Malignant Infantile Osteopetrosis with Bone Marrow Involvement

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ABSTRACT

Osteopetrosis (Marble bone disease) is a very rare congenital genetic disease of skeleton, resulting from defective bone resorption, due to functionally defective osteoclast, leading to accumulation of excessive bone mass. Malignant infantile osteopetrosis (MIO) is one of the varieties of osteopetrosis, which is fatal and is diagnosed in early infancy. Malignant infantile osteopetrosis is present with abnormal bone remodeling, hematological abnormities, features of extramedullary hematopoiesis. Radiology is the key of diagnosis. In this case, we present a 5-month-old male infant diagnosed as malignant infantile osteopetrosis, who presented with bronchopneumonia, anemia, thrombocytopenia, hepatosplenomegaly, failure to thrive (FTT).

KEY WORDS

Fatal, Genetic, Malignant infantile osteopetrosis

INTRODUCTION

Osteopetrosis is a rare genetic disease of bone resorption that occurs due to abnormal osteoclast activity.[1] It is also known as marble bone disease which was first described by Albers-Schönberg in 1904.[2] Osteopetrosis includes a group of metabolic bone diseases, which affects bone growth and remodeling resulting in generalized osteosclerosis, chance of pathologic fractures, pancytopenia and hepatosplenomegaly in severe cases.[3] Clinically, it is of three types: Infantile malignant autosomal recessive osteopetrosis or osteopetrosis congenita, intermediate osteopetrosis and autosomal dominant osteopetrosis or osteopetrosis tarda.[4-6] Incidence of autosomal dominant osteopetrosis is five in one lac live births and malignant infantile osteopetrosis (MIO) is one in 3 lac live births.[7,8] Among all the types, MIO affects the infant and is typically fatal during infancy or early childhood, if untreated.[1]

CASE REPORT

A 5-month old male infant (fig. 1), 2nd issue of consanguineous parents presented with the complaints of fever, cough and noisy breathing for 10 days in department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh on March, 2019. His birth history was uneventful and he was developmentally age appropriate. He was on exclusive breast feeding. There was no family history of short stature. He had a prior history of hospitalization for pneumonia at another centre two weeks before his current admission. On examination, he was mildly pale, anicteric and had prominent costochondral junction. Abdomen was distended with organomegaly (hepatomegaly: 7 cm and splenomegaly: 12 cm) and pulmonary auscultation revealed bilateral crepitations and ronchi. There were no features of neurological deficit which possibly excludes

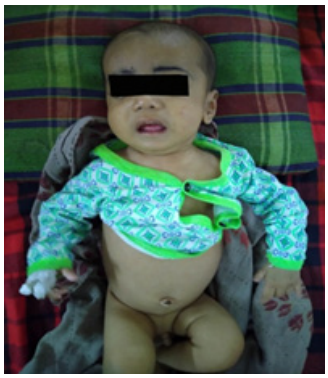

Figure 1. **Our case of malignant infantile osteopetrosis**

lipid storage disease clinically. Moreover, he had no other features suggestive of rickets. Weight for age and weight for length measurements were less than 3rd percentile. His investigations revealed hemoglobin- 10 g/dl and thrombocytopenia (Platelets: 50,000/cmm). Peripheral smear findings revealed normocytic normochromic anemia. For rickets-serum calcium (9.5 mg/dl), serum phosphorus (3.4 mg/dl), serum alkaline phosphatase (668 IU/L) were done. Ophthalmic examination showed normal findings which again excludes lipid storage disease. Plain radiograph of chest revealed increased bone density and pulmonary infiltration, plain X-ray of knee joints showed increase in bone density with obliteration of medullary cavity giving bone within bone appearance (fig. 2). Bone marrow study revealed numerous osteoclasts (fig. 3) compatible with osteopetrosis. There were no lipid laden macrophages or Gaucher cells in bone marrow study which excludes lipid storage disease. Moreover, normal levels of serum calcium and serum phosphorus along with absence of other typical findings (cupping, fraying and widening) of distal end of long bones in plain X-ray excludes Rickets. Finally, we diagnosed this case as malignant infantile osteopetrosis. Supportive treatment was given as broad spectrum antibiotics to counteract infection (pneumonia), along with calcitriol. Bone marrow transplantation was advised for the patient, but parents could not afford. We advised for routine follow up of patient.

DISCUSSION

MIO usually presents in early infancy and has a fatal outcome, if left untreated.[7] Our patient is diagnosed at five months of age.

MIO presents with features of bone marrow failure (like anaemia, bleeding manifestations and infections), hepatosplenomegaly, frontal bossing, characteristic macrocephaly, bone fractures, hypertelorism, exophthalmos, flattened nose, mandibular prognathism, cranial nerves palsy, dental problems, osteomyelitis of mandible, tetany, psychomotor delay and FTT. Bone marrow is replaced by the abnormal bone formation and fibrous tissue resulting decrease in hematopoietic

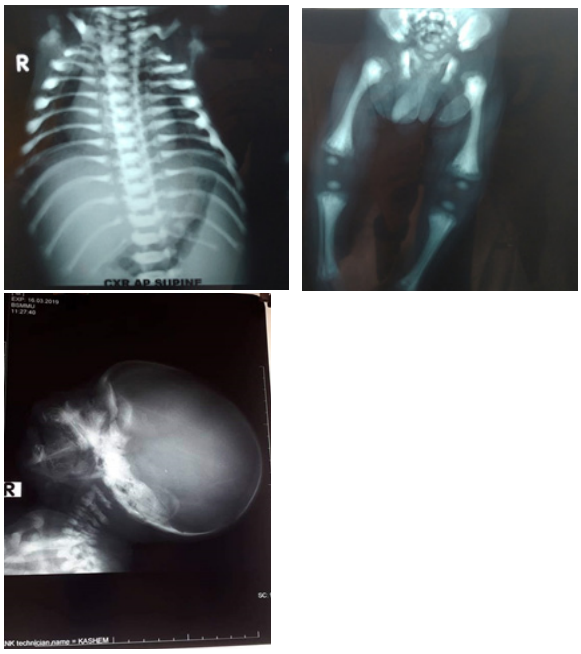

Figure 2. **X-ray with markedly increased bony density**

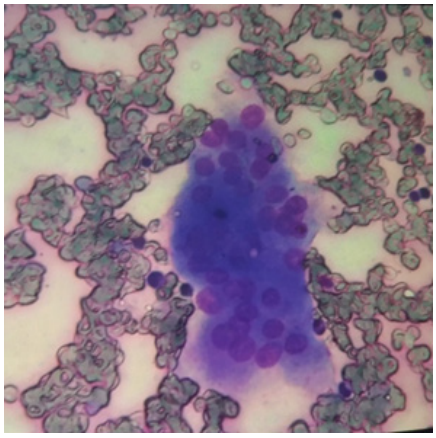

Figure 3. **BM study with numerous osteoclasts**

activity. Hepatosplenomegaly is due to extramedullary hematopoiesis.[8-12] Our patient presented with mild anaemia, prominent costochondral junction, hepato-splenomegaly and failure to thrive.

Cranial nerve palsy occurs due to gradual occlusion of the skull foramina as a result of abnormal expansion of hyperostotic bone. Optic atrophy is found in many cases.[10,13] No features of cranial nerve palsy were found in our patient.

In MIO, there is increased risk of infection due to bone marrow failure and presence of immunodeficiency.[8] Our patient presented with features of infection (fever, pneumonia).

Radiographs play a crucial role in the diagnosis of MIO. Radiographic features include increase in bone density with diffuse sclerosis. Bone modelling defects at the

metaphyses of long bones, such as funnel-like appearance and characteristic lucent bands may be present. Long bones show decreased marrow spaces with cortical thickening. The presence of "bone within bone" appearance is usually seen due to the dense shadow of the abnormal new bone within the outline of the normal bone, particularly in the vertebrae and phalanges. Focal sclerosis of vertebral end plates gives appearance of "sandwich" vertebrae and "rugger-jersey" spine may also be present.[14-16]

Our patient's X-ray of knee joints showed increase in bone density with obliteration of medullary cavity giving bone within bone appearance. Chest X-ray and X-ray skull revealed increased bone density.

In MIO, the abnormal bone formation and expansion interferes with medullary hematopoiesis. As radiographs are diagnostic, bone biopsy is not essential for diagnosis. Bone marrow trephine biopsy may be done to exclude differential diagnosis which shows narrowing of bone marrow spaces with marked hypocellularity, decrease in erythropoiesis, granulopoiesis and megakaryocytes. Abnormal bone formation with thickened multiple disorganized bony trabeculae with areas of patchy reticulin fibrosis and several interrupted pieces of ossified cartilage also found on Trephine biopsy. Patients with crowded bone marrow are more likely to have poor response to stem cell transplantation.[17-19] In our case, we went for bone marrow study which revealed numerous osteoclasts compatible with osteopetrosis.

Serum Ca++, phosphorus and alkaline phosphatase levels are usually in normal limits but S. Ca++ may be low, causing tetany. Due to large number of defective osteoclasts, acid phosphatase and Creatinine kinase isoform BB (CK-BB) level may increase.[20] In our patient, serum calcium and serum phosphorus were normal but serum alkaline phosphatase was high.

Current medical treatment includes corticosteroids, restriction of calcium, calcitriol, parathormone, erythropoietin and interferon gamma (IFNγ), but success rate is minimal.[20-22] Calcitriol increases bone resorption by stimulating dormant osteoclasts.[1] Our case was treated with calcitriol.

Definite treatment for MIO is stem cell transplantation with a variable success rate.[22,23] Parents of our patient could not afford for stem cell transplantation.

Around 75% of the patients with MIO die before six months of age. Death occurs due to recurrent infections like pneumonia or osteomyelitis with septicemia.[20,24,25] Our patient had two episodes of pneumonia.

Malignant infantile osteopetrosis (MIO) is a rare disease which should be considered in the infant with prominent costochondral junction, cytopenias and hepatosplenomegaly. Complete radiological investigations should be done to confirm the diagnosis including bone marrow study for numerous osteoclasts. Stem cell transplantation is the definite treatment.

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