Infantile Malignant Osteopetrosis: Report of 2 Cases With Osteomyelitis of the Jaws

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ABSTRACT

Infantile malignant osteopetrosis (IMO) is an uncommon autosomal recessive disease characterized by dense, brittle, sclerotic, radiopaque bones, which generally results in neurological and hematological abnormalities. In general, IMO is fatal, as patients fail to grow and expire due to complications of the disease such as severe chronic anemia, bleeding, and/or infections. In children with IMO, the development of the dentition is seriously disturbed. Patients with infantile osteopetrosis have a variety of signs and symptoms, including osteomyelitis of the jaws, which frequently and generally resists treatment. Infections may eventually become lethal; hence, jaw infection control is an important aspect of the disease for dentists and oral surgeons to consider. The purpose of this case report was to present 2 rare cases of pediatric patients (one of them died due to respiratory failure at 10 years old) diagnosed with osteopetrosis complicated by osteomyelitis of the jaw. (J Dent Child 2012;79(2):93-9)

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Osteopetrosis was first reported by Albers-Schönberg in 1904 as delayed physical development accompanied by bone fragility.[1] This disease, characterized by an increase in bone density, belongs to a heterogeneous group of uncommon, hereditary bone diseases with different clinical features.[2,3] Symptoms result from a differentiation and deficiency in the function of osteoclasts.[4] This functional deficiency forms dense and fragile bones, which are sensitive to fracture and infection due to the failure of bone remodeling. The result is so severe that most patients die because of anemia and infection before 20 years old.[5]

Osteopetrosis has a wide spectrum of genotypic, physiologic, and clinical manifestations. The overall incidence is difficult to estimate and is thought to be 1 in 100,000-500,000.[6] Although the etiology of the disease is not well known, there are 4 genes associated with the illness. These genes are reported as TCIRG1, CICN7, OSTM1, and PLEKHM1.[7]

Dentomaxillofacial findings include: facial deformities (frontal bossing, broad face, hypertelorism, snub nose); neurologic findings (nystagmus, optic atrophy, blindness, deafness, facial paralysis); nasal stuffiness; and dental problems.[8]

Some strategies have been reported in the literature for the treatment of osteopetrosis.[9,10] The prognosis for osteopetrosis is poor, with death usually occurring before 20 years old. The most common cause of death is related to the comorbidities of severe chronic anemia, bleeding, or infection.[11] Osteomyelitis is a well-recognized and very important complication of the disease. It occurs frequently after odontogenic infections or surgical dental procedures. It is a serious, life-threatening sequella, which occurs almost exclusively in the mandible followed by the maxilla, scapula, and extremities.[12] It generally resists treatments and recurs.[8,9] Thus, jaw infection control is a serious problem to manage for health professionals, especially for dentists.

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The purpose of this case report was to present 2 cases of the malignant recessive form of osteopetrosis associated with chronic osteomyelitis of the jaws.

CASE 1

A 9-year-old child was brought to our clinic in Erciyes University, (Dentistry Faculty, Kayseri, Turkey) by his parents complaining of swelling in his maxilla and delayed tooth eruption. Upon examination, we learned that the child was bedridden and had suffered from impairment since he was 2 years old. Pallor, macrocephaly with a wide face, exophthalmos, frontal bossing, hypertelorism, and retardation of growth were significant clinical findings (Figure 1a).

Clinical examination revealed limited opening of the mouth, and intraorally there was only 1 tooth present with no clinical crown due to severe caries. The patient's chief complaint, maxillary swelling, was located in the maxillary canine's vestibular region and had developed over several years, with intermittent recurrence, occasional bleeding, and an oroantral fistula (Figure 1b). Two years ago, he had a tooth extracted from his mandible, and the alveolar socket had not healed. The child's parents had sought medical care several times due to pain, pus drainage, and foul odor. Although the child had used many prescribed antibiotics, the symptoms had recurred from time to time. This was considered a case of chronic osteomyelitis (Figure 1c).

A panoramic radiograph was taken to examine the jaws. Both the maxilla and mandible showed high bone density. The increased radiopacity was so great that it was not possible to examine structures. In the panoramic radiograph, there were many unerupted teeth with no root formation or apical structure, and the crowns of the teeth were poorly calcified (Figure 1d). The child was initially diagnosed with congenital osteopetrosis when he was 2 months old. He and his twin sister were born in 2001 after an uncomplicated pregnancy. His twin sister and parents were healthy. Her panoramic image showed normal eruption of the primary and permanent teeth (Figure 1e).

There was a consanguineous relationship between the parents with no history of bone diseases. According to his medical reports, he also had a history of: headaches; hepatosplenomegaly; anemia; macroglossia; anosmia; temporal bossing; nasal flow; distended abdomen; vertigo; tussis; sicchasia; vomiting; and treble ecchymose. He also had a hyperemic oropharynx, bilateral atrophy of the optic discs, bilateral submandibular lymphodenopathy, lung infections (7 times in the last 5 years), blue sclera, throat pain, night sweats, and insomnia. The ear examination was normal. There was no history of noticeable hearing disturbances, facial paresis, or paralysis. Computed tomography (**CT**) imaging showed a generalized and "homogeneous increase in bone density (Figure 1h). Osteomyelitis was treated empirically with antibiotics. Local control of infection was well maintained; however, recurrent pneumonia occurred and the subject died of respiratory failure at 10 years old.

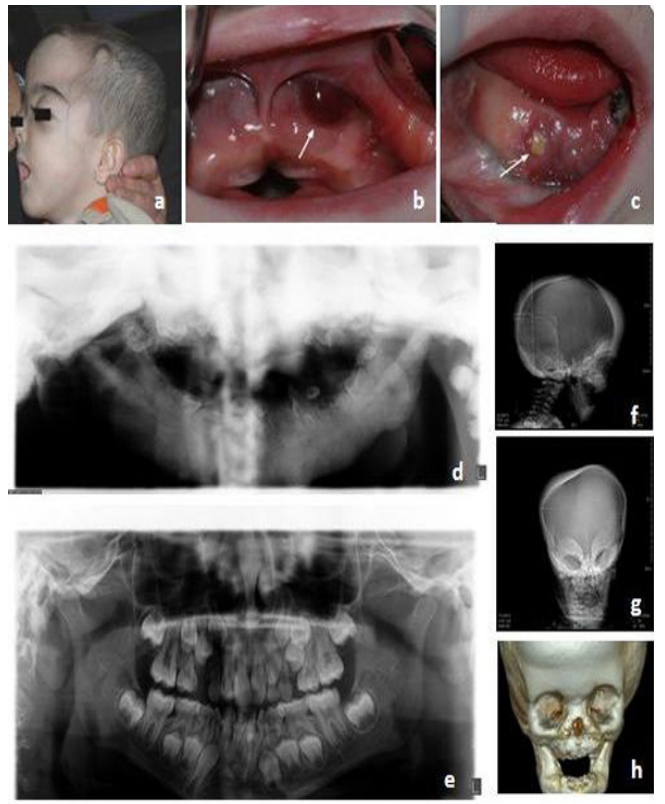

Figure 1. Patient with congenital osteopetrosis. Case 1: (a) Lateral view of the child's head showing pale, wide face, macrocephaly, and exophthalmos; (b) The swelling was located at the maxillary canine's vestibular region; (c) Chronic osteomyelitis of the mandible; (d) Panoramic radiograph showing overall increased bone density and several unerupted teeth in the maxilla and mandible; (e) Twin sister's panoramic image showing normal eruption with primary and permanent teeth; (f) Radiograph of the skull. Note the increased overall bone density; (g) Sclerotic orbital walls give a mask-like appearance; and (h) Three-dimensional computed tomography images showing the skull.

CASE 2

A 5-year-old boy was referred to our clinic for evaluation and treatment of osteomyelitis of the maxilla. Upon exam-ination, we observed impaired vision and a wide, pale face with macrocephaly (Figure 2a). One year previously, he had 2 primary teeth extracted; since then, he had suffered from recurrent swelling and inflammation of the extraction sites. As a result, he had regularly received antibiotic therapy. Upon clinical examination, 2 oral fistulas were detected in the maxillary incisor region (Figure 2b), while 2 root fragments of primary teeth were located in the lower central region (Figure 2c).The patient had limited opening of the mouth.

A panoramic radiograph was taken to examine the jaws, which showed diffuse bone density, especially of the maxilla. In addition, there were many unerupted

teeth with only poorly calcified crowns (Figure 2d). Correlating the radiographic features with the clinical features, the child was diagnosed with chronic suppurative osteomyelitis. Osteomyelitis was treated empirically with antibiotics. The parents reported that the patient had been able to see when he was a baby but had started to lose his sight since 1 year old. According to his medical records, he was born with hydrocephaly, which was undiagnosed until a CT was taken when he was 6 months old. A shunt was then placed in his skull (Figure 2e). He also had a history of anemia, hepatosplenomegaly, headaches, and recurring lung infections. Regarding his family history, he had a healthy brother, and parents with no history of bone diseases. There was a consanguineous relationship between the parents. Concerning his general health, other than antibiotics for unhealed extraction sites, he took no regular medication and attended follow-up visits every month in the department of hematology of Erciyes University, Medicine Faculty.

DISCUSSION

Osteopetrosis, also known as "marble bone disease,"[13,14] is a rare genetic bone disorder that results from a deficiency in the function and differentiation of osteoclasts.[15] This disease represents a heterogeneous series of rare, hereditary bone diseases with an increase in bone density and changeable clinical characteristics.[16] Normally, in osseous tissue remodeling, there is equilibrium in the activities of bone formation and resorption.[17] The basic defect in osteopetrosis is probably a failure of normal osteoclast function, since the number of osteoclasts present is often increased; however, because of their failure, bone is not resorbed.[18] The causes of osteoclast failure are unclear, but may involve abnormalities in the osteoclast stem cell or its microenvironment, osteoblast precursor cells or the mature heterokaryon, or bone matrix.[19]

The prevalence of the disease is estimated to be 0.005% of the population,[14] and the absolute nature of the disorder is unknown. Osteopetrosis is generally divided into 4 types: (1) osteopetrosis with renal tubular acidosis and cerebral calcifications; (2) benign type; (3) intermediate type; and (4) infantile malignant type.

Osteopetrosis with renal tubular acidosis and cerebral calcifications is the autosomal recessive type of osteopetrosis, which manifests in infancy with pathological fractures, short stature and, in most cases, mental retardation.[18] The benign type, the most common variant, usually affects mature individuals but has also been detected in the early teens and continues to develop until the end of bone growth.[20] Patients who have benign osteopetrosis are usually asymptomatic.[21] Intermediate type osteopetrosis may affect children or adults. It may present the same clinical symptoms as infantile osteopetrosis or be asymptomatic.[22,23]

Infantile malignant osteopetrosis exists at birth or appears within the first months of early childhood.

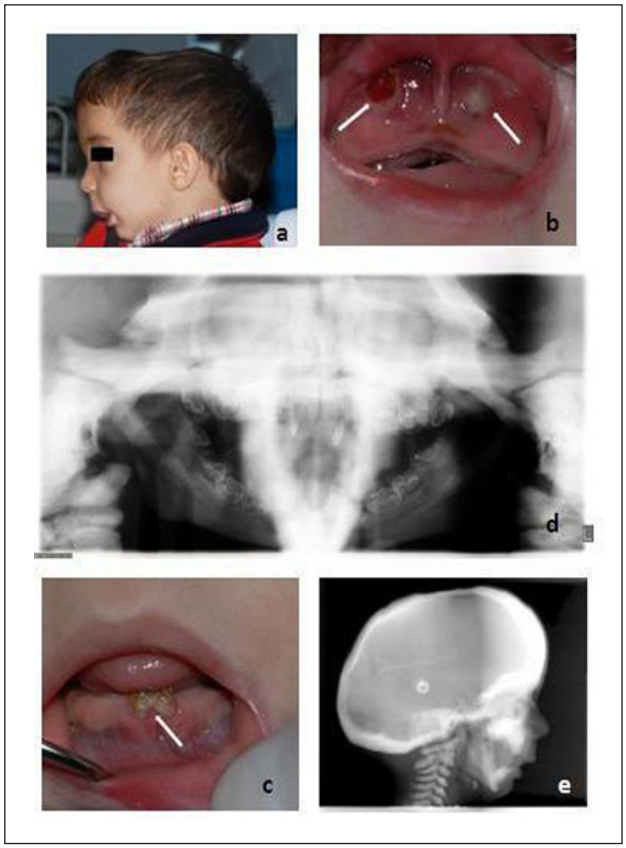

Figure 2. Patient with congenital osteopetrosis Case 2: (a) Lateral view of the child's head showing pale and wide face with macrocephaly; (b) Appearances of the unhealed chronic suppurative osteomyelitis and oral fistulas; (c) Appearances of root fragments in the mandible; (d) Panoramic radiograph of the child showing many unerupted and poorly calcified teeth crowns; and (e) Plain radiograph of the child's skull, in the form of macrocephaly, showing the placement of a shunt.

Osteopetrosis patients at birth or early infancy usually have a severe form of the disease and present with a diffusely sclerotic skeleton.[19] The diagnosis of osteopetrosis is, therefore, based on a history of numerous fractures and radiologic findings indicative of osteosclerosis, although the radiologic features are usually sufficient to make a definitive diagnosis.[24]

Clinical, hematological, and neurological symptoms include hepatomegaly, splenomegaly, hepatosplenomegaly, hydrocephalus, and dysmorphic features such as frontal bossing and macrocephaly, lymphadenopathy, severe anemia, blindness, frequent fractures, and cranial nerve compression. Many patients exhibit stunted growth and development. Its prognosis is generally poor and subjects seldom survive beyond adolescence.[25] Consequently, patients do not usually live beyond 20 years old.[8,26] The children that we present in this case report had the infantile malignant type of osteopetrosis, and they showed many of the clinical manifestations. The radiographic features of osteopetrosis include increased homogenous diffuse density in all bones. Upon radiographic evaluation, the trabecular pattern of the medullar

cavity may not be visible because of the increased density.

The contrast between the outer cortical border and the cancellous portion of the bone is decreased. Bone volume may be enlarged and represent relatively poor vascularity.[6]

Treatment of osteopetrosis has to be individualized because of the wide spectrum of clinical symptoms and complications. It is aimed at decreasing or arresting progressive hyperostosis, correcting anemia and thrombocytopenia, and treating infections. The oral cellulose phosphate, prednisone, low calcium diet, and recombinant human interferon gamma have been reported to be effective in some, but not all, patients.[15]

Blood and platelet transfusions or steroids, high-dose calcitriol, and hematopoietic stem cell transplantation (**HSCT**) are treatment alternatives.[10] Among these, HSCT is the only curative therapy for the disease.[9,10] Special attention should be paid to osteopetrosis patients due to their fragile bone status, resulting from defects in osteoclast function and consequent impaired wound healing.[27] Jalevik et al., reported that bone marrow transplantation induces normalization of osteoclast function, allowing normal bone homeostasis, which is a prerequisite for normal dental development and eruption of teeth. Coccia et al.,[29] performed bone marrow transplants from an unaffected sibling to another sibling with malignant osteopetrosis. In the infant with the condition, the disease was greatly ameliorated when Y-bearing osteoclasts were transferred, and the monocyte-macrophage function, previously defective, was restored.

To some extent, the body compensates for bone marrow failure by extramedullary hematopoiesis, resulting in hepatosplenomegaly, as noted in our cases.[30] The clinical presentation, radiological picture, and management procedures may vary according to the severity of the disease (Table 1).

Osteopetrosis' oral features are important, since this disease is often diagnosed as a result of oral changes. Reported dental alterations in osteopetrosis include: many unerupted teeth with no indication of root formation or apical structure; dental anomalies (agenesis and microdontia); ankylosis; a decrease in the size of the pulp chambers and root canals; shortening of the roots; poorly calcified teeth; congenitally missing teeth; malformed teeth; early tooth loss; enamel hypoplasia; and aplasia[9] (Table 1). A study of the mandible from a 10-year-old child with osteopetrosis at autopsy revealed areas of ankylosis at the dentin-bone interface of unerupted teeth, suggesting that failure of eruption is not only due to mechanical obstruction alone but also to ankylosis.[31]

Other problems in osteopetrosis include: hypomineralization of the enamel and dentin; disturbed dentinogenesis; propensity for tooth decay; thickened lamina dura; defects of the periodontal membrane; mandibular protrusion; and odontomes.[28] Enamel hypoplasia could be related to changes in calcium and phosphorus levels occurring with this disease.[32] Bjorvatn et al.,[33] reported a high degree of distortion in the primary molars and permanent teeth of children with malignant osteopetrosis. There was limited vertical growth of the alveolar ridge, with embedding of the teeth in the basal bone. Any injury or fenestration in the overlying oral mucosa may lead to osteitis and extraoral fistula formation.

In this report, clinically, our patients had only 1 or 2 primary roots. In addition, they displayed radiographic findings such as many unerupted teeth, with no indication of root formation or apical structure, malformed roots or crowns, and poor calcification. As teeth develop

Table 1. Head and Neck Manifestations of Osteopetrosis–associated Osteomyelitis of the Jaws

Orofacial findings	Dental problems (delayed tooth eruption and impaction, tooth root abnormalities, aplasia, unerupted and malformed teeth, enamel hypoplasia and early tooth loss), facial deformities (broad face, hypertelorism, snub nose, frontal bossing), neurologic findings (optic atrophy, nystagmus, blindness, deafness, facial paralysis), nasal stuffiness, and osteomyelitis as a complication of tooth extraction.
Diagnosis	Because of the differing severity of the various forms of osteopetrosis, a correct diagnosis is essential before proper therapy can be initiated.
Osteomyelitis in osteopetrosis	There is a high risk of developing severe infections like sepsis, and particularly osteomyelitis typically in mandible. Osteomyelitis requires rapid intervention with early diagnosis, drainage, debridement, bacterial culture and sensitivity testing followed by appropriate antibiotic therapy. Early diagnosis of osteomyelitis in patients with draining fistulas in the oral cavity and aggressive surgical intervention are extremely important issues in the management of these conditions. Surgical intervention is limited to necessary extractions, incision, drainage and possible palliative debridement.
Management	Local curettage and antibiogram-guided antibiotherapy seem to be the most reasonable treatment options (specific antibiotic recommendations: amoxicillin and clavulanic acid; amoxicillin and metronidazole; levofloxacin; clindamycin, etc). Hyperbaric oxygen therapy has documented a beneficial role in the treatment of mandibular osteomyelitis. Bone marrow transplantation may result in remarkable improvement among many infantile osteopetrosis patients, but may not benefit all because of the variety of the disease's underlying causes.

within the defective bone tissue, both the primary and the permanent dentition are frequently affected. Most teeth fail to erupt, or tooth enamel may be of poor quality and vulnerable to caries.

Dental procedures for osteopetrosis patients, especially the extraction of mandibular teeth, must be assessed and carried out with great caution.[34] There is a high risk of developing severe infections like sepsis and, in particular, osteomyelitis of the jaws. Osteomyelitis is an inflammatory condition of the bone that starts in the bone marrow Haversian systems and can extend to involve the cortex and periosteum.[35] It is well recognized that conditions that alter bone vascularity and compromise circulation may increase the risk of developing osteomyelitis.[36] The most likely contributing factor to necrosis of the bones is constriction of the canals housing the neurovascular bundles, which supply the teeth and jaws.[15]

In osteopetrosis patients, dental practitioners should be conscious of decreased bone vascularity and damaged white cell function, which may cause the development of osteomyelitis after dental extractions,[6] as was observed in both of our cases.

To minimize such problems, osteopetrosis patients should be encouraged to maintain good dental care and oral hygiene, because there is a potential risk of promoting osteomyelitis if surgical procedures are performed.[36] Professional prophylaxis or more intensive cleanings by dental hygienists may be more effective in controlling dental infections.[8] Dental caries and periodontitis causing osteomyelitis of the jawbones are frequently associated with this disease and require medical attention.[35] Osteomyelitis easily evolves into cellulitis and is potentially lethal by itself.

The dental management of osteopetrosis patients has to be individualized because of the wide spectrum of clinical symptoms and complications. Jalevik et al.,[28] reported the case of a 3-year-old boy who was treated under general anesthesia. Ten primary teeth were extracted and 3 teeth were restored due to severe caries and disintegration. The primary molars exhibited increased mobility due to poor root development. After treatment, dental check-ups were performed every third month, comprising of oral hygiene instructions and fluoride varnish application. Filho et al.,[38] reported 2 osteopetrosis patients. One of them was asymptomatic, whom the authors decided not to treat surgically either to insert implants or to remove the unerupted teeth because of the risk of osteomyelitis. A removable prosthesis also was constructed to improve the patient's function and esthetic appearence. The other patient did not want any form of restorative treatment, and, as the permanent maxillary right central incisor and permanent mandibular left first premolar were causing him pain, these were extracted and prophylactic antibiotics prescribed because of the risk of osteomyelitis. The patients were subsequently followed up and are now free of symptoms.

Although diagnosis is straightforward, osteomyelitis is difficult to treat, and the therapy is complex. Reported treatment modalities for osteomyelitis of the jaws include: antibiotic therapy[5,6,39,40]; incision and drainage; hyperbaric oxygen[40,41]; sequestrectomy; extraction of teeth; decortication; resection of the jaw; and immunotherapy.[42] Obturators are the favored method of filling the defect.[29] Free bone grafting is not recommended, as the blood supply to the graft bed is compromised. Use of a free vascularized, myo-osseous flap may be more favorable, but may be precluded because of the absence of a suitable donor site in these patients.[7] To avoid osteomyelitis in such patients, surgical operations—like necessary extractions, drainage incision, and possible palliative debridement—should be performed under antibiotic prophylaxis.[43]

Successful treatments in unresolved osteomyelitis cases have been reported in the literature,[40,43] including a case report of treatment with an extensive resection of the affected area by titanium plate reconstruction.[34] Albuquerque et al.,[36] suggests management with pentoxifilline and tocopherol, as these drugs have been proven effective in the treatment of mandibular osteoradionecrosis.

Barry et al.,[40] described the case of a 28-year-old woman whose osteomyelitis of the maxilla led to a diagnosis of generalized osteopetrosis. The patient was treated empirically with metronidazole 500 mg and cefuroxime 750 mg, 3 times daily, along with bethamethasone sodium phosphate 0.1% nasal drops. She improved after a few days and was transferred to outpatient care. Krithika et al.,[3] reported 4 cases of osteopetrosis, complicated by osteomyelitis of the jaws. All 4 cases were treated with intravenous antibiotic therapy and debridement of necrotic bone. For the 4 different patients, amoxicillin and clavulanic acid, cefotaxime (1 g twice daily for 5 days), amoxicillin (250 mg), metronidazole (200 mg three times daily for 7 days), and levofloxacin (500 mg once daily for a week) were used for treatment, respectively. A case of a pediatric patient diagnosed with osteopetrosis complicated by osteomyelitis in the maxilla was presented by Toranzo Fernandez et al.[35] The initial therapeutic management consisted of:

1. empirical antibiotic therapy (clindamycin 180 mg intravenously every 6 hours) accompanied with culture and sensitivities of the purulent debris;
2. correction of anemia (2 units of packed red blood cells); and
3. conservative surgical treatment consisting of curettage and debridement.

Long-term follow-up revealed that the patient was free of presenting symptoms and had normal laboratory values. In this case report, osteomyelitis was

resolved with antibiotic treatment (clindamycin 300 mg intravenously every 12 hours for 3 weeks), and the surviving patient is currently following up at the department of maxillofacial surgery in our facility Erciyes University, Dentistry Faculty.

In conclusion, osteopetrosis exhibits a wide variety of symptoms, which emphasizes the importance of a multidisciplinary approach. Family members of patients have great responsibilities, such as screening their children for early detection and appropriate interventions. They should be encouraged to maintain excellent oral hygiene and seek preventive dental care. When operative dental treatment is necessary, conservative treatment should be preferred over surgical interventions due to the risk of osteomyelitis. Osteopetrosis patients frequently present with the comorbidity of osteomyelitis; thus, dentists and oral surgeons play an important role in the treatment of this difficult disorder.

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