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Case Report

Malignant Infantile Osteopetrosis: A Case Report and Literature Review

Dr. Meryem Amaziane, MD[1]*, Pr. Bouchra Chkirate, MD[2]

[1]Resident in Pediatric Department 4, Children's Hospital of Rabat, Mohamed V University, Rabat, Morocco
[2]Head of Pediatric Department 4, Children's Hospital of Rabat, Mohamed V University, Rabat, Morocco

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***Corresponding Author:** Dr. Meryem Amaziane
Resident in Pediatric Department 4, Children's Hospital of Rabat, Mohamed V University, Rabat, Morocco

Abstract

Malignant infantile osteopetrosis is a rare hereditary bone disease characterized by defective bone resorption due to impaired osteoclast function or differentiation. This results in generalized osteosclerosis and leads to multiple complications including hematologic failure, neurological compression, skeletal deformities, dental anomalies, and facial dysmorphism. Diagnosis is based on a combination of clinical, biological, radiological, and genetic findings. The only curative treatment for severe forms is hematopoietic stem cell transplantation, which is most effective when performed early. New therapeutic strategies under investigation include gene therapy, immunomodulators, and targeted agents. Prognosis is influenced by the genetic subtype, age at diagnosis, and neurological involvement. Long-term multidisciplinary care is crucial to improve the quality of life of surviving patients.

Keywords: Osteopetrosis, Osteosclerosis, Osteoclast, Child.

INTRODUCTION

Osteopetrosis is a heterogeneous group of rare bone diseases characterised by a pathological increase in bone density due to a defect in bone resorption by osteoclasts [1]. Although the term suggests increased skeletal strength, this excessive density is in fact pathological, as it leads to paradoxical bone fragility and severe haematological and neurological complications, particularly in infantile forms [1].

Among these forms, malignant infantile osteopetrosis (MIO), or autosomal recessive osteopetrosis, is the most serious. It manifests itself in the first weeks or months of life, with an often-dramatic clinical picture: anaemia, thrombocytopenia, recurrent infections, facial abnormalities, progressive blindness or deafness [2]. The diagnosis is based on a combination of clinical, radiological, biological and, increasingly, genetic evidence, thanks to the identification of mutations affecting genes involved in osteoclast differentiation or function [2].

The prognosis remains poor in the absence of treatment, with high mortality before the age of five. However, haematopoietic stem cell transplantation (HSCT) has profoundly changed the course of certain forms of the disease, restoring effective osteoclast function in eligible patients [3].

This paper provides an update on this rare but serious condition, through a review of clinical, diagnostic and therapeutic data, supplemented by the observation of a paediatric case of malignant infantile osteopetrosis, illustrating the diagnostic difficulties and prognostic challenges of this pathology.

CASE PRESENTATION

We report the case of a 12-month-old female infant admitted to the pediatric department of the Children's Hospital of Rabat for macrocephaly and abdominal distension evolving since the age of six months, associated with pallor and ecchymoses.

Personal history:

The perinatal period was unremarkable. Psychomotor delay was noted, with inability to hold her head or sit by 12 months. She was unvaccinated according to the national immunization program.

Family history:

The parents were first-degree cousins. Three siblings had died in early childhood with similar presentations (psychomotor delay, macrocephaly,

hepatosplenomegaly, pallor). Two other siblings were healthy.

Clinical examination:

Overall, she was slightly hypotonic, reactive, apyretic, with pale skin and mucous membranes.

She is underweighting and short for her age, weighing 6 kg (-2 SD) and measuring 67 cm (-2 SD).

She had distinctive facial features: macrocephaly with a head circumference of 46 cm (+1SD), an open anterior fontanelle, a bulging forehead (Figure 1), sunset eyes and hypertelorism (Figure 2). Respiratory signs include intercostal retractions with bilateral snoring rales.

Abdominal examination reveals a distended abdomen (Figure 3) with hepatomegaly and a liver edge at 9.6 cm, as well as splenomegaly.

Skin examination revealed purpuric ecchymotic spots on the lower limbs and petechiae on the abdomen. Cardiac auscultation was normal.

During the ophthalmic examination, visual acuity was difficult to assess due to the patient's age. Nystagmus with bilateral strabismus and bilateral papillary atrophy were observed. It was impossible to perform a hearing test.

Figure 1: Macrocrania with a bulging forehead

Figure 2: Hypertelorism with cranial deformities

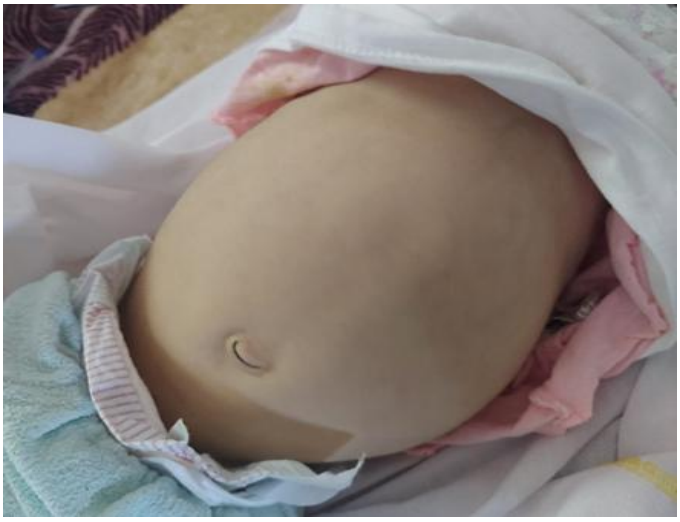

Figure 3: Abdominal distension

Laboratory findings: Hemogram showed severe anemia (Hb 4.6 g/dL), thrombocytopenia (20,000/µL), and leukocytosis (25,000/µL, lymphocyte-predominant). Liver and kidney function tests were normal. Calcium and phosphate levels were within normal limits, while parathyroid hormone was mildly elevated.

Imaging: Abdominal ultrasound showed that the liver was of normal size and that there was splenomegaly.

Standard chest X-ray showed condensed vertebral bodies, rib grilling and enlargement of the humeral metaphysis forming 'Ehrlenmeyer-flask' pattern (Figure 4). Frontal and profile X-rays of the skull revealed diffuse bone condensation and a condensed appearance of the skull base (Figure 6), orbital rims and upper jaw with a 'Harlequin mask appearance' image (Figure 5).

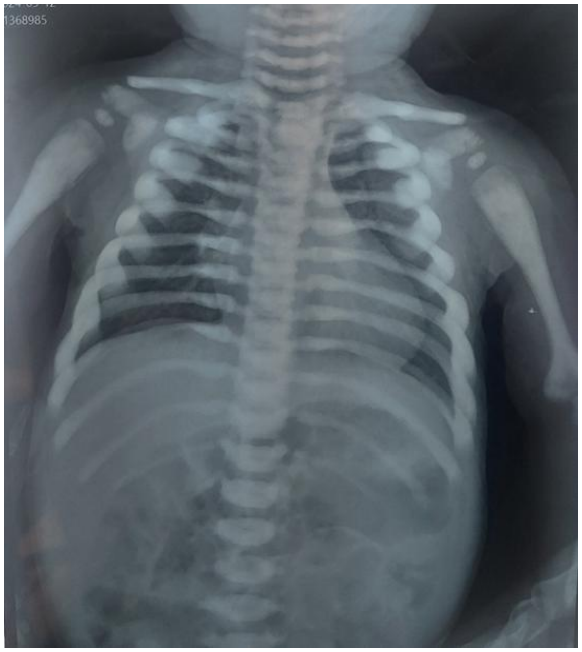

Figure 4: Condensed appearance of the vertebral bodies. Humeral metaphysis with 'Ehrlenmeyer-flask Deformity'

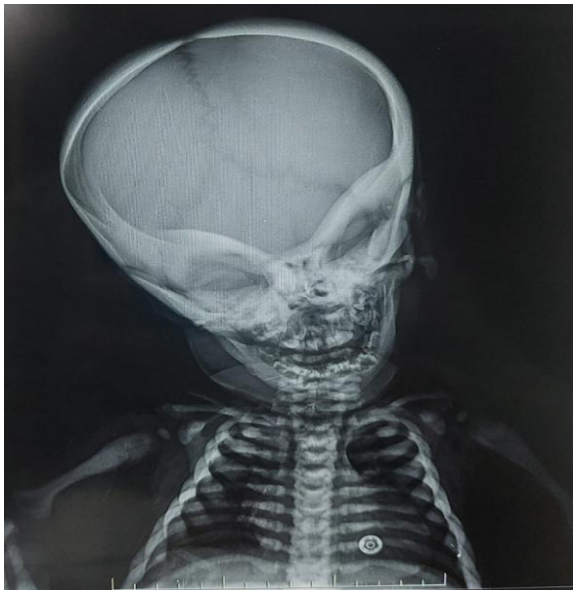

Figure 5: 'Harlequin mask appearance'

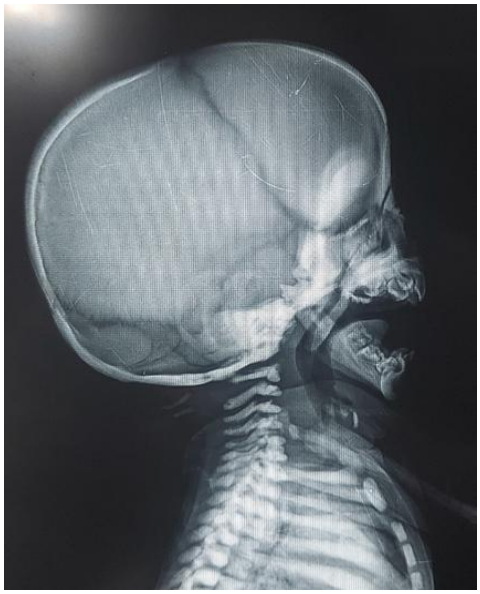

Figure 6: Condensed appearance of the base of the skull

Diagnosis and management:

Given the combination of anamnestic arguments (consanguinity of the parents and deaths among siblings with similar clinical presentations), clinical arguments (psychomotor retardation, macrocephaly, and pale skin and mucous membranes), and radiological arguments (condensed bones, enlarged metaphysis and the pathognomonic carnival mask appearance, a diagnosis of malignant infantile osteopetrosis was made.

Treatment and progression:

The patient received an initial platelet and red blood cell transfusion and was then placed on a monthly transfusion programme. She was put on amoxicillin-based antibiotic therapy due to the worsening of her respiratory symptoms.

Genetic testing was planned, but given the obvious clinical picture, the cost and the unavailability of the test in Morocco, it was not performed. Genetic counselling was provided to the family.

The patient became dependent on oxygen, making it necessary to discharge her with an oxygen concentrator for use at home.

DISCUSSION

Malignant infantile osteopetrosis (MIO) is a life-threatening disorder resulting from mutations in genes essential for osteoclast differentiation and function, most frequently *TCIRG1*, *CLCN7*, and *OSTM1* [1]. These mutations disrupt bone resorption, leading to pathological accumulation of dense but fragile bone. The autosomal recessive infantile form is the most severe, with an incidence of approximately 1 in 200,000 births [4].

Clinical Spectrum

MIO usually presents within the first year of life with pallor, recurrent infections, growth retardation, hepatosplenomegaly, and characteristic facial dysmorphism [5]. Neurological complications such as blindness, deafness, and hydrocephalus result from cranial nerve compression due to excessive bone deposition [6]. In our case, optic atrophy, strabismus, and developmental delay were prominent. These features are consistent with the literature, which emphasizes early neurological compromise as a major determinant of prognosis [6].

Diagnosis

Diagnosis combines clinical, radiological, and laboratory features. Radiographs typically show diffuse osteosclerosis, “sandwich vertebrae,” and metaphyseal flaring (“Ehrlenmeyer-flask” pattern) [7,8]. Skull radiographs may reveal the “Harlequin mask” appearance, pathognomonic for infantile osteopetrosis [7]. Laboratory investigations often demonstrate pancytopenia due to marrow space obliteration. Genetic testing, although not always available in low-resource settings, is increasingly considered the gold standard for confirming diagnosis, establishing genotype–phenotype correlation, and determining eligibility for HSCT [9].

Differential diagnosis

Several sclerosing bone dysplasias may mimic osteopetrosis, including pycnodysostosis, hypoparathyroidism, fluorosis, and Pyle’s metaphyseal dysplasia [10]. Differentiating these entities requires careful integration of radiographic, biochemical, and sometimes genetic data [11].

Treatment

HSCT remains the only curative treatment for MIO caused by mutations affecting osteoclast function. It restores normal osteoclastogenesis by providing healthy donor-derived hematopoietic cells. The best outcomes are observed when HSCT is performed within the first six months of life, before irreversible neurological damage occurs [12]. Unfortunately, in our patient, HSCT was not possible, and supportive care consisting of transfusions, antibiotics, and oxygen therapy was provided.

Supportive care is crucial and includes transfusions for anemia and thrombocytopenia, calcium and vitamin D supplementation for hypocalcemia, management of infections, and orthopedic and dental follow-up [13]. Emerging therapies, such as interferon-γ1b, have shown potential to improve hematopoiesis and reduce infections, although results remain modest [13]. Gene therapy approaches, including lentiviral correction of *TCIRG1* mutations, have shown encouraging preclinical results and may represent a future therapeutic option [14].

CONCLUSION

Malignant infantile osteopetrosis is a rare but life-threatening disorder with devastating hematologic and neurologic complications. Early recognition is crucial to initiate supportive care and evaluate the possibility of curative HSCT. Our case illustrates the diagnostic challenges and poor prognosis in resource-limited settings, highlighting the importance of early genetic counseling and the need for accessible therapeutic innovations.

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Ethical Approval: Our institution does not require ethical approval for reporting individual cases or case series

Informed Consent: Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article

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