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Case Report

Osteopetrosis, a Rare Cause for Bone Marrow Failure

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Abstract

Osteopetrosis is a rare genetic disorder characterized by functional defect of osteoclasts resulting in failure of bone resorption, increased bone sclerosis and bone marrow failure. Patients present with stunted growth, skeletal changes, hepatosplenomegaly, features of pancytopenia and characteristic radiological changes. Osteopetrosis has variable inheritance pattern. Diagnosis is made on the basis of history with clinical findings, characteristic radiological and bone marrow findings. We present a case of a 10 years old female child with stunted growth, frontal bossing, teeth abnormalities and characteristic radiological and bone marrow findings.

Key words: Osteopetrosis; marble bone disease; bone marrow failure

Introduction

Osteopetrosis (OP) refers to a group of rare genetic disorder characterized by increased bone density on radiographs**.** The condition varies in presentation and severity ranging from neonatal onset with life threatening complications such as bone marrow failure to an incidental finding. The term Osteopetrosis is derived from Greek, osteo meaning bone and petros meaning stone. OP is also known as marble bone disease and Albers-Scharberg disease, after the name of German radiologist who gave first description of disease.[1]

The primary underlying defect in all types of osteopetrosis is failure of the osteoclasts to reabsorb bone resulting in thickened sclerotic bones, which have poor mechanical properties. Increased bone fragility results from a failure of the collagen fibers to connect osteons properly and from defective remodelling of woven bone to compact bone. [2] This leads to generalized sclerosis of bone with an increased skeletal mass due to abnormally dense bone. Mutations in at least 10 genes have been identified. Generalized osteosclerosis is apparent radiographically, often with a "bone within a bone" appearance.[3] In severely affected patients, the medullary cavity is filled with endochondral new bone, with little space remaining for hematopoietic cells. This abnormality contributes to the brittleness of bone in osteopetrosis. The abnormal skeletal radiographs and microscopic appearance of bone can be reversed by hematopoietic stem-cell transplantation.[4] Overall, the incidence of the disease is estimated at 1 in 100,000-500,000. However, the actual incidence is unknown because no large epidemiological studies have been conducted so far.[5]

The condition may be inherited as Autosomal recessive, autosomal dominant or X- linked trait. Autosomal OP also known as malignant OP is the most severe of all genetic variants and manifests classically in first few months of life. Characteristic features include short stature, macrocephaly, frontal bossing, tooth eruption defects and dental caries. Increased bone density can produce weakness of bones resulting in predisposition to fractures and osteomyelitis. The expanding bone can narrow nerve foramens resulting in signs of nerve compression such as blindness, deafness and facial palsy. These children are also at a risk of developing hypocalcaemia which may result in tetanic seizures and secondary hyper parathyroidism. Hematological findings are due to obliteration of bone marrow cavity by bone, causing myelophthisic anemia, which manifests as a leukoerythroblastic picture on peripheral blood smear. The most severe complication of OP is bone marrow suppression resulting in life threatening pancytopenia. Hepatosplenomegaly is due to extra medullary hematopoiesis. Thrombocytopenia, leukopenia and anemia may also occur due to hypersplenism. Many patients of malignant recessive osteopetrosis become transfusion dependant. [6]

Variants of AROP may have neurological and renal manifestations. Autosomal dominant OP typically have onset in late childhood and adolescence. Patients classically have the radiographic signs of sandwich vertebrae, fractures, scoliosis, osteoarthritis and osteomyelitis particularly affecting mandible in association with dental caries and abscesses. X linked OP is rare and is characterized by immunodeficiency with ectodermal changes.

The diagnosis of OP depends upon clinical, radiographic and bone marrow findings. The classic radiological features of osteopetrosis include diffuse sclerosis, affecting the skull, spine, pelvis and appendicular bones, bone modelling

defects, "Bone-in-bone" appearance particularly in the vertebrae and phalanges and focal sclerosis of the skull base, pelvis and vertebral end plates giving "sandwich" appearance. Bone marrow typically shows increased bone density with reduction or absence of medullary cavity and markedly decreased hematopoietic tissue. Once the diagnosis of a primary osteopetrosis is made, it is important to distinguish between different subtypes as they have different responses to treatment, prognosis and recurrence risks.

We present a case of a 10 years old female child who presented with anemia and thrombocytopenia and on radiological evaluation and bone marrow examination was diagnosed as a case of Osteopetrosis.

Figure 1: Patient of Osteopetrosis showing:

a. frontal bossing; b. Dental abnormalities

Case Report

A ten years old female child presented in OPD at social security hospital Islamabad, with history of generalized bodyache and pain in legs for the past 4-5 years. She was the product of consanguineous marriage. There was no history of transfusion in the past. She was a short statured child and also had frontal bossing. On examination of oral cavity, dental caries was observed in many teeth. She was mildly pale. There was no lymphadenopathy or hepatosplenomegaly. Her blood complete picture showed Hb 8.4 gms/dl, TLC 8.4 x 10^6/l; platelet count 110 x 10^9/l, MCV 77.3 fl, MCH 23.1 pg and MCHC 29.9 g/dl. Her biochemical profile showed serum Calcium: 8.6 mg/dl, PO_4: 4.7 mg/dl and Alkaline Phosphatase: 559 IU/l. She was sent for radiological evaluation. X-rays of spine, skull, long bone and hands were taken. Radiological evaluation showed increased bone density with increased thickening of bony cortices with diagnosis of osteopetrosis. She was referred to us for bone marrow biopsy. Bony texture was stony hard. Bone marrow aspirate was hypocellular with hypoplastic erythroid, myeloid and megakaryocytic series cells. No abnormal cells were found. Histological section of trephine biopsy showed hypocellular bone marrow fragments with decrease in erythroid, myeloid and megakaryocytic series cells. Bone marrow fragments were replaced by new bone formation (at different stages of ossification). Final diagnosis was osteopetrosis.

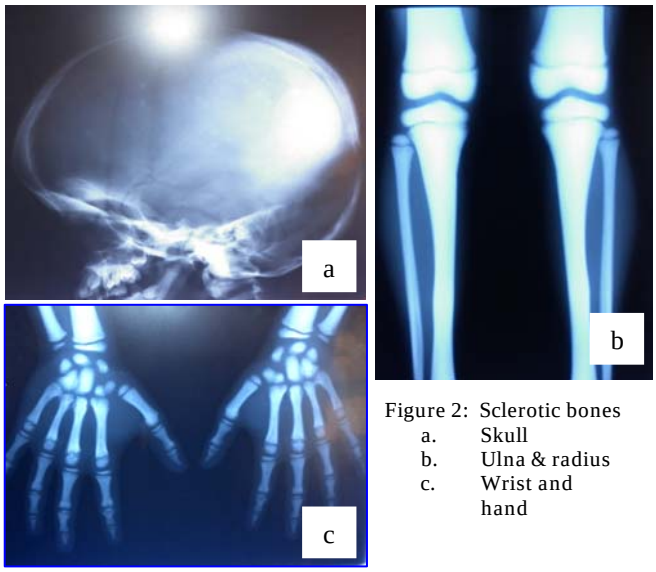

Figure 2: Sclerotic bones
a. Skull
b. Ulna & radius
c. Wrist and hand

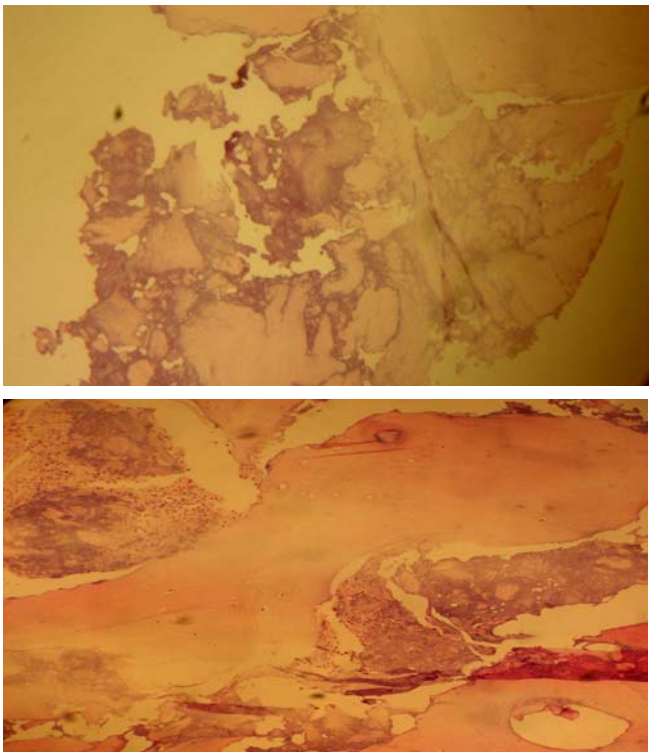

Figure 3: Trephine biopsy shows widening of bone trabeculae, and evidence of bone formation in the bone marrow fragments. Bone has encroached into the bone marrow replacing normal marrow cells

Discussion

Osteopetrosis, also called marble bone disease, was first described by Heinrich Albers-Schonberg in 1904 which is a heterogeneous group of heritable conditions in which there is a defect in bone resorption by osteoclasts. Hallmark of disease is increased bone density on radiographs resulting from failure of osteoclast development or function, decreased bone resorption and thickened sclerotic bone.

Osteopetrosis varies in severity depending on mode of inheritance and time of presentation. Based on the age, clinical, hematological and radiological features three distinct forms namely the infantile or AR, adult (AD) form, and intermediate OP.[7] The AR variety is also known as congenital or infantile or malignant OP occurs in infancy and has a rapid downhill course due to severe bone marrow failure.[8] Features of infantile osteopetrosis include dense and deformed bones, growth failure, anemia, hypoplastic dentition, chronic infection, splenomegaly and neurological impairment.

Adult type of OP has an autosomal dominant inheritance pattern and approximately one half of the patients are asymptomatic, and the diagnosis is made incidentally or is based on family history. Autosomal recessive osteopetrosis may have less severe manifestations and is known as "intermediate" autosomal recessive osteopetrosis (in which bony changes are there but bone marrow failure is not prominent and it has poor prognosis).[9] Recently a case has been described with abnormal bone modelling, increased bone density and histological features of osteopetrosis in a 12-year-old boy with extended bisphosphonate therapy. This case suggests that agents that inhibit the recruitment and function of osteoclasts, when given over an extended period of time, may cause a clinical picture comparable to heritable osteopetrosis and has been designated as acquired osteopetrosis.[10]

We present a case of autosomal recessive osteopetrosis which is probably of intermediate severity as she is 10 years old girl and has presented with bony changes and anemia but there is no history of transfusion in past. Her trephine showed sclerotic changes but there was still some residual marrow seen on bone marrow trephine. Her two siblings however died at the age of 3 and 3.5 years with same disease probably having severe form of malignant osteopetrosis. Osteopetrosis is a rare cause of anemia both in infantile and adult varieties, [11] due to replacement of hemopoietic tissue by bone marrow sclerosis. In a study done in India on clinical and laboratory features of 6 patients of infantile osteopetrosis in 5 years duration, increasing pallor and listlessness were the most common initial symptom. Other features included abdominal distension, fever, frontal bossing, nasal block, anemia and thrombocytopenia. [12] The risk of developing hematological impairment in the first year of life is about 75% and its onset within 3 months of life is indicative of a poor outcome.[13]

Infantile osteopetrosis requires treatment due to the adverse outcome associated with the disease. Calcitriol may help by stimulating dormant osteoclasts and, thus, stimulating bone resorption. However it only produces a modest clinical improvement, which is not sustained after discontinuation of therapy.[14] Erythropoietin can be used to correct anemia. Children with infantile osteopetrosis have disease-related complications that affect nutritional status. Good nutritional support can provide nutrients needed for improved growth and response to treatment in these patients. Recently, use of interferon gamma has been found to decrease the rate of infection and transfusion requirements after 24 months of therapy. The natural course of the disease results in survival of about 30% of patients at six years of age. Some may live till 2nd or 3rd decade but the quality of life is mostly poor. Bone marrow transplant is the only treatment that can be offered to cure the disease and has remarkably shown improvement in some cases of osteopetrosis. Recipients of HLA identical BMT have been reported to have 5 year survival of 79%.[15] It can cure both bone marrow failure and metabolic abnormalities. However in adult OP which has relatively normal bone marrow function no specific medical treatment exists.

Though rare, AR osteopetrosis should be considered in the differential diagnosis of an infant or young child presenting with anemia with or without hepatosplenomegaly. An accurate diagnosis is essential in view of availability *of* curative treatment and for genetic counseling.

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