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Case Report

Malignant Infantile Osteopetrosis: A Rare Genetic Disorder

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Abstract

Introduction: Osteopetrosis is a clinical syndrome characterized by impairment in the production or function of osteoclasts, leading to bone condensation. Symptoms and their onset depend on the disease's hereditary pattern.

Case Report: We report a 6-month-old female with dysmorphic features, failure to thrive, lymphadenopathy, hepatosplenomegaly, anemia, and thrombocytopenia. Born term by emergency lower cesarean section due to fetal distress, she was admitted into the neonatal intensive care unit (NICU) for 22 days. Complete blood count (CBC) showed hemoglobin (Hb) 13.6 g/dL, white blood cell (WBC) 14.3 × 10^9/L, platelet 30 × 10^9/L, manual 35 x 10^9/L. At the age of 6 weeks, she was seen in a hematology clinic for thrombocytopenia where she was admitted for bone marrow aspiration. The sample was inadequate, and no megakaryocytes were seen. A skeletal survey was done, it showed evidence of diffuse osteosclerosis overlying the bones, mainly long bones of the upper and lower limbs as well as the metacarpals, metatarsals, and phalangeal bones of both hands and feet. Congenital osteopetrosis was suspected, thus parents opted for second medical advice in Germany where a molecular genetic test confirmed the diagnosis.

Discussion: The patient presented with a wide range of symptoms, the diagnosis of osteopetrosis depends on skeletal radiology and is confirmed by the genetic test. Currently, hematopoietic stem cell transplantation (HSCT) is the only therapeutic intervention available causing it to be the sole opportunity for recovery; however, it cannot be used in all types of osteopetrosis.

Conclusion: The approach to such cases must be comprehensive and must be done by a multidisciplinary team to address and manage the existing symptoms and complications.

Keywords: osteopetrosis, thrombocytopenia, anemia, skeletal survey, molecular genetic test, hematopoietic stem cell transplantation (HSCT)

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1. Introduction

Osteopetrosis is a rare genetic disorder characterized by abnormal bone mass accumulation due to compromised osteoclast function [1]. Discovered in 1904 by German radiologist Albers-Schönberg, it leads to increased bone density due to osteoclast dysfunction [2]. Thirteen different forms of osteopetrosis were defined with a variable mode of inheritance, defective gene, and presentation.

Autosomal dominant osteopetrosis, also referred to as the benign type, occurs in 1: 20,000 live births with symptoms starting in late childhood or adolescence. In this type, 70% of patients have a mutation in the *CLCN7* gene. While the X-linked form results from a mutation in the *IKBKG* gene, the intermediate form occurs secondary to a mutation in *PLEKHM1* and *SNX10* genes with a variable presentation from one patient to another. However, the most severe form and the rarest is the autosomal recessive also known as malignant infantile osteopetrosis (MIO). Patients present with a wide range of symptoms according to the subtype of osteopetrosis, where some could be asymptomatic while others have a severe form to the extent of mortality.

MIO is a genetic condition that impairs skeletal development from prenatal growth. It starts during intrauterine life and appears during birth or in the early years of life. It has an incidence of 1 in 250,000 births and its presentation is considered the most serious compared to other forms [3].

Osteopetrosis is known for causing extremely thick or dense bones in the body. Patients present with fractures, micrognathia, and osteomyelitis. Bone condensation causes bone marrow failure, accounting for anemia and thrombocytopenia. Eating difficulties and/or growth retardation are present along with hepatosplenomegaly due to increased bone density, which interferes with cranial nerve function. There would be neurological issues such as blindness, deafness, and facial nerve paralysis resulting from the nerve compression caused by cranial hyperostosis. Macrocephaly and hydrocephalus are seen as well [4].

Accurate diagnosis and customized patient care plans are made by incorporating detailed patient history, examination, and a variety of investigations such as Skeletal X-ray where its findings are specific [4].

Biochemical tests can be used to diagnose osteopetrosis since they shed light on the physiological alterations occurring secondary to osteopetrosis. As a sign of bone condensation, calcium levels are expected to be low which may slightly elevate the serum phosphate levels. Hypocalcemia may also lead to an increase in the secretion of parathyroid hormone (PTH), causing secondary hyperparathyroidism. An elevation in the alkaline phosphatase levels is expected since its function is dephosphorylation, it is secreted by osteoblasts during bone formation for mineralization of the bone matrix. Pancytopenia is also a common finding but only in the late stages of the disease due to bone marrow failure.

High levels of the isoenzyme creatinine kinase BB may be a sign of pathological alterations, reflecting stress levels in the tissue. There are various forms of the enzyme creatine kinase (CK) depending on the

location. The isoenzyme CK-BB (or CK-1) is mainly found in the brain and smooth muscles. This isoenzyme consists of two subunits, one of them is referred to as the letter B, and the other unit is either the letter "M" since it would be found in the muscle or "B", indicating that it is in the brain.

Another enzyme that can provide insight into the underlying pathology is tartrate-resistant acid phosphatase (TRAP). It is secreted by osteoclasts and can be used to assess its activity, such as a decrease in the enzyme range might be a sign of poor bone resorption, which can be seen in osteopetrosis [4].

The clinical presentation along with the biochemical test results can form a differential diagnosis, but in the end, a molecular genetic test is mandatory to obtain the definitive diagnosis.

The molecular pathogenesis of osteopetrosis is complex where mutations can be seen in 23 genes. Identifying the mutated gene is essential to decide whether the patient is a candidate for management or not. The only definitive and currently available cure is certainly hematopoietic stem cell transplantation (HSCT) and that is applicable only for selective patients with mutations in the *TCIRG1, TNFRSF11A (RANK), SNX10, CAII, IKBKG, FERMT3,* and *CalDAG-GEF1* genes. However, if the mutations are found in other genes or there are severe neurological symptoms then only symptomatic treatment is available.

2. Case Report

We report a 6-month-old female patient born by emergency lower cesarean section due to fetal distress, at term where she was small for gestational age. There was meconium-stained liquor, birth weight of 2.1 kg, and Apgar score of 6 and 8 at 1 and 5 min, respectively. She was admitted into neonatal intensive care unit (NICU), she was stable but tachypnoeic (respiratory rate 64 bpm) with recession and was found to have micrognathia and hepatomegaly.

Investigations done included full blood count (FBC): Hb 16.9 g/dL, WBC 17.5 $\times 10^9$/L, platelet 58 $\times 10^9$/L, platelet manual 65 $\times 10^9$/L, and retic count 4%. She had thrombocytopenia on repeated complete blood count (CBC).

Further requested investigations included: Total bilirubin 3.2 µmol/L, indirect 2.7 µmol/L, C-reactive protein (CRP) negative, urea/electrolyte was normal, creatinine was 0.4 mg/dl. TORCH assay was performed but the results were normal, this assay tests for five infections including Toxoplasmosis, and other infections like syphilis, Rubella, Cytomegalovirus, and Herpes simplex virus.

Chest X-ray (CXR): Prominent vascular markings. Transient Tachypnoea of Newborn (TTN), the heart shadow shows an increased cardiothoracic ratio of 0.65. Blood culture showed no growth, CRP was negative. Creatinine phosphokinase (CPK): 1170 U/L, creatinine phosphokinase MB (CKMB): 1042 U/L, CKMB ratio was 89%. An echocardiogram (ECHO) was done for hyperdynamic precordium which showed small PDA (left to right shunt) and mild septal dyskinesia. Abdominal ultrasound (USS) showed hepatomegaly, while brain USS was normal.

Skull x-ray showed patent anterior fontanel and cranial sutures. No evidence of abnormal vascular markings was observed. No sign of abnormal intracranial calcifications, sella turcica appeared within normal size and contour. She was referred to an ophthalmologist and no findings were observed, and the fundoscopy was normal.

The patient was discharged on day 21, at the time CBC result showed: Hb 13.6 g/dL, WBC 14.3 × 10^9/L, platelet 30 × 10^9/L, manual 35 × 10^9/L. Follow-up appointments were given in the Hematology and Maxillofacial surgical clinic for micrognathia.

She has 2 older healthy sisters (4 and 2.5 years old). Her parents are 1st-degree cousins. No significant family history was reported other than G6PD deficiency.

At 47 days of life, she was seen at the hematology clinic for follow-up of neonatal thrombocytopenia, the patient was pale, not in distress, weight: 2.275 kg (below 3rd centile), height: 44.5 cm (below 3rd centile), and head circumference: 34 cm (below 3rd centile).

Vital signs: Temperature: 36.6˚C, pulse rate: 168 bpm, respiratory rate: 44/min, oxygen saturation: 99%. Upper and lower jaw were hypertrophied, lymphadenopathy, liver 3 cm below costal margin (BCM), and spleen 4 cm BCM.

FBC: Hb 7.1 g/dl, WBC 26 × 10^9/L, N 7%, L 82%, monocyte 7%, myelocyte 2%, NRBCs 10% platelet 25 × 10^9/L, and manual 33 × 10^9/L.

She was admitted for bone marrow aspirate, where the sample was inadequate, and no megakaryocytes were seen. Fewer atypical mononuclear cells were observed, whose nature cannot be identified by an ordinary stain. As such no definitive diagnosis was found, hence it is not possible to conclude a reactive versus malignant bone marrow reaction.

A skeletal survey was conducted, which showed evidence of diffuse osteosclerosis overlying the bones. This is apparent in the long bones depicted in Figure **1**, which shows the upper limbs, and in Figure **2**, which illustrates osteosclerosis in the lower limbs. Additionally, changes were observed in the metacarpals, metatarsals, and phalangeal bones of both the hands and feet.

The patient was discharged, and the parents traveled abroad for further investigation where the patient was admitted for 78 days.

Brain USS: prominent, not definitely expanded third ventricle and lateral ventricles bilaterally. Repeated after 20 days, showed progression of ventricular expansion and the brain atrophy. A lumber puncture examination was done to exclude other causes of neurodegenerative disease that could have caused the progressive atrophy of the brain; however, the result was unremarkable.

X-ray of the left forearm showed: generalized enhancement of bone capacity in accordance with suspected osteopetrosis. Hip USS showed: bilateral hip dysplasia kept on abduction splint for around 2 months. ECHO and electrocardiogram (ECG) were normal.

A molecular genetic test was done, and it detected a homozygous deletion (c.1875_1879del4; c.1879delCAAT) in the chloride potential-dependent channel 7 (*ClCn7*) gene at the end of exon 20, this

"out of frame" deletion leads to an early truncation of the ClCn7 protein. The diagnosis was confirmed based on both father and mother being heterozygous for the deletion (c.1875_1879del CACT) in Exon 20 the *ClCn7* gene, and are therefore carriers of this mutation.

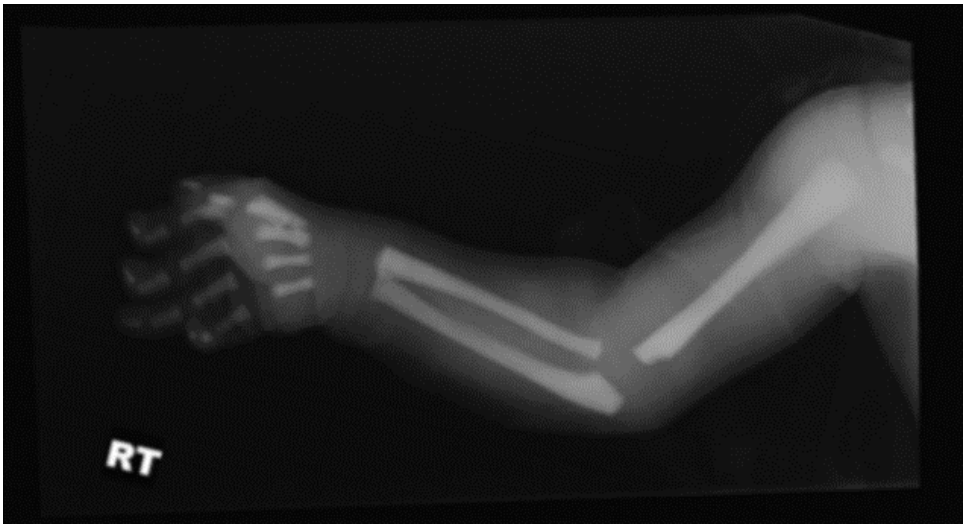

Figure 1: X-ray of the upper limb shows diffuse osteosclerosis.

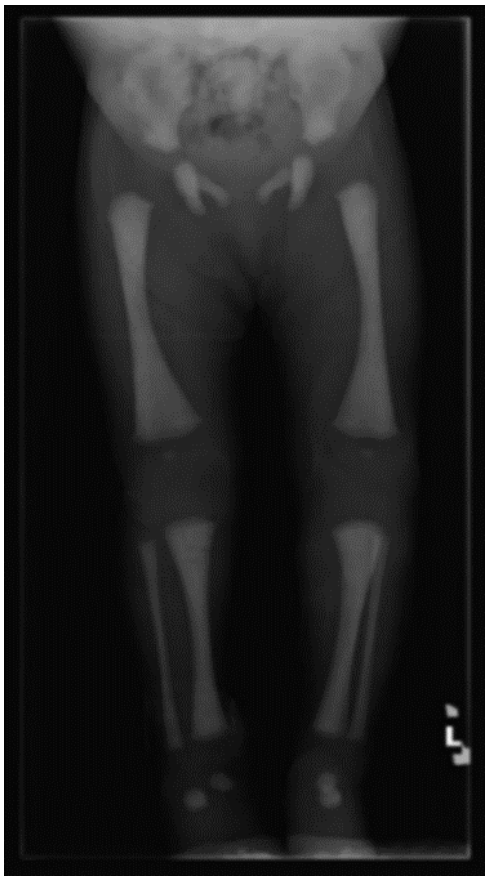

Figure 2: X-ray of the lower limb also shows diffuse osteosclerosis.

3. Discussion

Osteopetrosis is a condition characterized by bone condensation and has four subtypes. The first is MIO, which can be life-threatening if left untreated. It is the rarest and most severe type with an incidence of 1 in 250,000 newborns. The second is benign or adult osteopetrosis which is autosomal dominant, it presents later in life and is less severe. The third is intermediate osteopetrosis, which is between severe infantile and milder adult forms, it presents with variable symptoms and severity. The fourth subtype is carbonic anhydrase type II (CAII) deficiency, which causes disturbances in bone metabolism and requires specialized diagnostic and therapeutic considerations. Understanding these subtypes is crucial for accurate diagnosis and targeted interventions to address the specific needs of individuals affected by osteopetrosis [5].

The described patient was symptomatic since birth, with dysmorphic features, lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia, and failure to thrive.

Anemia and thrombocytopenia were due to continuous bone formation, thickening, and abnormal expansion affecting medullary hematopoiesis. This would lead to compensatory extra-medullary hematopoiesis, which causes hepatosplenomegaly as in the case above [6]. Investigations were done to exclude other causes of thrombocytopenia in neonates, but all were negative.

The diagnosis of osteopetrosis depends on skeletal radiology where there would be a significant increase in bone density with defective metaphyseal remodeling, and “a bone within a bone” appearance, these typical findings were seen in the patient which raised the suspicion of osteopetrosis being a strong differential diagnosis [7]. Based on the presenting history, radiographic findings, and molecular genetic test, the patient was diagnosed with MIO which has autosomal recessive inheritance [8].

Currently, HSCT is the only therapeutic intervention available causing it to be the sole opportunity for recovery. It would allow the dysfunctional osteoclasts to be substituted by functional cells, consequently, it must be done early in life before the occurrence of neurological symptoms [9]. Regarding the patient, she was not able to receive the transplant since by the time of diagnosis there was no donor found, and she already had developed neurological symptoms for which only symptomatic treatment could be offered. A similar case was reported in Taiwan in 2006, where a 2-year-old boy diagnosed with MIO at the age of 10 months received unrelated mismatched cord blood transplantation (CBT) since HSCT was not feasible due to a lack of a matching donor, the transplantation was a success. Although marrow transplant from an HLA-identical sibling or unrelated donor has a 5 year survival with a functioning graft of 50–70% [10]. However, CBT might be a feasible option in urgent cases where an identical donor is not available [11].

Radiographs play a key role in diagnosing MIO antenatally in families with a history or a tendency to have the disease, such as, genetic counseling is truly monumental in such cases. Although radiographs are essential, challenges persist in attaining definitive results during the antenatal life of the fetus. Thus, molecular diagnosis in this stage is much more desirable and accurate [12]. Early diagnosis is crucial so

that the patient before 3 months of age would undergo HSCT, which enhances neurological complications [13].

4. Conclusion

Osteopetrosis is a disease with complex underlying molecular pathogeneses causing osteoclast dysfunction. This complexity leads to the different types of diseases along with their various inheritable patterns. Infantile osteopetrosis being the most severe form, is the main cause of death of children in their first decade of life due to the suppression of the bone marrow. Morbidity and mortality vary depending on the subtype of osteopetrosis and its severity; therefore, early diagnosis and identification of the disease subtype enables the patient to receive treatment. The approach to such cases must be comprehensive and by a multidisciplinary team to address and manage the existing complications.

Statement of Ethics

The patients' parents gave their written consent to publish this case, including the publication of the images. The study complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Ethical Approval

Ethical approval was obtained from the Research Ethics Committee in Dubai Medical College and is referred to by the following: REC/DMCG/AY23-24/F 04.

Patient Informed Consent

Written patient informed consent was obtained from the patient's mother to publish the case according to any accompanied images.

Disclosure Statement

In the interest of transparency, it is important to note that Aya Mohammed Alsabbah is a family member of Mohammed Ali Alsabbah. While every effort has been made to ensure the objectivity and impartiality of the research and its reporting, we acknowledge the potential for a perceived conflict of interest due to the familial relationship between the authors. We would like to assure readers that this relationship has not influenced the integrity of the research, and all conclusions and findings presented in this case report

are based on rigorous analysis and unbiased interpretation of the data. There is no other statement to disclose.

Artificial Intelligence (AI) Disclosure Statement

This is an AI-unassisted work.

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Author Contributions

Aya Mohammed Alsabbah and Mohammed Ali Alsabbah: Wrote the manuscript. Mahmoud Ahmed Radaideh and Shafeeka Mohmed Saleh: Supervised and revised the manuscript. Rawan Ahmed Mehannae: Editing manuscript and supervised publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the author.

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