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Original Article

Malignant Infantile Osteopetrosis: A Rare Cause of Refractory Thrombocytopenia

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ABSTRACT

Background: Infantile Malignant Osteopetrosis (IMO) is a rare autosomal recessive bone disorder characterized by defective osteoclastic bone resorption, leading to excessive bone density and marrow failure. While rare (1 in 250,000 live births), it is a life-threatening condition that requires early identification to prevent irreversible neurological damage and mortality.

Case Presentation: A 25-day-old term male infant, born to third-degree consanguineous parents, presented for evaluation of an abnormal newborn screen (elevated 17-OH progesterone) and a facial rash. Clinical examination revealed significant splenomegaly (5 cm below the costal margin) and severe refractory thrombocytopenia (27,000 cells/cu.mm). Initial management for suspected sepsis, alloimmune thrombocytopenia, and TORCH infections was unsuccessful, with platelet counts remaining refractory to IV immunoglobulin and transfusions. A subsequent skeletal survey revealed diffuse skeletal sclerosis and pathognomonic "bone-within-bone" appearances in the long bones. Ophthalmic evaluation confirmed pale discs and foveal atrophy. Whole Exome Sequencing identified a likely pathogenic homozygous variant in the CLCN7 gene. Despite counseling on the necessity of hematopoietic stem cell transplantation (HSCT), the parents opted for conservative management due to the poor prognosis associated with this genetic variant.

Discussion: This case highlights IMO as a critical differential diagnosis for neonatal refractory thrombocytopenia and splenomegaly. The progressive obliteration of the medullary cavity leads to bone marrow insufficiency and compensatory extramedullary hematopoiesis. Early diagnosis is vital, as HSCT remains the only curative treatment; however, variants in genes like CLCN7 can involve primary CNS pathology, complicating the clinical outlook.

Conclusion: Clinicians should maintain a high index of suspicion for osteopetrosis in neonates with unexplained bicytopenia and organomegaly. Rapid radiographic screening and genetic testing are essential for timely intervention and informed genetic counseling for affected families.

Keywords*: Infantile Malignant Osteopetrosis; CLCN7 Gene Mutation; Neonatal Thrombocytopenia; Bone-Within-Bone Appearance; Hematopoietic Stem Cell Transplantation.*

INTRODUCTION

Infantile malignant osteopetrosis is a rare inherited bone disorder which is characterised by increased in bone density and bone formation due to dysfunctional osteoclastic bone resorption[1,2]. Osteopetrosis is also known as "Albers-Schonberg disease" or "marble bone disease". Radiologist Dr. Elberschönberg, was the first to describe this disease in 1904 [3] .This

disorder is rare and affects 1 in every 250,000 live births. It can be classified into malignant "infantile autosomal recessive" and benign type "adult autosomal dominant" and intermediate type according to its severity [4]. Malignant type is common in infancy and rapidly deteriorates leading to mortality in first year of life[5] . We report a neonate with refractory thrombocytopenia with splenomegaly who was diagnosed to be Infantile malignant osteopetrosis

CASE REPORT:

25 days old, 2nd born term male child with birth weight of 3.25 kgs, born via spontaneous vaginal delivery to a 3rd degree consanguineous couple, came for review in view of high 17 OH progesterone in Newborn Screening along with complaints of rash over face and scalp. The baby was on exclusive direct breastfeeding and no history of fever, bleeding manifestations, jaundice or seizures. Adequate weight gain present with current weight of 3.83kgs, CBC was sent along with 17 OH progesterone. Repeat serum progesterone level was normal (5.1 ng/mL). Baby was found to be thrombocytopenic (27000cells/cu.mm) and admitted for evaluation. On admission, baby was hemodynamically stable, spleen palpable 5 cm below the left costal margin.

Raised total wbc counts- 28,270cells/cu.mm, Peripheral smear done showed a picture of leukoerythroblastic picture with thrombocytopenia with normal platelet morphology. Direct Coombs Test was negative.in view of suspected late onset sepsis, baby was started on iv antibiotics. Inj.Vitamin K 1 mg IV stat dose given in view of thrombocytopenia. In view of splenomegaly and thrombocytopenia in the neonate, the differentials were Autoimmune thrombocytopenia and TORCH infection. TORCH profile was negative (IgM) in the child. Maternal TORCH panel was negative except toxoplasma was equivocal; IgG positive. Maternal ANA was negative. Diagnosis of probable alloimmune thrombocytopenia was made and the child was started on IV immunoglobulin 1 g/kg for 2 days which was found to be not effective. Platelet count was in declining trend 19,000 cells/cumm. One unit of platelet transfusion was given. Post platelet transfusion, platelets were 37,000 cells/cumm.

Hb was noticed to have a fall from 12.7 g/dL to 8.7 g/dL. Bone marrow suppression was suspected in view of bicytopenia. Peripheral smear showed no evidence of hemolysis. MRI Brain was done in view of missed TORCH (toxoplasmosis); it showed hypoplastic left transverse and sigmoid sinus. Skeletal survey showed evident osteopetrosis changes-diffuse sclerotic vertebrae and mid-bone within bone appearance in bilateral femur and tibia.

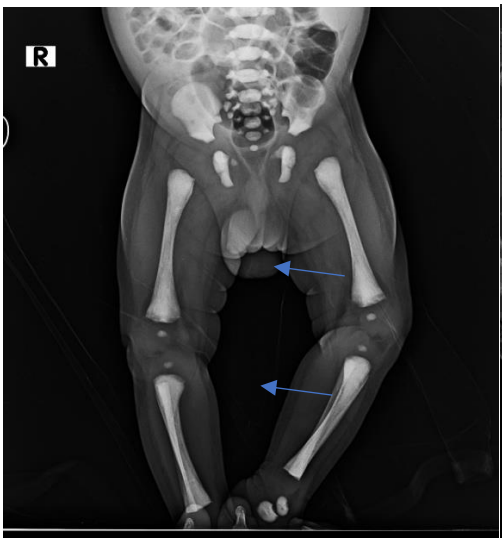

Figure A: Mid-bone within bone appearance in bilateral femur and tibia.

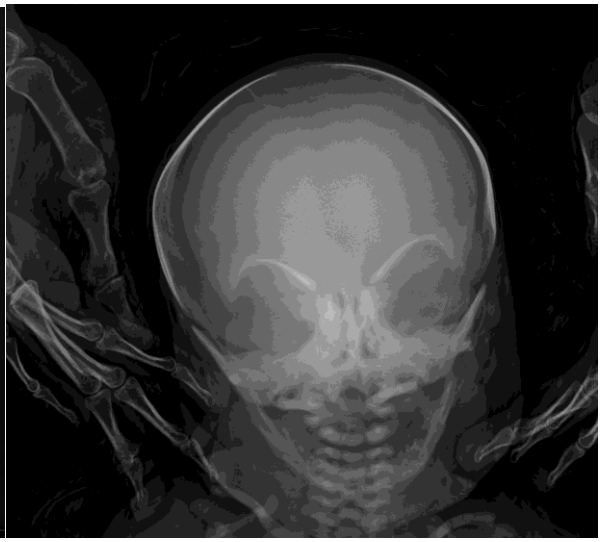

Figure B: "Harlequin mask "appearance of orbit.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
CLCN7 **(-)** (ENST00000382745.9) NM_001287.6	Intron 17	c.1617+119G>A	Homozygous	Osteopetrosis, autosomal recessive 4 (OMIM#611490)	Autosomal recessive	Likely Pathogenic **(PS3_S, PP1_Sup, PM2_M)**

Abbreviation: **_VS** - Very Strong, **_S** - Strong, **_M** - Moderate, **_Sup** - Supporting

No significant clinically relevant variants were detected in the mitochondrial genome.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous variant in intron 17 of the ***CLCN7*** gene (**chr16:g.1450378C>T; c.1617+119G>A; Depth: 267x**) was detected (Table). The observed variant has previously been reported in patients affected with osteopetrosis

Ophthalmic evaluation showed pale disc and foveal atrophy. Whole Exome Sequencing (WES) detected likely pathogenic homozygous variant of CLCN7 gene in intron 17, which results in guanine replacing adenine, which is an intronic single nucleotide variant resulting in autosomal recessive pattern of inheritance.

HLA typing was sent for sibling and family. Serum calcium and phosphorous were sent (Calcium-9.2mg/dl; phosphorous-4mg/dl). Baby was started on oral calcium and phosphorous supplements. Parents were counselled regarding the nature of the disease and poor prognosis of autosomal recessive variant. Parents were also counselled about the available treatment option Hematopoietic stem cell transplant and 5-year survival rate. But the parents were not willing due to the poor prognosis of the disease variant. Baby is on regular follow-up.

DISCUSSION

The above-described case by us depicts infantile malignant osteopetrosis presented 8as refractory thrombocytopenia with splenomegaly and fundus changes at 25 days of life. Infantile malignant osteopetrosis is seen in 1 in 250,000 births with autosomal recessive pattern and 1:20,000 births with autosomal dominant pattern. It is due to impaired osteoclast-mediated bone resorption. The failure to remodel primary bone results in diffuse skeletal sclerosis and progressive narrowing of the medullary cavities, leading to bone marrow insufficiency and associated clinical manifestations. Clinical features include failure to thrive, recurrent hospitalisations, anaemia, easy bruising, macrocephaly, fractures, hypocalcaemia seizures, compressive neuropathies, and roving eye movements and deafness. In untreated cases, complete visual loss occurs and hearing loss also affects nearly 80% of such children [6]. The diagnosis is primarily established through a combination of clinical presentation, haematological abnormalities, and characteristic radiographic findings.

Early imaging typically demonstrates generalized skeletal sclerosis. As the condition progresses, radiographs reveal the pathognomonic “bone-within-a-bone” configuration, reflecting disordered bone remodelling and excessive mineralization. Hemolysis resulting from hypersplenism worsens the anemia and thrombocytopenia. Hematological impairment occurs within the first year of life in about 75% of patients and its presence within 3 months of age is indicative of poor prognosis. Infantile malignant osteopetrosis (IMO) has been linked to pathogenic variants in multiple genes involved in osteoclast function. Approximately 50% of cases are attributed to autosomal recessive mutations in TCIRG1, which encodes the a3 subunit of the vacuolar H^+-ATPase (V-ATPase) proton pump. Mutations in CLCN7, responsible for the chloride channel 7 protein, account for nearly 10–15% of affected individuals. Less frequently implicated genes include OSTM1 (osteopetrosis-associated transmembrane protein 1) and SNX10 (sorting nexin 10), each contributing to roughly 4% of cases[7]. In CLCN 7 and OSTM1 forms will have primary CNS involvement and they do not benefit from HSCT.
Hematopoietic stem cell transplantation (HSCT) is currently the only definitive treatment. Bone marrow failure and age <1 year at diagnosis are sufficient for HSCT referral. Corticosteroids are used as second-line management if HSCT is not feasible[8] . Early transplantation is strongly recommended, as it significantly lowers the likelihood of permanent neurological impairment that may develop during infancy. The most favourable outcomes have been reported in patients receiving transplants from human leukocyte antigen (HLA)–matched sibling donors, with a reported 5-year survival rate of approximately 79% in recipients of HLA-identical grafts. In the absence of HSCT, the prognosis remains poor, and many

affected children succumb during infancy or early childhood[9] . Parathyroid hormone, calcitriol, interferon-gamma, and corticosteroids, have been employed in the management of osteopetrosis with variable and generally limited success[10].

CONCLUSION

Osteopetrosis should be considered as a differential diagnosis of any infant presenting as thrombocytopenia with splenomegaly and sclerotic changes. Ophthalmic evaluation to be done in all cases of osteopetrosis since various studies shows ophthalmic changes are consistent with osteopetrosis. Timely and accurate diagnosis is therefore essential to facilitate early referral for transplantation and to provide appropriate genetic counselling. Given the autosomal recessive inheritance pattern, subsequent siblings carry a 25% risk of being affected.

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