Malignant Infantile Osteopetrosis

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ABSTRACT

Background: Malignant infantile osteopetrosis (MIOP) is an autosomal recessive disorder which is characterized by densely sclerotic bone due to defective function of osteoclasts. Overgrowth of bone results in nerve compression and reduction of marrow spaces. It may be complicated by rickets. The main genetic causes are the mutations in the TCIRG1 and CLCN7 genes. Stem cell transplantation offers the only hope for cure. Early diagnosis is of prime importance. **Case Presentation:** We report a four month old female infant, who was diagnosed to have MIOP while being evaluated for raised total count, thrombocytopenia, hepatosplenomegaly and optic atrophy. An infantogram helped us clinch the diagnosis as she had most of the radiological signs that have been described. She was also found to have co-existent rickets. Mutation analysis and hematopoietic stem cell transplantation were deferred by her parents due to financial constraints. **Conclusion:** MIOP should be kept in mind when the patient presents with hematological abnormalities such as anemia, thrombocytopenia and leukemoid reaction along with hepatosplenomegaly and optic atrophy. Our case is worthy of mention, because a high index of suspicion and meticulous interpretation of the infantogram helped us arrive at the diagnosis.

Key words: Hematological abnormalities; infantogram; malignant infantile osteopetrosis

Introduction

Malignant infantile osteopetrosis (MIOP) is an autosomal recessive disorder, which presents early in life with extreme sclerosis of the skeleton. It is characterized by reduced activity of osteoclasts, resulting in generalized osteosclerosis.[1] Abnormal osteoclast activity coupled with normal bone formation by osteoblasts leads to the development of densely sclerotic fragile bones.[2] Overgrowth of cranial nerve foramina results in cranial nerve compression, frequently affecting the optic, auditory, and facial nerves, giving rise to optic atrophy, deafness, and facial palsy, respectively.[1] Reduction of bone marrow spaces gives rise to anemia, thrombocytopenia, and extramedullary hematopoiesis, leading to hepatosplenomegaly.[1] Leukemoid reaction and leukoerythroblastosis are known to occur.[1,3] There is a failure to thrive, and these infants are prone to recurrent infections, osteomyelitis, and fractures.[1,4] Hematopoietic stem cell transplantation presently offers the only hope for cure.[5] We present the case of a female infant with MIOP, who presented to us with hematological abnormalities, failure to thrive and blindness.

Case Report

A 4-month-old female infant was referred to our hospital for further evaluation of raised total blood count, thrombocytopenia, and hepatosplenomegaly. She was delivered after a full-term normal pregnancy. Her birth weight was 3.5 kg and had an Apgar score of 9/10. She had received appropriate immunization to date. Her weight on presentation was 4.0 kg. The infant had gained only 0.5 kg weight over the period of 4 months since birth. Her parents noted that baby's gaze was not following light or other objects. Cranial examination revealed a bulging anterior fontanelle

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with frontal bossing. Funduscopic examination showed bilateral optic atrophy and baby did not follow or fixate on a light source. There was hepatosplenomegaly with the liver 4 cm and spleen 5 cm below the right and left subcostal margins, respectively.

Laboratory investigation revealed hemoglobin was 7.5 g/dL (range: 11–14 g/dL) and platelet count was 50,000/mm^3 (range: 150,000–400,000/mm^3). Peripheral smear showed a leukoerythroblastic blood picture with normocytic normochromic anemia and thrombocytopenia. Serum alkaline phosphatase was elevated (538 U/L) (range: Up to 300 U/L). Serum calcium was in the lower normal limit (8.5 mg/dL) (range: 8.5–11.5 mg/dL) but other biochemical parameters were normal. Repeated attempts at bone marrow aspiration yielded dry tap on each occasion.

With the provisional diagnosis of osteopetrosis in mind, a skeletal survey of the infant was conducted. The infantogram revealed a generalized increase in bone density with loss of corticomedullary differentiation [Figure 1]. The left humerus had "bone within-bone" appearance. There was widening, cupping, and splaying of the metaphysis of the radius and ulna, suggestive of coexisting rickets [Figure 2a]. The vertebral end plates were sclerosed, resulting in "sandwich vertebrae" [Figure 2b]. The distal end of the left femur had the characteristic "erlenmeyer flask" deformity [Figure 2c]. There was increased thickness of the skull base, sclerosis of the orbits, and sphenoid bones resulting in "harlequin mask appearance" [Figure 2d].

Patient received calcium and Vitamin D supplementation. Her parents were counseled on the need for mutation analysis and hematopoietic stem cell transplantation, which they declined due to financial constraints.

Discussion

The term osteopetrosis is derived from the Greek words "osteo" meaning bone and "petros," stone. It is also referred to as "marble bone disease" and "Albers-Schönberg disease," after the German radiologist who first described the condition in 1904.[6] It comprises a clinically and genetically heterogeneous group of conditions. Three clinical variants that have been described are (1) MIOP, an autosomal recessive disorder; (2) the autosomal dominant type that presents during adolescence and are a more benign form; and (3) osteopetrosis combined with renal tubular acidosis due to carbonic anhydrase II deficiency. Increased bone density on radiographs is the hallmark of the condition.[3]

The incidence of MIOP is 1:250,000 in the general population. It is more frequent in certain ethnic groups including inhabitants of Costa-Rica in whom its incidence is much higher than elsewhere (3.4:100,000).[7] Although there are several published case reports, there is no data about the exact prevalence in India.[8]

MIOP is present at birth or develops within the first few months of life.[7] Our patient presented to us at 4 months of age. Abnormal bone formation and fibrous tissue replace the bone marrow giving rise to anemia, thrombocytopenia, and leukoerythroblastosis, all of which were evident in our patient's peripheral smear. Extramedullary hematopoiesis leads to hepatosplenomegaly.[1] The extramedullary hematopoiesis leading to hepatosplenomegaly was noted in the index patient. Sclerotic bony changes and marrow fibrosis leads to a dry bone marrow tap as was encountered in our case. This phenomenon has previously been reported by Ashraf *et al*.[9] Bony overgrowth causes compression of the optic foramina leading to optic atrophy. Our patient had bilateral optic atrophy. Hearing loss affects approximately 78% of individuals with MIOP;[10] however, the patient presented did not undergo an audiology assessment as the facility is not

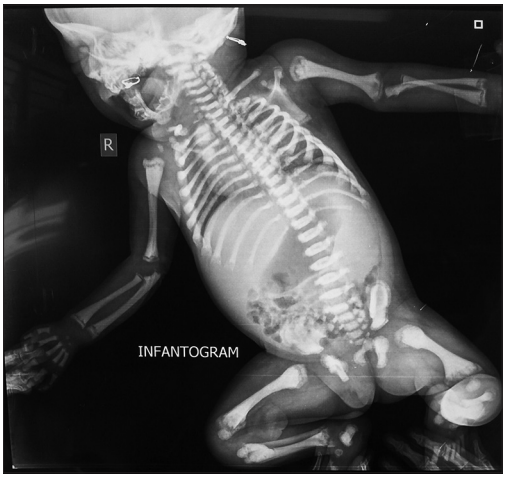

Figure 1: Infantogram: Generalized skeletal sclerosis

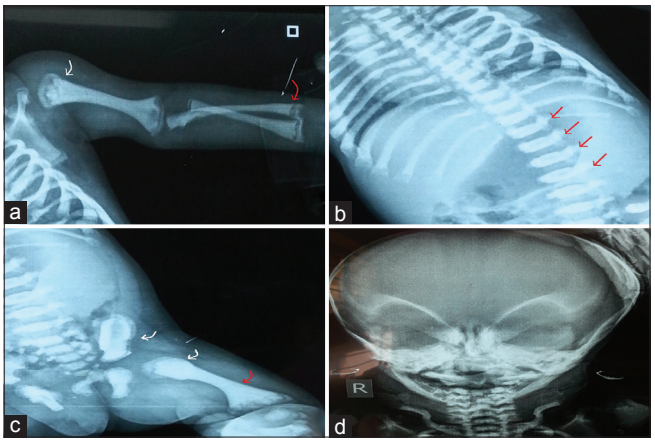

Figure 2: (a) X-ray of left upper limb: Bone within-bone appearance of humerus (white arrow) and widening, cupping, and splaying of metaphysis of radius and ulna (red arrow), (b) X-ray of spine: Sclerosis of end plates of vertebrae – "sandwich vertebrae"(red arrow), (c) X-ray of left femur: Erlenmeyer flask deformity of distal end of the left femur (red arrow), bone within-bone appearance of the left iliac bone (white arrow), (d) X-ray of skull: Sclerosis of skull base. There is sclerosis of the orbits and the sphenoid resulting in the "harlequin mask" appearance

available in our hospital. Infants with MIOP have failure to thrive and are prone to recurrent infections.[1,3] Our patient had gained only 0.5 kg weight over the period of 4 months since birth.

A variety of radiological signs has been described in the literature. There is a generalized increase in bone density along with "bone within-bone" appearance which is characteristic and diagnostic.[1] Increased thickness of skull base, along with sclerosis of orbits and sphenoid results in the "harlequin mask appearance".[4] Bone remodeling defects at the metaphysis of long bones leads to a funnel-like appearance ("erlenmeyer flask" deformity).[10] Sclerosis of vertebral end plates results in "sandwich vertebrae" and "rugger-jersey" spine.[10] MIOP may be complicated by rickets. Rickets is a paradoxical feature of MIOP. Despite markedly positive total body calcium, the serum calcium, and phosphorus product are insufficient to mineralize the newly formed chondroid and osteoid. The osteoclasts are unable to maintain a normal calcium-phosphorus balance in extracellular fluid despite a positive total body calcium balance. More than 99% of total body calcium is sequestered by the skeleton leading to a paradoxical decrease in the serum calcium, which is often exacerbated by inadequate dietary intake of calcium.[11,12] Osteomyelitis and multiple fractures are known to occur.[4] Our patients had most of the features of osteopetrosis, except osteomyelitis, and fractures. There was evidence of rickets as well.

Phadke *et al*. have described the mutations in Indian patients with autosomal recessive MIOP. The most common mutations were in the TCIRG1 gene. Mutations were also noted in the CLCN7, OSTM1, and PHLEKM1 genes.[8] Hematopoietic stem cell transplantation is the optimal therapy for MIOP, with a success rate of 50%. However, there is unsatisfactory rescue of growth and visual deterioration.[3,5] Our patient did not undergo mutational analysis or bone marrow transplantation due to financial constraints.

Conclusion

MIOP should be considered when patient presents with hematological abnormalities such as anemia, thrombocytopenia, and leukemoid reaction along with hepatosplenomegaly and cranial nerve palsies such as optic atrophy. Our case is worthy of mention because a high index of suspicion and accurate interpretation of the infantogram helped us clinch the diagnosis. The early diagnosis made in this case if followed up with the appropriate management will prevent the morbidity and mortality usually associated with MIOP.

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Conflicts of interest
There are no conflicts of interest.

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