

She was again seen at 1 year 3 months old due to redness of the right eye and a notable amblyopia. CT scan of the orbit revealed subperiosteal abscess with resultant inward displacement of the medial rectus muscle. Hematologic abnormalities such as anemia, thrombocytopenia and leukocytosis were persistent. Repeat bone marrow biopsy, TORCH profile, hemoglobin electrophoresis and cranial CT scan all revealed normal results. However, on repeat chest X-ray, an increase in bone density with a thick dense skull and vertebra, and an appearance of a 'bone within bone' was seen. Thus, supported by the clinical history and the finding of generalized osteosclerosis on X-ray, a diagnosis of osteopetrosis was made (Figure 1).

She had global developmental delay. She sat at 1 year old and walked well at 1 year 10 months old. She started babbling at 1 year old, scribbled at 2 years old and had social smile at 6 months old.

Corresponding author: Mary Anne D. Chiong, MD
Institute of Human Genetics, National Institutes of Health,
University of the Philippines Manila
625 Pedro Gil Street, Ermita Manila 1000, Philippines
Telephone: +632 536 7002
E-mail: madchiong@post.upm.edu.ph

She was the youngest in a sibship of three born to a non-consanguineous couple. No other family member has a similar condition.

When examined, she was active, awake and cooperative. Her height, weight and head circumference were all below the 5th percentile for age. She had frontal bossing, cervical lymphadenopathy, hepatosplenomegaly and generalized pallor. Examinations of the lungs, heart and genitalia were unremarkable. Neurologic examination was likewise normal.

Bone marrow transplantation was discussed and planned with the family. However, human leukocyte antigen (HLA) typing done on her potential donor siblings did not match

with the patient. She is currently on supportive medical treatment which include blood transfusions, steroid therapy, aggressive treatment of infections and precautions for fractures. Regular ophthalmologic evaluation is likewise being done.

Discussion

Autosomal recessive malignant infantile osteopetrosis is a rare congenital disorder of heterogenous pathophysiology in which failure of osteoclastic bone resorption leads to increased bone mass. This further results to poor osseous growth and remodeling, compression symptoms of cranial nerves and failure of marrow cavities to develop.

Affected children usually present within the first years of life and frequently within the first 3 months. Parental concern regarding the child's vision is the most common presenting complaint. Failure to achieve normal visual milestones, roving eye movements and/or squint are often reported. This occurs as part of the cranial nerve entrapment neuropathies associated with overgrowth of cranial nerve foramina and the foramen magnum resulting to nerve compression – progressively affecting the optic, facial, oculomotor and auditory nerves and possible hydrocephalus. Likewise, hematologic abnormalities and hepatosplenomegaly are invariably present at an early age. Defective osseous tissue tends to replace bone marrow which causes bone marrow failure with resultant hepatosplenomegaly, hypersplenism and hemolysis.^{3,4}

Our patient presented with signs of bone marrow failure more than the eye problems when she was initially seen. Amblyopia is a nonspecific finding and may be caused by any condition that affects normal visual development or use of the eyes. Optic nerve compression may explain this finding.

Because hepatosplenomegaly and hematologic abnormalities are prominent early in the course of the disease, the correct clinical diagnosis is often mistaken for the more common childhood hematologic diseases such as leukemia and thalassemia. Frequently, it is the distinctive sclerotic bony changes seen on a serendipitously performed X-ray that alerts the clinician. If the radiological appearance is supportive and the child has features of anemia and compensatory erythropoietic hepatosplenomegaly and/or visual impairment, the diagnosis is highly likely.

Radiologic features usually are diagnostic. The bones may be uniformly sclerotic with alternating sclerotic and lucent bands noted in iliac wings and near ends of long bones. The bones may appear clublike or show an appearance of a bone within bone (endobone). The entire skull is thickened and dense, the sinuses are small and underpneumatized, the vertebrae may be extremely radiodense and show alternating bands known as the “rugger-jersey” sign. Radiographs may also show evidence of fractures or signs of osteomyelitis.⁵

The diagnosis can further be confirmed by bone biopsy, although it is not usually required for diagnostic purposes unless the initial diagnosis is unclear or the child's clinical



A



B

Figure 1. Generalized osteosclerosis or increase in bone density was noted on babygram. A.) antero-posterior view B.) lateral view.

progress varies significantly from the established phenotype. A molecular diagnosis is also possible.

So far, mutations involving three genes have been recognized to cause human osteopetrosis. The carbonic anhydrase type II gene has been found to account for a small portion of a particular form of intermediate osteopetrosis characterized by renal tubular acidosis, cerebral calcifications and mental retardation. None of these additional concerns were apparent in our patient. The other gene implicated in osteopetrosis code for proteins that are responsible for primary charged ions through the cell membrane. Mutations in the gene *ATP6i* (*TCIRG1*) coding for an osteoclast specific $\alpha 3$ subunit V-ATpase vacuolar pump have been found in approximately 50% of affected children with malignant infantile osteopetrosis. This protein is responsible for creating the highly acidic microenvironment underneath the osteoclasts resorbing lacuna required for the solubilization of the hydroxyapatite crystal of bone. Recently, mutations in the *CLC7* (*CLCN 7*) chloride channel have been found to also cause infantile recessive osteopetrosis. This gene can likewise cause a more mildly disease in an autosomal dominant fashion.^{6,7} Likewise, a subset of osteoclast-poor autosomal recessive osteopetrosis has been recognized as due to a defect in *TNFSF11* (also called *RANKL* or *TRANCE*, coding for the *RANKL* protein), a master gene driving osteoclast differentiation which also plays a role in the immune system, which raises the possibility that defects in this pathway might cause osteopetrosis with immunodeficiency.⁸

Initial management of malignant osteopetrosis should focus on establishing the severity and extent of the disease. The majority of patients, because of failure of bone marrow development, are anemic and many become transfusion dependent. The generation of superoxide by peripheral blood leukocytes is defective in these patients and this along with anemia, poor nutrition, recurrent hospital admissions, and frequent ear, nose and throat complications result in a greatly increased susceptibility to infections. Visual impairment is usually progressive and unfortunately, an improvement in visual status is unlikely despite treatment. Optic nerve decompression is a hazardous procedure and reports suggest success only in mildly affected older children. Hearing is less commonly affected than vision with approximately a third of patients having some degree of hearing loss. Other cranial nerves may also be involved and may manifest with paucity of facial expression in some or difficulties with feeding and swallowing. Developmental delay if present is usually consistent with the extent of physical and visual impairments and the severity of the chronic illness the child has suffered. Failure to thrive is seen in many osteopetrotic children and is a result of the chronic anemia, feeding problems caused by bulbar nerve involvement, nasal congestion and subsequent infections. It would also seem prudent to perform a cardiac assessment in all patients as there have been reports of pulmonary hypertension, pulmonary valve stenosis and pulmonary regurgitation. Orthopedic problems include fractures and

abnormalities in head shape such as macrocephaly, frontal bossing and craniosynostosis. Also, children frequently have dental problems such as failure of tooth eruption, recurrent caries and abnormal dentinogenesis. Disturbance of calcium homeostasis has been well described in malignant osteopetrosis. Normal osteoblast function unbalanced by compensatory osteoclast function pushes some osteopenic children into hypocalcemia. Malignant infantile osteopetrosis presenting with neonatal hypocalcemia has been reported.⁹⁻¹¹

Medical treatment of malignant osteopetrosis include: (1) Calcitriol - appears to help stimulate dominant osteoclasts and thus stimulate bone resorption. Calcitriol in large doses along with restricted calcium intake occasionally improves osteopetrosis dramatically; (2) Corticosteroids have been used to stimulate bone resorption and treat anemia. It has been associated with a significant reduction of skeletal density, improvement of laboratory findings and prevention of severe complications especially if treatment commences early; (3) Treatment with gamma interferon has been shown to produce long term benefit. Increased bone resorption and hematopoiesis and improved leukocyte function were seen in a small number of patients studied.^{2,12,13}

Bone marrow transplantation is the only treatment that has been proven to significantly alter the course of the disease. While successful recipients may continue to have minor orthopedic and dental problems and their vision rarely significantly improves, their hematopoietic potential is restored and the long term prognosis is favorable. The success of engraftment and the outcome are very dependent however, on the availability of HLA match. The five year disease free survival in patients with an HLA identical sibling donor was reported at 79%. Recipients of non-genotypically identical grafts had significantly worse results with only a 13% five year disease free survival in those receiving marrow from an HLA haplotype mismatched related donor.¹⁴

In some patients because of the severity of the disease, aggressive treatment is not warranted and palliative care is indicated. Adequate pain relief is essential and the assistance of support services should be sought.

Genetic counseling was done on the family and is also an important aspect of management. The process aimed to discuss with the family the clinical condition, management options and recurrence risk within the family. Since malignant infantile osteopetrosis is a genetic disorder with an autosomal recessive pattern of inheritance, there is a 25% risk of having another affected child with each subsequent pregnancy.

Since the gene for malignant osteopetrosis has already been mapped, prenatal diagnosis can be done as early as 10-16 weeks age of gestation by mutation analysis of the fetal DNA. Affected fetuses may undergo bone marrow transplantation early after birth.¹⁵ A recent report on the rescue of malignant osteopetrosis in mouse models by hematopoietic stem cell transplantation in utero holds promise for other possible treatments for this condition other than bone marrow transplantation in the future.¹⁶

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