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Acute maxillary osteomyelitis in a patient affected by malignant infantile osteopetrosis: report of a rare case of survival

Osteomielite maxilar aguda em paciente acometido por osteopetrose infantil maligna: relato de um caso raro de sobrevida

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ABSTRACT: Infantile malignant osteopetrosis (IMO) is the most severe form of osteopetrosis (OP), which is a group of rare and hereditary disorders that affect the human skeleton by increasing bone density. One of its main consequences is bone marrow invasion by bone sclerosis, leading to progressive bone marrow failure and aplasia, which predisposes to several infections, including osteomyelitis. It is a disease with 99% mortality by the age of ten and an incidence of 1:500,000 live births. The only available treatment is early bone marrow transplantation. The case report describes a 14-year old male patient, diagnosed with IMO since childhood and admitted to the emergency room of the Albert Sabin Children's Hospital with right facial edema and local pain that started one month before admission. Acute osteomyelitis of the maxilla was diagnosed based on physical examination and complementary tests. In addition to the current condition, the patient had several complications from his underlying disease. He developed sepsis during hospitalization, used antibiotic therapy, and was discharged after one month for home palliative care.

Keywords: Osteopetrosis/complications; Survival; Osteomyelitis; Adolescent.

RESUMO: A osteopetrose infantil maligna (OIM) é a forma mais grave de osteopetrose (OP), que é um grupo de desordens raras e hereditárias que acometem o esqueleto humano, tornando-o mais denso. Uma das suas principais consequências é a invasão medular por esclerose óssea, levando a progressiva insuficiência medular e aplasia, o que predispõe a inúmeras infecções graves, incluindo a osteomielite. É uma doença que possui mortalidade de 99% até os dez anos de idade, com incidência de 1:500.000 nascidos vivos, cujo único tratamento disponível é o transplante de medula óssea precoce. O caso relatado é de um paciente do sexo masculino, 14 anos, com diagnóstico de OIM desde a infância, admitido na emergência do Hospital Infantil Albert Sabin com edema e dor facial à direita de início há um mês. Com base no exame físico e nos exames complementares foi diagnosticada osteomielite maxilar aguda. Além do quadro atual, o paciente possuía diversas sequelas da sua doença de base. Evoluiu com sepse durante a internação, fez uso de antibioticoterapia, e obteve alta hospitalar após um mês para cuidados paliativos domiciliares.

Descritores: Osteopetrose/complicações; Sobrevida; Osteomielite; Adolescente.

Study conducted at the Albert Sabin Children's Hospital

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INTRODUCTION

Osteopetrosis (OP) refers to a group of rare hereditary disorders that affect the human skeleton by increasing bone density[1]. Mutations in more than 12 genes have been identified as responsible for these disorders, which are more common in children of consanguineous parents[2,3].

The exact worldwide incidence of OP is unknown, but its malignant form is believed to affect one person in every 100,000 to 500,000 of the general population. The disease has a wide spectrum of clinical presentation and can be classified into three main types: infantile malignant OP, intermediate OP and adult OP[4]. Infantile malignant OP is the most severe form of the disease and its symptoms usually start in the first months or first years of life, with pancytopenia and splenomegaly[5]. The survival time of these children is very short. About 70% of them die before the age of six, and up to 99% before the age of 10[6]. For these children, early bone marrow transplantation is the only possible curative treatment[7].

The main cause of hospitalization and death from the disease is progressive bone marrow failure, caused by bone sclerosis that gets to the bone marrow and leads to aplasia[8]. Thus, death in the first decade of life is usually associated with infection secondary to neutropenia, hemorrhage secondary to thrombocytopenia or severe anemia[9].

In addition to several hematological and neurological complications of the disease, an infection commonly associated with OP is facial osteomyelitis, which usually affects the mandible and, more rarely, the maxilla. It usually occurs due to tooth extraction or poor condition of the teeth and is associated with high morbidity[10].

The present study aims to report the case of a 14-year-old adolescent boy with infantile malignant osteopetrosis and several complications of the disease, including a case of acute osteomyelitis of the maxilla.

CASE REPORT

Adolescent, 14 years old, male, born in a small city in the state of Ceará, son of consanguineous parents, followed at the oncology and hematology outpatient clinic of the Albert Sabin Children's Hospital (HIAS) due to bone marrow failure secondary to infantile malignant osteopetrosis (IMO). Patient arrived at the emergency department of the HIAS with a history of a right facial edema with local pain and no fever, which started one month before admission. He then sought medical attention in his city and was prescribed oral antibiotics. Ten days before the admission, symptoms worsened, and the patient went to the HIAS at the city of Fortaleza.

The medical history revealed that the patient had anemia since he was two months old and had a late diagnosis of IMO, at age four. The parents reported that they had another child who died from the same disease a few years after being born. The patient had previous hospitalizations for complications secondary to bone marrow failure. In 2012, the patient had an enucleation of the right eye that required a tracheostomy due to difficult orotracheal intubation during the surgical procedure. Regarding life habits, the mother reported that she found it difficult to clean the child's oral cavity.

On admission, the patient was pale (2/4+), afebrile, active, macrocephalic, blind, with bilateral hearing impairment, tachypneic, tachycardic, tracheostomized, with a right facial edema in the maxillary region, (Figure 1A), showing signs of inflammation, with an enucleation scar on the right eye and exophthalmos in the left eye. The cardiac and pulmonary auscultation did not reveal any abnormalities. Abdomen was globular and hard, with palpable hepatosplenomegaly below the umbilical scar (Figure 1B).

Laboratory tests showed anemia (hemoglobin of 8.1 g/dL), thrombocytopenia (35.390 platelets/mm³), lactate dehydrogenase (LDH) of 1071 U/L, alkaline phosphatase of 131 U/L normal renal function and normal electrolytes (Table 1). It was not possible to obtain a precise image of the lung parenchyma on the chest X-ray due to the high bone density in the rib cage (Figure 2).

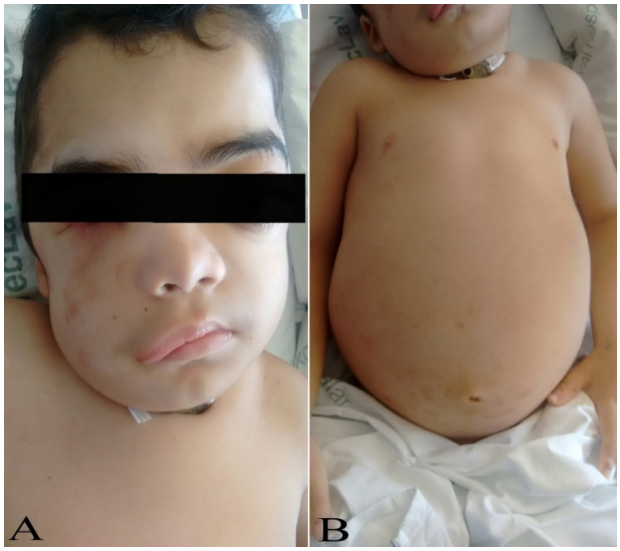

Figure 1 – Findings on physical examination. A) Right facial edema in the maxillary region. B) Hard, globose abdomen with palpable hepatosplenomegaly up to the right iliac fossa

Table 1 – Laboratory tests during hospitalization

Tests	1st day of hospitalization	12th day of hospitalization	20th day of hospitalization	Reference values
Hemoglobin	8.1 g/dL*	7.3 g/dL*	8.2 g/dL*	12-16 g/Dl
Leukocytes	5.630/mm³*	2.660/mm³*	4.312/mm³*	4.500-13.500/mm³
Neutrophils	2.983/mm³*	1.197/mm³*	2.630/mm³*	4.300-5.300/mm³
Platelets	35.390/mm³*	20.440/mm³*	34.130/mm³*	150.000-440.000/mm³
Reticulocytes	5.56%*	-	-	0.5-2.5%
Albumin	3.4 g/dL*	-	-	3.5-5 g/dL
C-reactive protein		192 mg/dL*	-	<10 mg/dL
Sodium	139 mEq/L	-	123 mEq/L*	135-145 mEq/L
Potassium	3.8 mEq/L	-	3.7 mEq/L	3.5-5.5 mEq/L
Calcium	9.25 mg/dL	-	6.25 mg/dL*	8.5-10.5 mg/dL
Magnesium	1.8 mg/dL*	-	1.1 mg/dL*	1.9-2.5 mg/dL
Chlorine	-	-	88 mEq/L*	97-106 mEq/L
Phosphorus	5.4 mg/dL	-	2.7 mg/dL	2.5-5.6 mg/dL
Alkaline phosphatase	131 U/L	135 U/L	-	65-300 U/L
LDH	1071 U/L*	1177 U/L*	1019 U/L*	230-450 U/L
Serum creatinine	0.2 mg/dL*	-	0.2 mg/dL*	0.6-1.3 mg/dL
Urea	27 mg/dL	-	-	5-40 mg/dL

Notes: *: Tests with alterations; LDH: lactate dehydrogenase

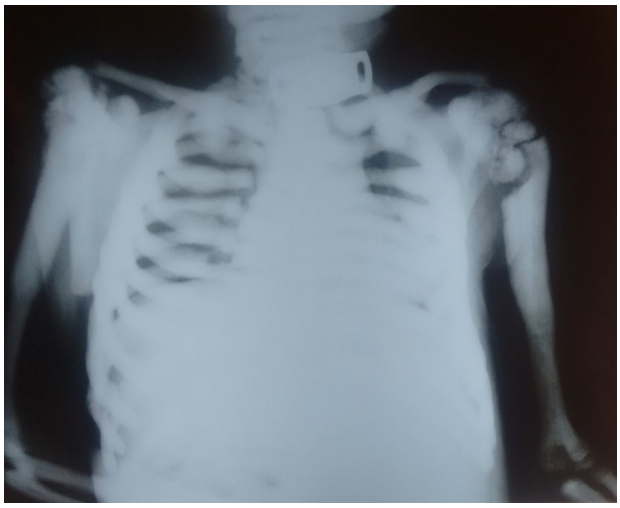

Figure 2 – Chest X-ray showing severe sclerosis of ribs

It was decided to start the patient on intravenous antibiotic therapy with oxacillin and ceftriaxone and to admit him to the general pediatric ward. After two days, patient developed pancytopenia (Hb: 6.6 g/dL; 3394 leukocytes/mm³ and 27.390 platelets/mm³), bleeding from the tracheal tube and epistaxis. Red blood cells and platelets were transfused. Contrast-enhanced cranial tomography showed a subcutaneous edema on the right side of the face and severe sclerosis in the facial bones due to the underlying disease, which made it impossible to define the area of osteomyelitis (Figure 3). Dexamethasone was applied for seven days and led to partial improvement of edema and pain.

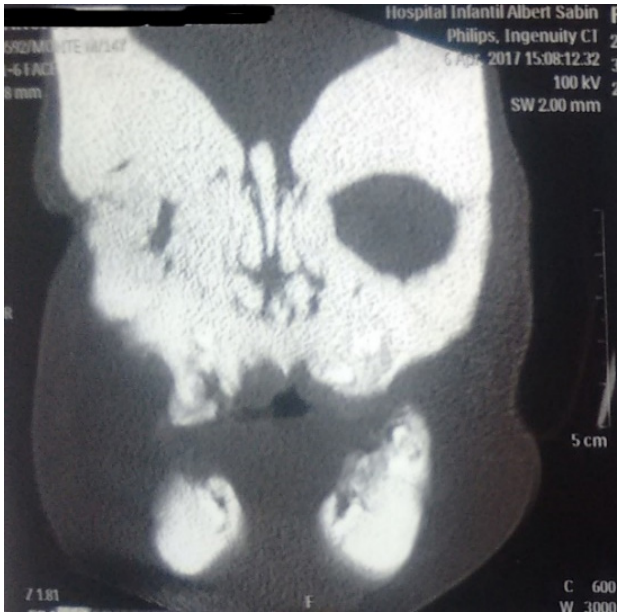

Figure 3 – Contrast-enhanced tomography of the face showing right subcutaneous edema and bone sclerosis in the face

The oral and maxillary surgery team confirmed the diagnosis of osteomyelitis of the maxilla when observing that the oral cavity showed an inflammatory process, which created an infection gateway next to a defective tooth

eruption in the right maxilla (Figure 4). The proposed approach was to continue antibiotic therapy and clean the oral cavity, as surgical procedures were not indicated due to the high risk of hemorrhage.

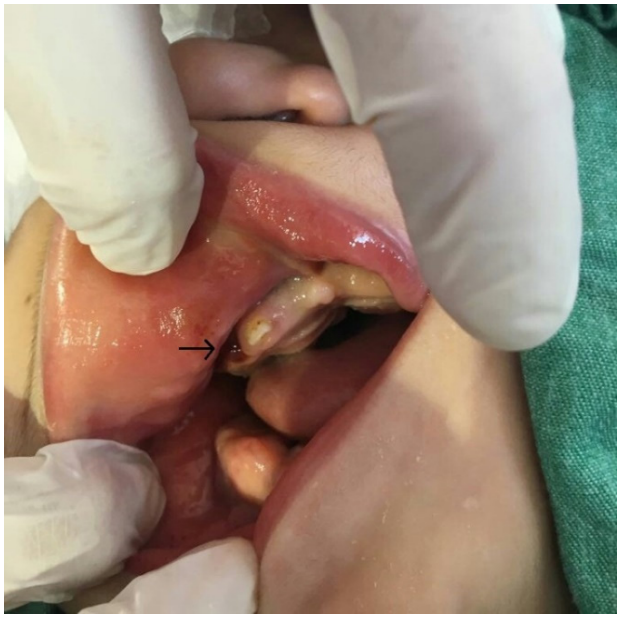

Figure 4 – Image showing the lack of teeth eruptions in almost the entire oral cavity. Arrow showing probable infection gateway, next to the defective tooth eruption in the right maxilla

Around the twelfth day of hospitalization, the patient started to develop diarrhea, daily fever spikes, tachypnea, tachycardia, worsening of general condition and desaturation, requiring supplemental oxygen 35% through a Venturi mask. He also became drowsy and hypoactive. The antimicrobial spectrum was then expanded with vancomycin and cefepime. Due to persistent thrombocytopenia, bleeding from the tracheal tube and epistaxis became more frequent, but with small amounts. The oncology and hematology service recommended blood transfusion only if there were a large volume of bleeding. The family was informed of the clinical condition, the underlying disease and the prognosis of the patient, and asked not to be transferred to the ICU. The patient progressed with worsening of general condition, water-electrolytic imbalance, increased LDH (1019 U/L), serum sodium of 123 mEq/L, calcium of 6.2 mg/dL, chlorine of 88 mEq/L and magnesium of 1.1 mg/dL (Table 1). He was then referred to an isolation ward at the Pediatric Cancer Center (CPC), where he would have greater support for palliative care. After approximately one month of hospitalization and broad-spectrum antibiotic therapy, improvement of sepsis was achieved, and the patient was discharged from the CPC to be followed up on an outpatient center for palliative care.

DISCUSSION

Osteopetrosis is a rare hereditary disease with a wide spectrum of presentation, which includes a benign autosomal dominant form that manifests only in adulthood, and an infantile malignant form, with autosomal recessive inheritance and a high rate of morbidity and mortality[4].

The case report describes a 14-year-old adolescent with the most severe malignant form of the disease, which has an overall incidence of around one patient for every 250,000 to 500,000 live births[4,11]. This form of the disease usually starts in the first months after birth, with anemia and splenomegaly. The patient studied had a survival time longer than expected. According to previous scientific reports, these patients have a short life expectancy, and 99% of them die by 10 years old[5,6]. The patient's parents had two important risk factors that are cited in the literature: they were first cousins and had another child who died from the same disease within the first years of life[12].

The patient arrived at the Albert Sabin Children's Hospital (HIAS) with a complaint of a right facial edema, inflammatory signs and local pain. The physical examination of the oral cavity showed a focus of infection and inflammation in the right maxilla, not involving the mandible. This finding corroborated the diagnosis of one of the main acute complications of osteopetrosis, osteomyelitis of the mandible or, less frequently, of the maxilla, as evidenced by a review of 47 cases of facial osteomyelitis in patients with osteopetrosis, which found that only 27.7% of the cases were limited to the maxilla[13].

The main risk factors in this context are tooth extraction or poor condition of the teeth. As there is a decrease in the number of leukocytes and a venous insufficiency in the bones, patients with OP tend to develop infection in the bone tissue, which may progress to osteonecrosis[10].

The adolescent had a defective tooth eruption and had never had a tooth extraction, but his mother reported poor hygiene of the oral cavity because the patient did not cooperate with this procedure, which in fact may have predisposed to osteomyelitis.

Contrast-enhanced tomography of the face did not contribute to the diagnosis, due to dense bone sclerosis that made it difficult to define the area of osteomyelitis.

The most common etiologic agent in osteomyelitis of the maxilla is Staphylococcus aureus, followed by hemolytic Streptococcus and Pneumococcus and some gram-negative bacteria. However, the initial treatment with oxacillin and ceftriaxone did not provide clinical improvement in the case reported, which then required a broad antimicrobial spectrum with vancomycin and cefepime. It is important to remember that antibiotic therapy does not have good healing rates among these patients, as the increased bone density makes it difficult

for substances to reach the infection site. Thus, the best treatment would be surgery to remove the infection focus[14].

As the laboratory data indicated an advanced state of the disease, that is, platelet counts of less than 30,000 per mm³, epistaxis and bleeding through the tracheal tube, the oral and maxillary surgical team of the HIAS suggested maintaining the intravenous antibiotic therapy, despite it not being the standard treatment, and surgical procedures were contraindicated[15].

In addition to the predisposition to osteomyelitis, there are many chronic complications of the disease[16]. The key factor in osteopetrosis is the lack of activity of osteoclasts (cells responsible for bone resorption), which are inactivated by genetic mutations. As osteoblasts continue their physiological role, an exaggerated growth of bone mass and the consequent sclerosis of the bones lead to the various signs and symptoms of the disease[17].

The main consequence of increased bone density is bone marrow failure, which leads to pancytopenia and extramedullary hematopoiesis, with subsequent development of hepatosplenomegaly[15]. In a more advanced stage, the patient may develop bone marrow aplasia, and die within the first decade of life, usually from infections secondary to neutropenia, bleeding secondary to thrombocytopenia or severe anemia[9].

Physical examination showed several factors that are common to the disease and compatible with those reported in other articles: macrocephaly, exophthalmos, eye enucleation, tracheostomy due to difficult orotracheal intubation and massive hepatosplenomegaly[18]. Paradoxically, these patients may also have bone fragility, which increases their predisposition to fractures, choanal stenosis and respiratory and eating difficulties[19]. Neurological manifestations are also common in this context, due to the obstruction of the foramina, through which the cranial nerves and some important blood vessels pass[20]. Blindness, deafness, facial paralysis and hydrocephalus are some of these manifestations[1]. The patient in this study was blind and had bilateral hearing impairment.

The diagnosis of OP depends mainly on radiographic and laboratory tests[16]. Images show generalized sclerosis of bones, as evidenced by the chest X-ray and tomography of the face, thickened calvarium, increased medullary density leading to a "bone-within-bone" appearance, among others radiological changes[11].

Another typical aspect of the diagnosis of OP is a laboratory test showing pancytopenia, increased LDH and alkaline phosphatase, hypocalcemia and possible reduction in immunoglobulin[19]. The patient had an LDH of 1071 U/L, severe pancytopenia, platelets of 27,390 per mm³ and hypocalcemia of 6.2 mg/dL, caused by a deficit in bone resorption[11].

Regarding the treatment of IMO, the only therapy that can change the course of the disease is bone marrow transplantation (BMT), which can increase patient survival, provided it is done very early and through a donor as compatible as possible, preferably one with identical HLA[7,20]. However, BMT involves several risks and a large number of patients will still develop sequelae despite of treatment[21]. The patient in this study, despite having anemia since the age of two months, had a late diagnosis of OP, due to socioeconomic problems common to a lot of Brazilians. Life in small cities often hinders access to tertiary health centers, where the majority of specialists are. Therefore, this report also aims to alert pediatricians and general practitioners to the existence of this rare disease and to the need to make an early diagnosis.

CONCLUSION

Although rare, IMO has high scientific relevance, as it is associated with high morbidity and mortality and it is a source of physical and emotional stress for family members. This case report showed an important acute complication, osteomyelitis of the maxilla, caused by poor dental hygiene in a patient with predisposition to this type of infection. Therefore, it is necessary to disclose the existence of this rare disease, so that the diagnosis can be made early and complications can be avoided.

Contribution of the authors: *Lobo BLV*: contributed with the conception, design, research, analysis and interpretation of data and writing of the manuscript; *Dias NFF*: contributed with the research, analysis and interpretation of data, elaboration of images and writing of the manuscript; *Lemos, MLC*: contributed with the design, critical review and final approval of the manuscript; *Albuquerque LC*: contributed with the design, critical review and final approval of the manuscript

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