

Case Report

Malignant infantile osteopetrosis with rickets presenting with bicytopenia in septic shock: case report

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ABSTRACT

Malignant infantile osteopetrosis is a rare, fatal autosomal recessive disorder due to abnormal osteoclast activity. We report a 1-year-old infant, born to consanguineously married couple, who presented to our ER with acute respiratory distress and bicytopenia. He had tender hepatomegaly, splenomegaly, failure to thrive and features of rickets. He was evaluated previously for possible hydrocephalus secondary to his abnormal shape of head with proptosis, MRI revealed a subarachnoid cyst, but possibility of osteopetrosis was missed. Skeletal radiographs done later detected dense, sclerotic bone with sandwich vertebra, provided a delayed diagnosis of MIOP. Rickets, a paradoxical association, was also seen in our case, with low serum calcium and vitamin D3 levels. He succumbed due to severe bronchopneumonia with septic shock. Early diagnosis and timely hematopoietic stem cell transplant are the only curative approach for MIOP, which is otherwise fatal.

Keywords: Osteopetrosis, Hepatomegaly, Splenomegaly, Pancytopenia, Rickets

INTRODUCTION

Malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form of skeletal dysplasia characterized by impaired bone resorption with endochondral formation replacing haematopoietic cells in the medullary cavity. Fracture risk is consequently increased due to bone fragility. Reduction in hematopoietic stem cells cause thrombocytopenia and anemia, with increased susceptibility to infections. We report a case of MIOP who presented to us in sepsis and acute respiratory distress with an unusual association with vitamin D deficient rickets.

CASE REPORT

We report a case of 1-year-old male infant who was brought to our ER with severe respiratory distress, with failure to thrive and dysmorphic features. At arrival, baby was severely tachypneic, gasping with air hunger and had to be intubated on emergency basis and connected to

ventilator. Examination revealed bilateral bronchial breathing with crepitations, protuberant abdomen with hepatosplenomegaly, abnormally shaped long bones of extremities. blood gases revealed both metabolic and respiratory acidosis with high lactate, with X-ray showing diffuse bilateral patches. His rapid antigen test for SARS-CoV2 was negative. In light of above presentation, baby was considered to have bronchopneumonia in sepsis with shock. Rapid fluid boluses were infused, blood cultures sent and broad-spectrum antibiotics were initiated. Infantogram revealed increased bone density of all mineralised bones.

Blood workup revealed severe normocytic normochromic anemia with thrombocytopenia, neutrophilic leucocytosis and grossly elevated C-reactive peptide levels. The baby continued to deteriorate despite acidosis correction and succumbed within 12 hours of admission with massive pulmonary bleed secondary to disseminated intravascular coagulation from sepsis. Baby was first born to third degree consanguinity, with no history of similar

dysmorphism or recurrent abortions in their extended family. He was a term, small for gestation baby, born via caesarean section due to maternal eclampsia and admitted in NICU for 10 days with perinatal asphyxia and sepsis. The baby had macrocephaly, with prominent forehead, proptosis, low set ears, and broad facial profile. He had delay in all developmental milestones predominately motor and was hypotonic.

He was evaluated for his dysmorphic features and was initially suspected to have hydrocephalus due to his abnormal shape of skull at 3 months of age. Ultrasound abdomen showed hepatosplenomegaly. MRI brain revealed delayed myelination with thinning of corpus callosum with subarachnoid cyst. Serology for toxoplasma, rubella, cytomegalovirus, herpes, and hepatitis virus was negative. He was treated multiple times on outpatient basis for repeated infections. Poor nutrition led to worsening of his nutritional status with consequent development of vitamin D deficient rickets- low serum calcium and vitamin D3 levels and X-ray features of metaphyseal splaying.

He had persistent bicytopenia since early infancy, indicative of bone marrow failure syndrome, but was incompletely evaluated, until very late, when he presented to us in severe hypoxic respiratory failure from bronchopneumonia and sepsis. Bicytopenia with increased predisposition for infections, craniosynostosis and characteristic X-ray findings of thick, dense and sclerotic long bones, pointed towards the definitive diagnosis of infantile osteopetrosis.

Though we could not save our child due to delayed and severe presentation, we offered our patient's parents genetic consultation with prenatal diagnosis for the forthcoming pregnancies.

In Figure 2, uniform sclerosis of long bones, ribs, endobone appearance in tarsal bones and sandwich appearance of vertebra. Also note metaphyseal splaying with increased unmineralised osteopenia suggestive of associated rickets.



Figure 1: Facial dysmorphism with prominent forehead, depressed nasal bridge and proptosis.



Figure 2: Radiographs showing anteroposterior view of (A) chest wall; (B) both lower limbs.

DISCUSSION

Osteopetrosis is an osteosclerosing type of skeletal dysplasia, with increased bone density on radiographs due to abnormalities in osteoclast differentiation or function, with four subtypes- malignant infantile OP, benign or adult OP, intermediate OP and carbon anhydrase type II deficiency. MIOP is the autosomal recessively inherited form which begins in utero, presenting at birth or within the first year of life, with incidence of 1 in 250000 births.¹

The increase in bone mass leads to phenotypic features such as macrocephaly and frontal bossing. Tooth eruption and longitudinal growth of bones is impaired with a short stature and predisposition to fractures and osteomyelitis. The obliteration of bone marrow spaces 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. Neurological manifestations 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. MRI brain may show delayed myelination with diffuse progressive cortical and subcortical atrophy.^{2,3}

Characteristic radiographic findings in osteopetrosis include a marked increase in bone density with defective metaphyseal remodeling, and “bone within a bone” appearance. Alternating sclerotic and lucent bands can give the vertebrae a ‘sandwich’ appearance. CT scan can be used to assess auditory and optic canal. With intense positive balance of body calcium, MIOP association with rickets uncommon. As a paradoxical complication of infantile osteopetrosis, rickets may result from the inability of the osteoclasts to maintain a normal calcium-phosphorus balance in the extracellular fluid.^{4,5} Genetic testing can be used to confirm the diagnosis, differentiate between subtypes, information regarding prognosis, likely response to treatment and recurrence risks. Bone biopsy can distinguish between osteoclast-poor and osteoclast-rich subtypes of MIOP. Alternative diagnosis to consider for MIOP include pseudohypoparathyroidism,

pyknodysostosis, hypoparathyroidism, lead or fluoride poisoning and leukemia.⁶

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. Hematopoietic stem cell transplantation (HSCT) offers the only chance of cure for MIOP; it should be performed early before the irreversible neurologic impairment. Supportive treatment includes management of complications, antibiotic therapy for infections, nutritional measures and supplementation with calcium and vitamin D.¹

Genetic counseling is important. Antenatal diagnosis in families with MIOP may be possible using radiographs, thus allowing haematopoietic stem cell transplantation before the age of 3 months with the aim of improving neurological outcomes.

CONCLUSION

Although diagnosis of MIOP is easy and depends mainly on radiographic examination, it's often delayed due to rarity of the disease and lack of clinical suspicion. Early diagnosis and timely HSCT is the only curative treatment approach for MIOP, an otherwise fatal disease.

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