

Malignant infantile osteopetrosis, presenting as hemolytic anemia: a case report

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Abstract

The occurrence of malignant infantile osteopetrosis is observed in early stages of life along with increased sclerosis of the skeleton and decreased bone marrow spaces. The bone marrow damage of the disease leads to anemia, extramedullary hematopoiesis secondary to anemia, which result in hepatosplenomegaly, cranial nerves compression (optic nerve atrophy), and severe growth failure. The characteristic symptoms of the disease are fractures, visual damage, and bone marrow failure resulting in severe anemia. A 4-month-old infant presented with severe anemia and hepatosplenomegaly, bilateral optic atrophy, and acute respiratory tract infection. It was first thought to be hemolytic anemia or intrauterine infection. Radiological features, bone marrow studies, and clinical progression clinched the diagnosis of malignant infantile osteopetrosis. As it is a rare cause of severe anemia, clinicians should have sufficient idea about it.

KEY WORDS: Osteopetrosis, anemia, optic atrophy, hepatosplenomegaly

Introduction

The characteristic feature of malignant infantile osteopetrosis (MIOP), an autosomal recessive disorder, is the decreased activity of osteoclasts leading to generalized bone osteosclerosis. Densely sclerotic fragile bones are formed because of the defective osteoclast activity along with regular bone formation by osteoblasts.^[1] Consequent impaired bone resorption and endochondral formation replaces the hematopoietic cells in the medullary cavity are replaced by the subsequent damaged bone resorption and endochondral formation, which further elevates the occurrence of fractures owing to bone fragility. Moreover, hematological abnormalities such as thrombocytopenia, anemia, susceptibility to infections, and extramedullary hematopoiesis can result because of the decrease in hematopoietic cells. The

cranial nerve foramina overgrows, which leads to nerve compression that regularly affects the optic, auditory, and facial nerves. The disease is fatal in infancy and is cured with hematopoietic stem cell transplantation (SCT), with a rate of success by 50% and unsatisfactory rescue of growth and visual deterioration.^[2]

Case Report

A 4-month-old male infant was referred to the pediatric emergency with complaint of progressive pallor for 15 days, cough, fever, and breathlessness for 10 days. He was having similar history before 2 months and was treated in a local hospital with antibiotics and blood transfusion. He was born to a third-degree consanguineous family and possessed two dead siblings with similar presentation. He was having no history of birth asphyxia. The child was yet to attain neck holding, was not doing visual fixation on bright objects, and on examination, was febrile and irritable. He was having severe pallor, tachypnea, chest indrawing, nasal flaring, lethargy, poor feeding, drooling of saliva, and grunting. Systemic examination revealed hepatomegaly with the liver noted to be 5 cm and splenomegaly with the spleen noted to be 3 cm. He was having bilateral crepitations in chest. The patient underwent an open anterior fontanel with 5 × 5 cm in size. His weight

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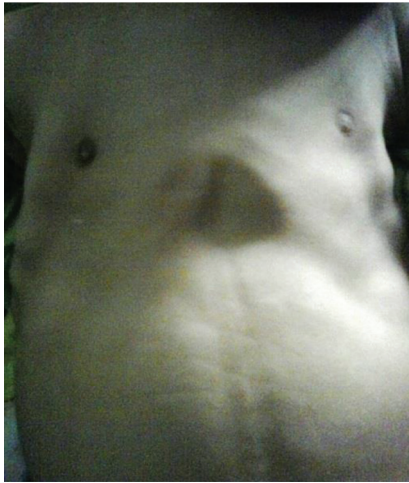


Figure 1: Chest deformity: indrawing, and abnormal rib cage.



Figure 4: Dense rib in X-ray.



Figure 2: Widened wrist.



Figure 3: Dense bone in X-ray of hand.

was 4.6 kg, length 53 cm, and head circumference 38 cm. He showed pale appearance, and fundoscopic examination showed optic atrophy bilaterally. He was having hepatosplenomegaly, deformed thorax, and widened wrist joint [Figures 1 and 2]. On investigation, the following results were obtained: Hb, 4.6 g%; TLC, 8,200; and TPC, 40,000. More investigations were done to look for the cause of anemia. He showed normocytic anemia and reticulocytosis. Peripheral blood smear was significant for leukoerythroblastosis. Chest X-Ray revealed very dense ribs and dense bone in wrists and limbs [Figures 3 and 4]. Hb electrophoresis revealed AA band. Liver enzymes were raised as follows: AST, 118 IU; ALT, 132 IU; ALK PO, and 750 IU. Ultrasonography of abdomen revealed hepatosplenomegaly. A computed axial tomographic scan of orbits demonstrated the narrowing of the optic foramina bilaterally. Bone marrow aspiration showed hypocellularity. Fundoscopy showed bilateral optic atrophy. On performing arterial blood gas, the blood pH and other parameters were at normal levels. Urinary pH was at normal level along with other routine urinary parameters. TORCH panel results came to be negative. Echocardiography showed normal findings.

Our initial diagnosis was congenitally acquired infection (TORCH) or a kind of storage disease, but physical examination and laboratory results confirmed the diagnosis of osteopetrosis (OP). The absence of any metabolic acidosis with an alkaline urine pH and the absence of cerebral calcifications excluded a diagnosis of carbonic anhydrase II deficiency syndrome. Familial erythrophagocytic lymphohistiocytosis and familial histoplasmosis were also considered in the differential diagnosis. Peripheral blood smear, bone marrow aspiration, and radiological features did not support the diseases. The child was treated in line of ARI and, after stabilization, referred to higher center for stem cell therapy.

Discussion

OP is class of bone diseases, with characteristic features such as osteoclast failure and defective bone resorption. The hallmark of this disease is elevated bone density on radiographs because of aberrations in osteoclast differentiation or function.^[3]

There are four subtypes of OP^[4]: (a) malignant or infantile OP; (b) benign or adult OP; (c) intermediate OP; and (d) carbon anhydrase type II (CAII) deficiency.

It has three forms of inheritance: autosomal recessive, autosomal dominant, and X-linked inheritance. Autosomal recessive osteopetrosis (ARO) may have the most severe course, with an incidence of 1:250,000 in general population. The incidence is very high in Costa Rica.^[5] Bone mass increase results in phenotypic structures such as macrocephaly and frontal bossing. In addition, defects in tooth eruption are seen. The Impaired growth in longitudinal direction of bones leads to short physique and tendency to fractures and osteomyelitis.^[6] The atypical growth of the bone hinders with medullary hematopoiesis, which leads to in life-threatening anemia, thrombocytopenia, greater susceptibility to infections, and secondary expansion of extramedullary hematopoiesis sites such as the liver and spleen. Secondary to the obstruction of the foramina by which the cranial nerves, spinal cord, and major blood vessels oblique the skull, leading to blindness, hearing loss, facial palsy, and hydrocephalus, are the most common neurological defects in OP.^[6] Visual damage occurs owing to bony infringement on the optic foramina, which is a usual primary symptom.^[7] Optic atrophy is also present in a significant number of cases. Radiologic findings showed elevated bone density with damaged metaphyseal remodeling (it was an evident feature in our case). The “bone within-bone” appearance is characteristic and of diagnostic value.^[5] Genetic testing confirms the diagnosis, differentiates between the different subtypes of OP, and gives information regarding prognosis, response to treatment, and chance of recurrence. Osteoclast malfunction resulting in primary sclerosing conditions of bone must be differentiated from several conditions wherein bone sclerosis results as a secondary phenomenon. Some alternative diagnosis to consider include pseudohypoparathyroidism, pycnodysostosis, and hypoparathyroidism; chemical poisoning (e.g., lead, fluoride, and beryllium); malignancies (myeloproliferative diseases and leukemia); and sickle cell disease.^[5] SCT is the only curative therapy for patients with MIOP, and it should be performed as soon as the diagnosis is made because neurologic impairment occurs in early infancy and will become irreversible even after successful SCT. Successful results have been achieved in patients transplanted with HLA-matched sibling donor stem cells.^[8]

Vitamin D supplements, corticosteroids, interferon, and erythropoietin form the suitable medications. The bone marrow transplantation is the conclusive therapy, and the 5-year survival rate for recipients of HLA-identical bone marrow transplants is 79%.^[7] Genetic consultation plays a vital role as prenatal detection of OP early in pregnancy is indicative for the pregnancy to be terminated.^[9]

Conclusion

Anemia with hepatosplenomegaly is a common presentation of hemolytic anemia in infancy. But, other rare diseases such as our indexed case can present in similar fashion. So, MIOP is a possibility if child is having features of hemolytic anemia and hyperdensity of bones. Knowledge of these types of presentations will help clinicians diagnose early and prevent many dreaded complications.

References

- Gerritsen EJ, Vossen JM, van Loo IH, Hermans J, Helfrich MH, Griscelli C, et al. Autosomal recessive osteopetrosis: variability of findings at diagnosis and during the natural course. *Pediatrics* 1994;93(2):247–53.
- Engiz O, Kara S, Bagrul D, Lahr G, Alioglu B, Arıkan I, et al. Infantile malignant osteopetrosis: a rare cause of neonatal hypocalcemia. *J Pediatr Endocrinol Metab* 2012;25(11–12):1205–7.
- Stark Z, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis* 2009;4(1):5.
- Lam DK1, Sándor GK, Holmes HI, Carmichael RP, Clokie CM. Marble bone disease: a review of osteopetrosis and its oral health implications for dentists. *J Can Dent Assoc* 2007;73(9):839–44.
- Subramaniam A, Singh A, Chavan M, Kunte S. Autosomal recessive osteopetrosis: case report of two siblings. *Oral Radiol* 2008;24(2):80–4.
- Steward CG. Neurological aspects of osteopetrosis. *Neuropathol Appl Neurobiol* 2003;29(2):87–97.
- Venkateshwar V, Vaidya A, Roy P, Songeeta S, De JK. Osteopetrosis. *Med J Armed Forces India* 2003;59(4):344–6.
- Tsuji Y, Ito S, Isoda T, Kajiwara M, Nagasawa M, Morio T, et al. Successful nonmyeloablative cord blood transplantation for an infant with malignant infantile osteopetrosis. *J Pediatr Hematol Oncol* 2005;27(9):495–8.
- Besbas N, Draaken M, Ludwig M, Deren O, Orhan D, Bilginer Y, et al. A novel CLCN7 mutation resulting in a most severe form of autosomal recessive osteopetrosis. *Eur J Pediatr* 2009;168(12):1449–54.

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