Infantile Osteomyelitis Secondary to Malignant Osteopetrosis

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Abstract Osteopetrosis (OP) is a rare congenital disorder (present at birth) in which the bones become over dense. This results from an imbalance between the formation of bone and the resorption of the bone. Thickening of the bones which become abnormally dense due to an inherited defect in bone resorption, the process in which old bone is broken down and removed so that new bone can be added to the skeleton. Osteoclasts are the cells responsible for bone resorption. In osteopetrosis the osteoclasts do not perform normally. This flaw in bone resorption results in bones that are abnormally dense, yet are fragile and easily broken. Osteopetrosis is also known as Albers–Schonberg disease, generalized congenital osteosclerosis, ivory bones, marble bones, osteosclerosis fragilis generalisata. In this article, we have described about the diagnosis and medical and surgical management of osteopetrosis reported case to our hospital.

Keywords Osteomyelitis · Osteopetrosis ·
Marble bone disease

Introduction

Osteopetrosis (OP) is a rare hereditary bone disorder of heterogeneous pathophysiology in which failure of osteoclastic bone resorption leads to increased bone mass. It is also known as marble bone disease because of the dense rock like appearance of the bone [osteobone, petros-stone]. A German radiologist Albers–Schonberg first described OP in 1904. The condition is quite rare, incidence has been reported at 1 in 20,000–5 lac for the dominant form and 1 in 2 lac for the recessive malignant form.

Infantile malignant OP is a rare recessive disorder characterized by dense, sclerotic, fragile, radio-opaque bones; neurological abnormalities; anemia and thrombocytopenia with subsequent extramedullary hematopoiesis and impaired vision and hearing caused by encroachment of the foramina and nerve canals [1]. Infants are diagnosed with this form of OP immediately or shortly after birth. These patients often have pathological fractures, osteomyelitis of long bones and repeated rate of infections.

The incidence of osteomyelitis has dramatically declined since the induction of antibiotics. When it occurs now, the possibility of predisposing immunosuppressive conditions or underlying bony disease (such as Paget's diseases, OP) should be considered [2, 3]. Local infection such as odontogenic infection is more likely to lead to osteomyelitis, which is a complication in 10% of reported cases of osteopetrosis [2]. These cases have occurred almost exclusively in the mandible. Osteomyelitis is more common in mandible and long bones and seen rarely in maxilla, probably because of the thin cortical bone and rich collateral blood supply [1, 4]. This article presents a case of aggressive unresolved osteomyelitis of maxilla in a child with infantile osteopetrosis. The significance of medical and surgical management of osteomyelitis in OP is elaborated.

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Case Report

A three and half year old male patient was referred to department of oral and maxillofacial surgery, Modern Dental College and Research Centre with the chief complaint of pus draining from upper left canine region since a month, which was associated with progressive swelling and pain. Patient was apparently alright one month back, overnight he developed swelling on left side of the face associated with pain; they consulted a physician who prescribed medicines for five days. Swelling did not subside with this, he was referred to a pediatrician. Incision and drainage was done by the pediatrician through intraoral drainage. Blood investigations showed severe anemia, Hemoglobin was 6 g%, 3 pint of blood was transfused. After one week patient was discharged. After 15 days there was discharge of foul odored pus from the oral cavity and was referred to the dental college.

On general physical examination, the patient was short statured with delayed physical mile stones. He was poorly nourished, had stunted growth and was blind since birth (Fig. 1). Patient was pale and was not ictric. The left submandibular lymph nodes were palpable and tender. His neck was short with tortuous and engorged facial and neck veins. Abdomen was distended with hepatomegaly and splenomegaly (Fig. 1). Head and neck examination revealed dolicocephalic skull, proptosis, hypertelorism with alternating convergent squint, flattened malar eminence, and loss of nasolabial fold and deviation of mouth to

Fig. 1 Patient poorly built and distended abdomen

Fig. 2 Deviation of mouth with absence of nasolabial fold

left with positive Bell's sign suggestive of facial palsy (Fig. 2).

On extra-oral examination, left side of the face was swollen (Fig. 3). Swelling was extending from ala of nose to canthus tragus line anteroposteriorly and superoinferiorly from the infraorbital rim to upper lip. Surface of the skin was erythematous, tender, warm and firm on palpation. On intraoral examination, he had high arched palate with edentulous upper and lower ridges. Draining sinuses at left canine region present (Fig. 4), swelling in the same region with obliterated vestibule.

Orthopantomograph (Fig. 5) showed generalized dense bone with unerupted tooth buds. Left maxillary canine region showed widened follicles of tooth buds seen. There was increased opacity of facial bones. CT scan showed multiple unerupted teeth and dense facial bones (Fig. 6). The surrounding bone in canine and premolar region had moth eaten appearance (Fig. 6). There was loss of lamina dura in canine and premolar region. There appeared to be a reactive bony sclerosis in the vicinity of the left maxillary

Fig. 3 Facial asymmetry observed due to the swelling on the left side

Fig. 4 Intraoral examination

region. His chest and skull radiographs showed diffuse osteosclerosis and chalky appearance of the ribs, thoracic vertebrae and cranium (Fig. 7).

His blood investigations showed severe microcytic, hypochromic anemia. Correlating the radiographic features with the clinical features, the case was diagnosed as chronic suppurative osteomyelitis of maxilla in a child with infantile malignant OP. Sinus tract excision and curettage of lesion was done subsequently and sent for histopathological examination.

Microscopic examination of the submitted specimen from the area affected by osteomyelitis showed irregular interlacing sclerotic non vital bone exhibiting loss of the osteocytes from lacunae (Fig. 8). Medullary spaces show the fibrous connective tissue). No evidence of hematopoietic marrow or blood vessels was present. The patient was on regular follow up for a year. The patient was pale and anemic when reported after 2 months. He was transfused with blood every 3 months. The parents of the patient were trained to irrigate the wound by antiseptic solution (betadine + saline) regularly. Patient was advised for hyperbaric

Fig. 6 CT scan showing moth eaten appearance

oxygen therapy and bone marrow transplantation (BMT) for which patient refused due to cost. We lost the track of the patient after year.

Discussion

Albers-Schonberg first reported osteopetrosis in 1904. In 1921, Schulze described it as a marmokronchan/marble bone disease after observing this peculiar appearance in six cases from German literature. In 1926, Karshner termed this disease entity as ‘osteopetrosis’ (stone like or petrified) and noted that increased hardness more closely resembled limestone than that of marble [5]. This disease is extremely rare, inherited disorder caused by mutations on the CLCN7 gene where by bones harden, becoming denser.

Fig. 5 OPG with multiple unerupted tooth buds

Fig. 7 Chest, skull and vertebrae showing chalky white appearance

Fig. 8 Irregular interlacing sclerotic bone. Medullary spaces filled with fibrous tissue

There are four types of OP (a) malignant or infantile OP, (b) Benign or adult OP, (c) intermediate OP, and (d) carbon anhydrase type II (CAII) deficiency. Each of us carry two copies of the CLCN7 (chloride channel 7) gene (one from mother and another from father). Autosomal dominant OP occurs when a person receives one mutated CLCN7 gene from one parent and one normal CLCN from other parent [6].

Autosomal recessive osteopetrosis or malignant infantile OP occurs when a person inherits two copies of the mutated CLCN7 gene from their parents [6]. Malignant OP generally begins in utero, often resulting in still birth. It is characterized in the first few months of life with failure to thrive, malignant hypocalcemia, anemia, thrombocytopenia and fractures [6]. Our reported case shows all these characters without bony fractures. The principal manifestations are anemia, infections, sensory disorders and fractures due to generalized bone condensation. Moreover, 75% of patients with infantile osteopetrosis die before the age of six due to recurrent infections, especially pneumonia, or osteomyelitis complicated by septicemia. This patient had recurrent respiratory infections and osteomyelitis of maxilla.

Hyperostosis crowds the marrow cavity leading to extramedullary hematopoiesis with resultant hepatosplenomegaly [6, 7], which was present in this case. Recurrent

infections were common in the child which could be due to defect in the macrophage killing of bacteria. Cranial nerve entrapment, neuropathies occur due to failure of the foramina to widen completely in the skull, and the manifestations include deafness, proptosis and hydrocephalus. The bony encroachment on the optic foramina leads to optic atrophy and blindness. The above patient was born blind but his auditory functions were normal. These patients show retarded growth, exophthalmosis, hypertelorism, flattened nose, mandibular prognathism and cranial nerve palsies. All these hallmark features were present in this case except palsies.

The development of dentition is severely disturbed in children with OP. Dental findings include delayed tooth eruption and impaction, aplasia, unerupted malformed tooth, enamel hypoplasia and early tooth loss [8]. The case above mentioned presented with all unerupted upper and lower teeth. The other findings were malformed crowns and roots and thickening of lamina dura.

Benign OP or Autosomal dominant osteopetrosis occurs when a person inherits one copy of the mutated CLCN7 gene from their mother or father. Severity varies tremendously, even among the same mutation in the same family. Mutated gene can have either mild, moderate or severe forms of OP. Cases are diagnosed as adults and suffer from frequent pathological fractures of long bones; however healing is better than malignant op. Osteomyelitis, pain, degenerative arthritis and headache can also be present. Progressive compression of foramina can lead to nerve palsies, blindness, deafness or stroke. Presence of anemia, hepatosplenomegaly, with blindness since birth and recurrent infections with osteomyelitis of maxilla distinguish the present case from benign form.

There are individuals with symptoms that do not fit clearly into the other recognizable categories; some literatures present this as a third type of osteopetrosis known as intermediate osteopetrosis [6]. These individuals will generally have a diagnosis in the first decade of life and symptoms more severe than those described as benign osteopetrosis, including blindness, deafness and hematological symptoms. There will be no familial history of osteopetrosis, leading to conclusion that this form is recessive.

The other form of osteopetrosis is caused by deficiency of carbon anhydrase type II (CAII). The gene responsible for producing CAII is found on chromosome 8 (at 8q22). CAII has activity in bones, kidney and the brain and all of these organs are affected in this type of disease. Symptoms in this type of osteopetrosis include increased bone density with tendency to fracture easily. Other symptoms may include intracranial calcifications, sensorineural hearing loss and developmental delays. These patients will have renal tubular acidosis. CAII also have an important role in brain development and children who are affected often

develop cerebral calcification and experience developmental delays [6]. This form of the disease usually causes symptoms in the first few years of life although X-rays are normal at birth. Unlike malignant osteopetrosis, blood problems tend to be minor or absent [6].

Osteomyelitis is well documented complication of osteopetrosis. This disease can be severe and difficult to treat in the osteopetrotic patient [6]. Usually occurs in the long bones and mandible. Osteomyelitis of the maxilla is very rare, due to thin cortical bone and rich collateral blood supply. Osteomyelitis secondary to osteopetrosis tends to be refractory because of the reduced blood supply and accompanying anemia and neutropenia [2]. There are very few reports of successful treatment and in many cases the osteomyelitis remains unresolved indefinitely.

Treatment of osteomyelitis of jaws includes early diagnosis, drainage of pus, bacteriologic culture and antibiotic sensitivity testing with appropriate antibiotic therapy, and supportive therapy. The surgical treatment includes debridement, saucerisation, decortication, resection and reconstruction of the jaw if needed and hyperbaric oxygen therapy. These modalities have all been used in the treatment of osteomyelitis of the jaws secondary to osteopetrosis, but resection and hyperbaric oxygen are the only successful methods of treatment. Obturators are the favored method of filling the defect. Free bone grafting is not recommended, as blood supply to the graft bed is compromised.

Initially this patient was treated with intraoral incision and drainage of pus, but infection did not subside, he underwent surgical debridement and systemic antibiotic therapy for a week followed by oral amoxicillin for three weeks. Lucchesi et al. reported use of long term antibiotics and calcitonin in the treatment of chronic osteomyelitis of mandible; he used cefradine, metronidazole and calcitonin injections for one month. He concluded that long term use of antibiotics resolved the osteomyelitis and use of calcitonin reduced bone pain and promoted healing [9] in our case long term use of amoxicillin did not show any improvement due to severity of osteomyelitis.

Nuray et al. treated a case of bimaxillary osteomyelitis secondary to infantile osteopetrosis with use of topical phenytoin in 12 year old boy. He used topical phenytoin (PHT diphenylhydantoin) administration to promote secondary wound healing. The wound was irrigated with 0.9% saline and then PHT powder was applied in uniform, thin layer on the wound surface in a dose of 20 mg/cm² as described by Lodha et al. [1]. This treatment was given for two weeks. The effects of PHT are accelerated formation of granulation tissue, decreased inflammatory response, reduced wound exudation, reduced bacterial contamination and decreased local bone pain. The patient and parents were unco-operative to receive this modality of treatment.

Management of patients with osteopetrosis requires a comprehensive approach to characters tic, clinical problems including hematological and metabolic abnormalities, fracture deformity, bone pain osteomyelitis and neurological sequel [10]. Children with OP have been treated with [calcitrol] 1,25 dihydroxy vitamin D in an effort to provoke osteoclast to resorb bone. Recombinant human interferon gamma increases the bone resorption, hematopoiesis and leukocytic formation. Large doses of corticosteroid drugs (such as prednisolone) may be given for short time to patients with impaired red blood cell or platelet production. However, if continued for long periods, may reduce the growth velocity of children and predispose them to infection. The only potential curative therapy for malignant infantile osteopetrosis [MIOP] at this time is a successful hematopoietic stem cell/bone marrow transplant [BMT], using either bone marrow or peripheral blood stem cells from an allogenic donor. BMT replaces abnormal osteoclasts with normal cells and is reserved only for the most severe cases of osteopetrosis [11]. Good nutrition is important to ensure normal growth and development of children with osteopetrosis.

Conclusion: infantile malignant OP is a lethal disease. The difficulty in obtaining conclusive results by sonographic evaluation of fetus in utero makes prenatal molecular diagnosis highly desirable [12]. Malignant osteopetrosis generally begins in utero and diagnosis can be made by radiographic examinations, it is often delayed due to rarity of the disease and lack of clinical suspicion. Often results in stillbirth or sometimes appears very early in life. It progresses rapidly with the patient failing to survive even infancy. Early diagnosis and newer drugs can significantly reduce mortality rate.

Osteomyelitis is now such a rare entity that, when presented with osteomyelitis of the maxilla or intractable osteomyelitis of the mandible, the oral surgeon should consider the possibility of osteopetrosis as an underlying cause.

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