



Malignant Osteopetrosis, a Rare Cause of Bicytopenia in Infants: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author KLO designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AR and AH managed the analyses of the study. Authors RA and AA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1330956

Editor(s):

(1) Dr. Mohamed Essa, Sultan Qaboos University, Oman.

Reviewers:

(1) Mohammad Ayati Firoozabadi, Tehran University of Medical Sciences, Iran.

(2) Bruno Chrcanovic, Malmö University, Sweden.

(3) Ali R. Al-Khatib, University of Mosul, Iraq.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/68312>

Received 12 March 2021

Accepted 24 May 2021

Published 08 June 2021

Case Report

ABSTRACT

Osteopetrosis is an autosomal metabolic bone disease caused by a functional abnormality of the osteoclasts. Two main forms exist, the dominant benign form and the recessive malignant form. We describe in our patient the recessive malignant form retained according to all the clinical, biological and especially radiological criteria. We also report in this work the elements of description of the disease in the literature in comparison with the data of our patient, which allows us to emphasize the severity of the ocular and bone damage requiring an early marrow transplant which alone seems to cure the disease.

Keywords: Osteopetrosis; marble bone; bicytopenia; carnival wolf; transplantation.

1. INTRODUCTION

Osteopetrosis, or "marble bone disease", is a rare metabolic bone disease due to a rare and

functional abnormality of osteoclasts, cells of hematopoietic origin of the macrophagic lineage [1]. The disease is characterized by spontaneous and repetitive bone fractures, due to fragility of

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the bone tissue and by filling of the hematopoietic medullary cavities with sclera [2].

We report in this work a case of osteopetrosis in its autosomal recessive "malignant" form, diagnosed in the pediatric department of the Mohammed V military hospital in Rabat.

2. CASE REPORT

A, 2-month-old male infant, 2nd of 2 siblings, of non-consanguineous parents resulting from a follow-up pregnancy carried to term, upper delivery with good adaptation to extra-uterine life with an imprecise birth weight, having received BCG and anti Hepatitis B vaccine as well as a dose of vitamin D, under exclusive breastfeeding.

A was hospitalized twice in a provincial hospital. The first at day 39 for a cutaneous-mucous subicterus on a pale background, for which he was transfused with 1 red blood cell pellet following an anemia at 6 g / dl associated with a thrombocytopenia objectified on the CBC, and the second following the rapid onset of pallor and difficulty in breathing, then a biological, radiological assessment, genetic consultation and ophthalmological examination were performed. The infant was put on CYMEVAN for 07 days, then at the request of the parents they were sent at 2 months of life in our department for diagnostic and therapeutic management.

The clinical examination on admission found an infant in fairly good general condition, with a staturo-weight loss at -2DS, a macrocrania at + 2DS, a facial dysmorphism with a bulging forehead, retrognathism and low implanted ears (Fig.1) ; the ENT examination revealed gingival enlargement with a pointed palate. Neurologically, the infant presents with axial hypotonia, with bilateral horizontal nystagmus and sunset eyes. Pleuropulmonary examination revealed the presence of a costal string, a discreet intercostal indrawing with bilateral snoring groans on auscultation (Fig. 2). Abdominal examination showed the presence of splenomegaly through 2 fingers and hepatomegaly at 9 cm. The remainder of the physical examination was otherwise normal.

The initial assessment objectified normochromic normocytic anemia at 7.5 g / dl, with thrombocytopenia at 44,000, hypophosphatemia at 21 mg / l, alkaline phosphatase elevated at 1801 IU / l, without hydro-electrolyte disturbances, with a normal urinary ionogram;

viral and TORSCH serologies were also negative. The medullogram showed rare megakaryocytes with the absence of overload cells. Ophthalmologic examination revealed divergent strabismus with atrophic and hypoplastic pale papillae. The radiological assessment, in particular cerebral CT and APT, was normal apart from a homogeneous hepatosplenomegaly; the standard radiography objectified a densification of the costal arches, an increase in the bone density involving the cortical and spongy bone with complete disappearance of the cortico-medullary limit with a metaphyseal widening of the long bones achieving the "Erlenmeyer flask deformity" aspect or "in club" (Figs. 3,4). The x-ray of the skull showed a "carnival wolf" appearance (Fig. 5).

In view of the typical clinical, biological and especially radiological signs, the diagnosis of recessive malignant osteopetrosis was made for our patient.

The patient was transfused twice. In addition, a bone marrow transplant discussion is underway and HLA typing was therefore requested for his sister.

3. DISCUSSION

Osteopetrosis was first described in 1904 by the German radiologist Heinrich Albers-Schönberg (1865-1921) in a 26-year-old young man with multiple fractures of the femur [3]. In 1926, it was also called marble bone disease by Karchner because of the condensed radiological appearance of the bone tissue. In 1993, only 300 cases were described in the literature according to Shapiro [4,5]. In the 1960s, two clinical forms were listed: an autosomal dominant "benign" form and an autosomal recessive malignant form which was described in our patient. This has a poorer prognosis, usually fatal during the first years of life without treatment [6].

The hereditary forms of human osteopetrosis all seem to be transmitted in an autosomal, dominant or recessive fashion, and all have as a common denominator a bone resorption disorder linked to osteoclasts [7] Several mutations have been sought and found in patients with the disease. osteopetrosis: Mutations in the C1CN7 genes located on chromosome 16p13.3 found mainly in benign osteoporosis type II and more rarely in the malignant form. Other mutations have been detected such as TC1GR1 and GL or OSTM1 especially in malignant infantile osteopetrosis and sometimes in benign type II osteopetrosis [7,8,9].

More recently the involvement of an inactivating mutation in the gene encoding RANKL has been described, leading to a decrease in the number

of osteoclasts. [9]. For our patient who has the recessive malignant form, genetic research was not carried out for lack of means. (Table 1).

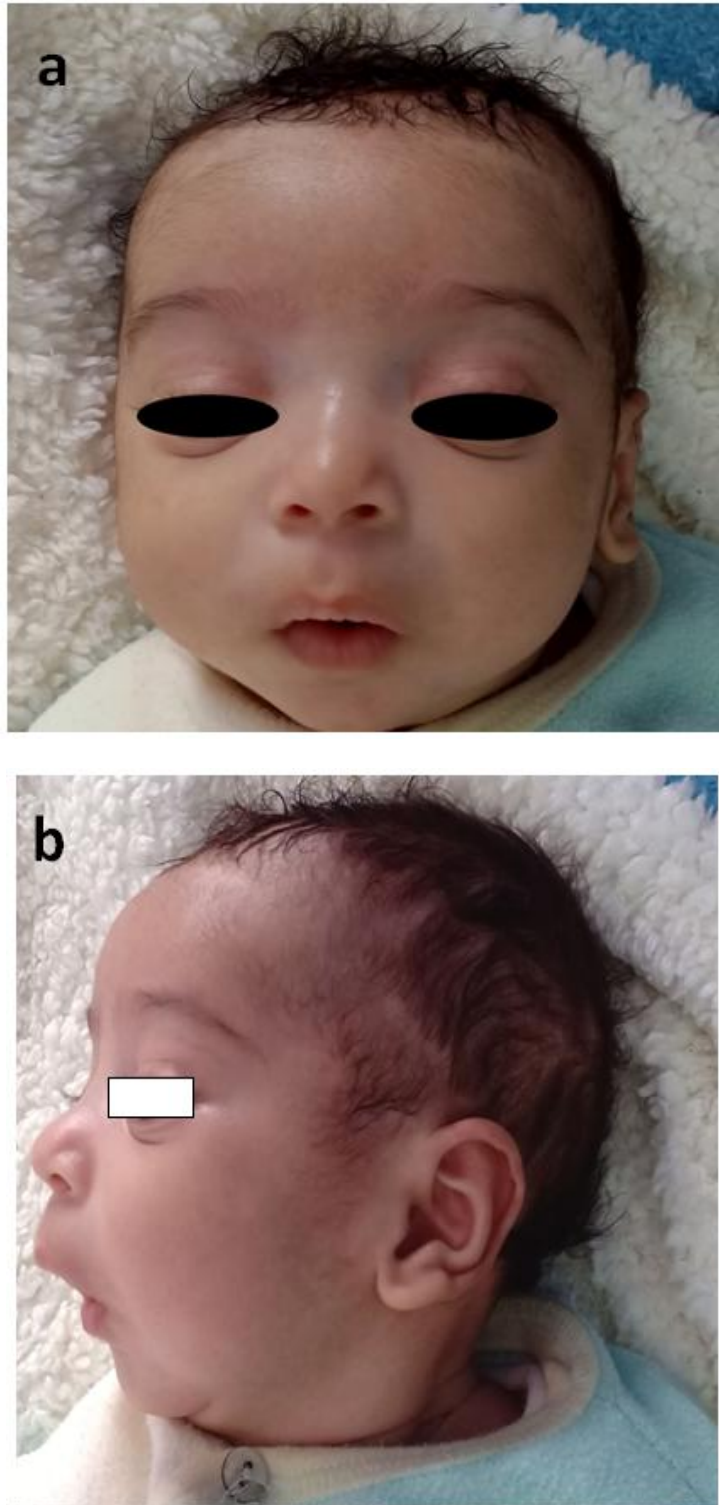


Fig. 1. Aspect of the face seen from the front (a) and profile (b) showing the frontal bulge and micrognathism



Fig. 2. Thorax with appearance of a costal chain



Fig. 3. AP chest x-ray showing bone densification of the ribs and upper limb bones

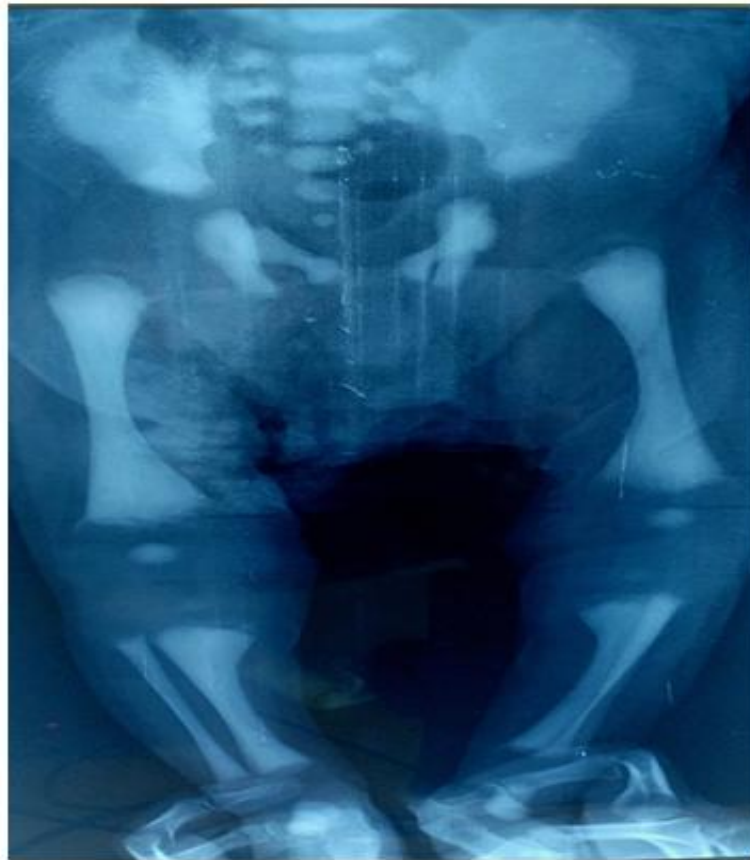


Fig. 4. X-ray of the lower limbs showing an increase in the bone density involving the cortical and spongy bone with complete disappearance of the cortico-medullary limit with a metaphyseal widening of the long bones

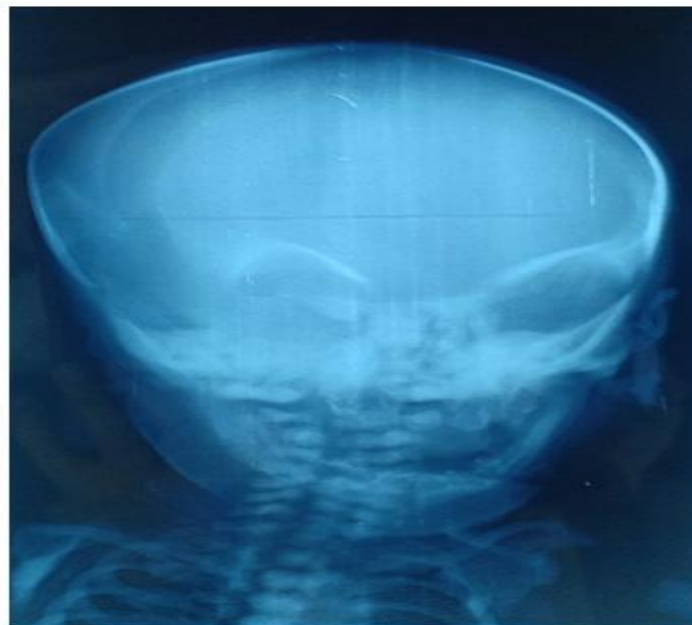


Fig. 5. Frontal x-ray of the skull showing osteocondensation of the orbital edges and the upper jaw with a "spectacle" or "carnival wolf" appearance

Table 1. Main clinical manifestations found in 50 cases of malignant osteopetrosis, according to Johnston et al [17]

Clinical signs	Frequency%	Our patient
Optic atrophy	78	Present
Splenomegaly	62	Present
Hepatomegaly	48	Present
Delay in height and weight	36	Present
Frontal prominence	34	present
Fractures	28	None
Deafness	22	Undetermined
Enlargement of the cranial perimeter	22	Present
Osteomyelitis	18	NONE
Lymphadenopathy	18	NONE
Génu valgum	16	NONE
Facial paralysis	10	NONE
Chest deformities	8	Present

This malignant form has a frequency of occurrence which is low. It is between 1 / 200,000 and 1 / 300,000 births. Nevertheless, the risk is higher in consanguineous parents, up to 20% (6.9), with a particularly high incidence in Costa Rica with 3.4 / 100,000 births on average [10], although parents of our patient are not consanguineous.

Clinically, the diagnosis is most often made during the first months of life; it is most often an association of pathological fractures of the transverse or oblique type, a delay in height-weight development found in our patient, and frequent infections of the upper aero-digestive tract, often of viral origin. Sometimes it is manifested by nasal obstruction due to insufficient development of the paranasal sinuses [4,11]. Patients generally present with a pale complexion, sometimes with petechial or ecchymotic purpura [12]. Signs of rickets may be associated with a slight curvature of the lower extremities, the presence of a costal chain with a narrow thorax and epiphyseal bulges.

The affected children often present an enlargement of the skull with a frontal prominence, during the first year of life, giving these children a characteristic facial morphology. Several cases of hydrocephalus have been reported [13]. This leads to macrocephaly, a consequence of the petrification of the base of the skull and insufficient return circulation. Hepato-splenomegaly is constant and precocious, and is also found in our patient.

Most cranial nerves can be compressed by the progressive obliteration of the foramina at the base of the skull. We can note:

- * Visual disturbances that appear between the 2nd and 4th month of life, in the form of optic nerve atrophy with papillary edema, horizonto-rotatory nystagmus, mobility of the eyeballs associated with asynergy and pupillary tremor, with a decrease in visual acuity which is often irreversible.
- * Hearing disorders in particular deafness and reduced hearing acuity which are frequent in patients with osteopetrosis, linked in particular to compression of the vestibulo-cochlear nerve. 78% of patients would have hearing loss [14].

Oral and dental abnormalities are still present. This is most often a delayed eruption, agenesis, dental aplasia, enamel hypoplasia, increased sensitivity to tooth decay [15,16], disruption or delayed tooth eruption, or dental malocclusion [17].

In the autosomal recessive osteopetrosis that we describe in our patient, Fractures are a common complication. They mainly affect the long bones in their diaphyseal, metaphyseal or epiphyseal portion [4]. On the psychomotor level, there is most often a delay as well as other disorders such as agenesis of the corpus callosum or neuroaxonal dystrophy.

In addition to clinical signs, the diagnosis of osteopetrosis in its autosomal recessive form is based on radiological workup data; indeed it is a diffuse osteocondensation affecting the cortical (hyperostosis) and the spongy tissue (osteosclerosis), with an aspect of "bone in the bone" (bonewithin-a-bone [9] giving a club aspect. at the level of the metaphyseal region of the long bones ("Erlenmeyer-flask deformity").

The vertebrae are dense with a “diabolo” or “sandwich” aspect of the vertebral bodies by opacification of the upper and lower edges. The aspect is characteristic. The image is said in “carnival wolf”, reflecting a massive condensation of the base of the skull, the orbital edges and the upper jaw. This aspect was also found in our patient.

Bone scintigraphy as well as bone computed tomography can provide more details on the location and size of the lesions found, as well as looking for their complications such as osteomyelitis or non-visible fractures [4]. The indications for bone scintigraphy are limited in the setting of osteopetrosis. It is useful for confirming the diagnosis of osteomyelitis or an occult fracture.

MRI can be used as an indicator of bone marrow activity. The malignant form is characterized by a complete absence of signal for the vertebral bodies which therefore appear black, and contrast with the adjacent intervertebral discs. She finds further interest in evaluating the effectiveness of bone marrow transplantation by showing the recolonization of medullary cavities by the graft [4,18]. Otherwise, these two examinations were not carried out on our patient.

Ophthalmologic examination shows papillary edema without reduction in visual acuity, which gradually deteriorates by compression of the optic nerve [19]. In our patient, the papillae were atrophic and hypoplastic from the outset. Visual evoked potentials should be performed regularly in patients with osteopetrosis. Latency is a sign of nerve compression often seen before imaging.

Biologically, hypermineralization of the bone results in almost complete obliteration of the medullary ducts and suffocation of the hematopoietic marrow; bicytopenia is most often noted, as in our patient, or pancytopenia (anemia, neutropenia and thrombocytopenia) secondary to bone marrow hypoplasia or aplasia [20], most often managed by repeated transfusions. Without radical treatment, the progressive worsening of blood disorders can be fatal.

According to Saphiro, the phospho-calcium balance is normal except in severe forms of the disease; in our patient we noted a normal calcemia contrasting with a very high PAL. Secondary hyperparathyroidism with high levels of PTH, and calcitriol can sometimes be

observed indicating a calcium deficiency necessary for chondroid and osteoid mineralization leading to secondary rickets. [4,11].

A bone biopsy, performed mainly from the iliac bone, can confirm the diagnosis showing an increased number of osteoclasts, or a change in the brush border. However, it does not usually seem necessary for the diagnosis [5,21,22].

4. CONCLUSION

Osteopetrosis is a rare condition. The diagnosis is made on the basis of clinical and radiographic arguments. To date, there is no specific treatment, apart from that of complications of the disease such as transfusion, antibiotic therapy, vitamin therapy, orthopedic treatment, etc., except for bone marrow transplantation in malignant forms which appear to be very expensive. (2.5) We also emphasize the value of antenatal screening for taking early disease burden. For our patient, the management is symptomatic, and consists of an iterative transfusion and management of infectious complications. The marrow transplant is being discussed in our patient.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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