

Case Report

Autosomal recessive infantile osteopetrosis: case report with radiological review

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ABSTRACT

Autosomal recessive type of osteopetrosis or infantile malignant osteopetrosis is a rare congenital disorder of bone resorption characterised by generalised skeletal densification. Incidence is estimated around 1/2,00,000 live births. Osteopetrosis has been reported in most ethnic groups, although, as the disease is very rare, it is more frequently seen in ethnic groups where consanguinity is common. Bone marrow failure, fractures and visual impairment are the classical features of the disease, which begins in early infancy or in foetal life. It results from the failure of osteoclasts to resorb immature bone. This leads to abnormal bone marrow cavity formation and to the clinical signs and symptoms of bone marrow failure. It is accompanied by hepatosplenomegaly due to compensatory extramedullary hematopoiesis. Because of rarity of this type of osteopetrosis, we would like to report this case of a female child who presented with cough, fever and anemia at the age of 3 years.

Keywords: Autosomal recessive osteopetrosis, Fatal, Failure to thrive, Hepatosplenomegaly, Malignant infantile osteopetrosis, Osteopetrosis

INTRODUCTION

Autosomal recessive type of osteopetrosis or infantile malignant osteopetrosis is a rare congenital disorder of bone resorption characterised by generalised skeletal densification.¹ It is divided into three types: autosomal recessive malignant osteopetrosis, intermediate osteopetrosis and autosomal dominant osteopetrosis. The later usually presents in late childhood or adult life with mild symptoms.² Incidence is estimated at 1/2,00,000 live births and in most cases found to be fatal.¹ Osteopetrosis has been reported in most ethnic groups, although, as the disease is very rare, it is more frequently seen in ethnic groups where consanguinity is common. Bone marrow failure, fractures and visual impairment are the classical features of the disease, which begins in early infancy or in foetal life. It results from the failure of osteoclasts to resorb immature bone.¹ This leads to abnormal bone marrow cavity formation and to the

clinical signs and symptoms of bone marrow failure. It is accompanied by hepatosplenomegaly due to compensatory extramedullary hematopoiesis, a characteristic macrocephaly with frontal bossing, exophthalmus, bone fractures, and failure to thrive.^{1,3} Because of rarity of this type of osteopetrosis, we would like to report this case of a female child who presented with cough, fever and anemia at the age of 3 years.

CASE REPORT

A 3-year-old female child born to secondary consanguineous marriage to a Hindu family presented with delayed milestones of development, cough and fever from the past 15 days and hyperventilation. On general body examination, her vitals were; febrile (101oF), pulse rate of 87/min and respiratory rate of 62/min. Laboratory investigations revealed: hemoglobin of 6g/dl, with total leukocyte count of 5000/cm³ with differential count of P-

30%, L-60%, E-4% and platelet count was 46,000/mm³. A peripheral smear showed normocytic with hyperchromic cells. Serum calcium ion and serum proteins were 9.1 and 6.4 respectively. Serum ALP levels were 4200 IU/L. An abdominal ultrasound revealed mild hepatomegaly with significantly enlarged spleen measuring 11.4cm. Also, a complete skeletal survey was done which showed thick, dense and sclerotic bones with marked cortical thickening and a bone within a bone appearance Figure 1.

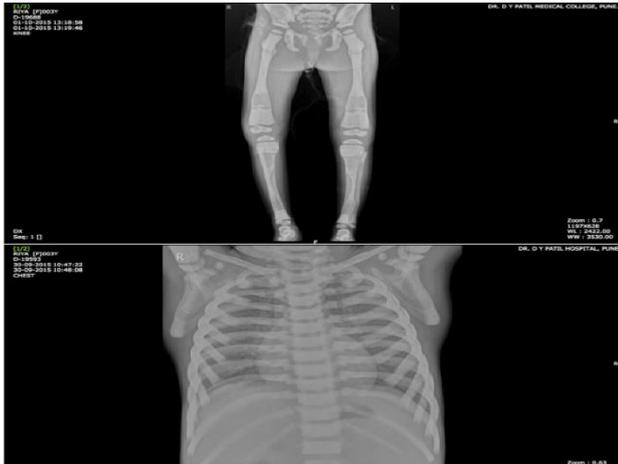


Figure 1: Chest x-ray and skeletal survey show dense bones with bone within a bone deformity

CT scan of brain revealed mild diffused thickening of skull vault, skull base and both the petrous bones with bilateral chronic subdural hematoma (R>L) Figure 2.

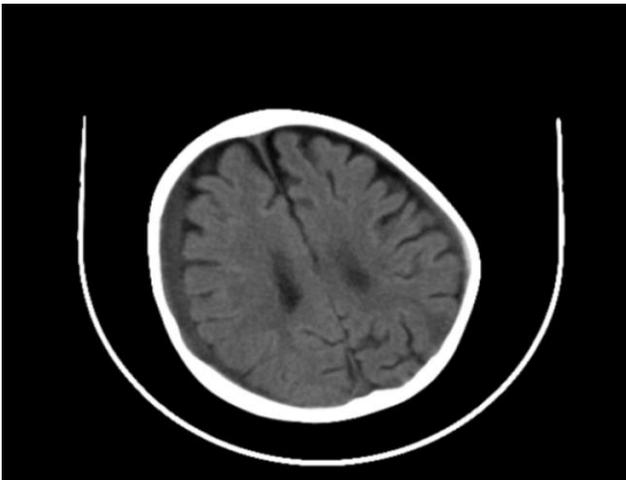


Figure 2: NECT head showing diffuse skull vault thickening with SDH

She was diagnosed as a case of osteopetrosis with anemia. She was treated with antibiotics, blood transfusion, calcium, and vitamin D.

The findings were confirmed on histopathological examination which revealed dense and irregular bone

trabeculae and woven bone with cartilaginous elements Figure 1. Scant marrow elements seen with osteoclasts and blood clots suggestive of osteopetrosis.

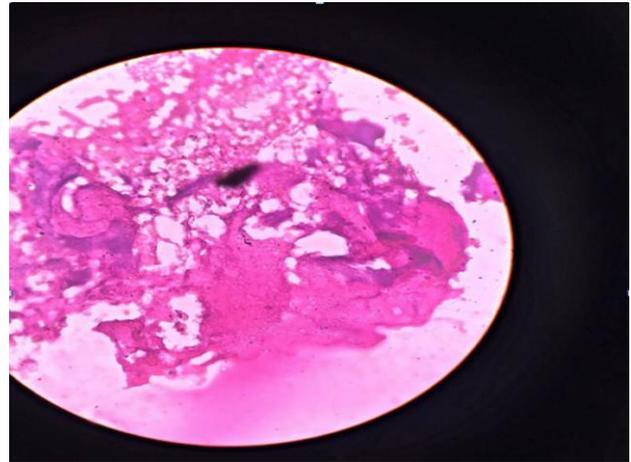


Fig. 3: Histo-pathological confirmation

DISCUSSION

Osteopetrosis is clinically a highly heterogeneous group of conditions that share the hallmark of increased bone density on radiographs due to abnormalities in osteoclast differentiation or function. There are four subtypes of osteopetrosis (a) malignant or infantile osteopetrosis, (b) Benign or adult osteopetrosis, (c) intermediate osteopetrosis, and (d) carbon anhydrase type II (CAII) deficiency.⁵

Malignant infantile osteopetrosis is the autosomal recessively inherited form of this disease that generally begins in utero, it presents at birth or within the first year of life and is associated with increased severity compared to the autosomal dominant form.⁶⁻⁹ Our patient had the symptoms since the age of four months. It has an incidence of 1 in 250,000 births, with a particularly high incidence reported in Costa Rica (3.4:100000).^{10,11}

The increase in bone mass leads to phenotypic features such as macrocephaly and frontal bossing. Tooth eruption defects are also common. The longitudinal growth of bones is impaired with a short stature and predisposition to fractures and osteomyelitis.

Our reported case showed all these characters except bony fractures and osteomyelitis.

The abnormal expansion of bone interferes with medullary haematopoiesis, resulting in life-threatening anemia, thrombocytopenia, increased susceptibility to infections, and secondary expansion of extramedullary haematopoiesis sites such as the liver and spleen.

The most commonly observed neurological manifestations of osteopetrosis are secondary to obstruction of the foramina through which the cranial

nerves, spinal cord and major blood vessels transverse the skull, resulting in blindness, hearing loss, facial palsy and hydrocephalus.^{12,13} Distinct from these compressive phenomena, some patients with autosomal recessive osteopetrosis variants (neuropathic ARO) display signs of primary neurodegeneration including primary seizures in the setting of normal calcium levels, developmental delay, hypotonia, retinal atrophy and sensorineural deafness.¹² Reported brain MRI findings include significantly delayed myelination and diffuse progressive cortical and subcortical atrophy.^{14,15} Children with malignant infantile osteopetrosis are at risk of developing hypocalcaemia, with attendant tetanic seizures and secondary hyperparathyroidism.^{17,8} Rickets has been also observed as a complication of malignant infantile.¹⁶ The above patient showed hypocalcaemia.

Characteristic radiographic findings in osteopetrosis include a marked increase in bone density with defective metaphyseal remodeling, and a “bone within a bone” appearance.¹⁰ Alternating sclerotic and lucent bands can give the vertebrae a ‘sandwich’ appearance. Computerized tomography scan can be used for diagnosis and to determine the effect of the treatment. It is also used to assess auditory and optic canal.¹⁷ The skeletal survey and CT scan of our patient was specific for radiologic findings of osteopetrosis.

Primary sclerosing conditions of bone caused by osteoclast dysfunction need to be distinguished from the large number of conditions in which bone sclerosis can occur as a secondary phenomenon. Some alternative diagnosis to consider include pseudohypoparathyroidism, pyknodysostosis, and hypoparathyroidism, chemical poisoning (e.g., lead, fluoride, and beryllium), malignancies (myeloproliferative diseases and leukemia).¹⁰

Based on clinical history, radiographic findings, our case was diagnosed as the infantile or malignant type, with autosomal recessive inheritance. Management of patients with osteopetrosis requires a comprehensive approach to characteristic clinical problems including hematological and metabolic abnormalities, recurrent infections, bone complications and neurological sequel.¹⁸

At present, Hematopoietic stem cell transplantation (HSCT) offers the only chance of cure for MIOP; it should be performed early before the irreversible neurologic impairment. HSCT replaces abnormal osteoclasts with normal cells, given the high associated morbidity and mortality it's reserved only for the most severe cases of osteopetrosis.⁶ Successful results have been achieved in patients transplanted with allogenic donor stem cells.¹⁹ Furthermore, non-allogenic HSCT may be an option to treat MIOP, it showed high survival rate and restoration of hematopoiesis in haploid transplant patients.²⁰

In our case, HSCT was not performed given its high cost; therefore, treatment was largely supportive and was aimed at providing surveillance and symptomatic management of complications such as antibiotic therapy, calcium and vitamin D supplementation and nutritional measures.

Genetic counseling is important. Antenatal diagnosis in families with malignant infantile osteopetrosis may be possible using radiographs thus allowing haematopoietic stem cell transplantation (HSCT) before the age of 3 months with the aim of improving neurological outcomes.²¹ However, the difficulty in obtaining conclusive results by radiographic evaluation of fetus in utero makes prenatal molecular diagnosis highly desirable.²²

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