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REVIEW

Three-Year Dentition Follow-up of a Paediatric Case with Malignant Infantile Osteopetrosis: A Review of the Literature

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Abstract

Malignant infantile osteopetrosis [MIO], the most severe form of osteopetrosis, also known as marble bone disease, has a high rate of infant mortality and causes severe medical and dental outcomes in children. The general oral findings of this disease are reduced vascularisation of the jawbone as a result of impaired osteoclastic activity, eruption disorders, embedded teeth, missing teeth, dental hypoplasia and misshaping, excessive luxations associated with undeveloped roots, increased incidence of decay, and periodontal membrane defects. The current case patient was diagnosed with MIO at 4 months of age and underwent bone marrow transplantation at the age 3 years. The dentition development of the male patient was followed by regular dental examinations from the years 7 through 10. The tooth development of a MIO paediatric patient is presented in this case report with a review of the literature.

Keywords: Malignant infantile osteopetrosis, oral findings, tooth eruption disorders, paediatric dentistry

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Introduction

Malignant infantile osteopetrosis [MIO], a very rare hereditary bone disease, was first described by Albers-Schönberg in 1904. With MIO also known as stone bone disease, Albers-Schönberg disease as well as marble bone disease – osteoclast dysfunction is seen, bones harden, and fragility increases.

General findings include osteosclerosis, lymphadenopathy, hepatosplenomegaly, and anaemia [1]. Four forms of osteopetrosis are known. The malignant type of autosomal recessive form does not contain any oncological conditions. However, it is so named because of the prognosis and severity of the disease. It often causes the death of young children [2-3].

The intermediate autosomal recessive form usually attracts clinical attention in the first decade of life. In this type of disease, pathological fractures and neuropathies due to progressive cranial nerve compressions are usually seen, but their lives continue until adulthood. There are two subclassifications of autosomal dominant osteopetrosis and the disease is asymptomatic in adulthood. Type I does not have an increased risk of pathological fractures and is manifested by regional osteosclerotic thickening of the cranial dome. Type II patients usually present with anemia, pathological fracture, or arthritis in adulthood [4].

Due to impaired bone structure, normal bone marrow function cannot be maintained in MIO congenita patients. The exit foramina of the cranial nerves narrow as a result of abnormal osteoclast activity, this causes a loss of function and injury through compression of the paired nerves, especially the optic nerve [5]. These patients usually die in infancy because of bone marrow deficiency and severe infection [6]. The only proven treatment method for this disease is bone marrow transplantation.

Severe bone marrow deficiency is seen in MIO, which generally results in developmental and growth retardation, blindness, deafness, hydrocephaly, proptosis [exophthalmos], hepatosplenomegaly, severe anaemia, recurrent bone fractures, and pancytopenia [decreased erythrocyte, leukocyte, and thrombocyte cell counts] [7,8].

Severe developmental disorders are seen in the teeth of children with MIO. Reduced vascularity of the bone, severe anaemia, and a compromised immune system can cause several oral and maxillofacial complications. Osteomyelitis, especially in the mandibular bone, and odontogenic infection are common [9]. Dental findings include delayed dental eruption, shape disorders and embedding of the teeth, enamel hypoplasia and hypomineralisation, abnormal pulp chambers, developmental disorders of the teeth roots, early tooth loss, a tendency to early decay, periodontal membrane defects and a thicken- ed lamina dura [10-12].

In this case report, tooth development and 3-year clinical follow-up of a pediatric patient with malignant infantile osteopetrosis are presented in the light of the literature. We think that the first dental development and clinical follow-up of this disease in a pediatric patient with a diagnosis of malignant infantile osteopetrosis with a high mortality rate will contribute to the literature.

Patient History

Medical History

A male patient was born prematurely on the 35th week of pregnancy in 2011 by normal vaginal delivery. The parents were consanguineous and there was no medical history of any of the siblings of the patient. During the neonatal period, the patient had a history of recurrent sepsis and associated hospitalization. The medical history of the patient showed also sight loss [associated with premature retinopathy], hearing loss, operated bilateral scrotal hernia, transverse nystagmus, developmental and growth retardation, and frequent blood transfusions due to anaemia. No organomegaly was observed.

The patient presented at another center at the age of 8 months, because of low hemoglobin,

changes in calcium, phosphorus, and alkaline phosphatase values, and suspicious radiological images. For further screening, a bone marrow biopsy and genetic analysis were performed, which led to the diagnosis of MIO congenita [Figure 1].

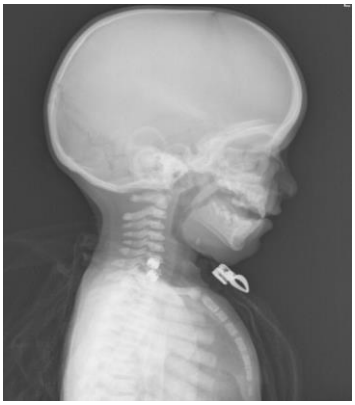

Figure 1: *Lateral cranial and cervical radiograph of the patient taken at age 8 months.*

At the age of 3, the patient underwent bone marrow transplantation. Cyclosporine and hydrocortisone were used for 6 months. There was a history of hospitalization due to secondary adrenal failure associated with long-term hydrocortisone use. Due to the frequent sepsis and hospitalization of the patient, there was also long-term use of broad-spectrum antibiotics. During the patient's long-term follow-up, developmental retardation was observed, and bone densitometry was not within normal physiological limits.

Dental History

A 7-year-old male patient presented to our clinic. In the extraoral examination, protrusions were found in the frontal region of the face and in the mandible, and ocular strabismus was observed [Figure 2].

In the intraoral examination of the patient, dental hypoplasia, atypical crown shapes and caries were found. Mobility was seen in the lower permanent right first molar, and there was an anterior crossbite and open bite.

Figure 2: *A frontal face image of the patient taken at the age of 7 years.*

In the radiographic examination, fillings and caries were seen in some deciduous teeth, and there were no permanent tooth germs in any of the second premolars, except the right lower second premolar. Moreover, the tooth germs were not in the direction of eruption, especially in the right lower central tooth and there was no root development in the lower first molar. Abnormal pulp chambers and thickening in the lamina dura were also observed. Increased radio-opacity was observed associated with increased sclerosis in the maxilla and mandible [Figure 3].

The consultation was requested from the paediatric endocrinology department before the dental procedures. Under the consultation guidance, some deciduous teeth and the right lower first molar were extracted under local anaesthesia, and caries showing cavitation were restored. Fluoride prophylaxis and initial periodontal treatment were applied. Oral mouthwash containing chlorhexidine gluconate was prescribed. Oral hygiene education was given and tooth brushing habit was tried to be gained. Protective applications were continued in each session.

In the oral examination of the patient at the age of 10, there was determined retained deciduous teeth, misshapen upper permanent teeth with rotation, enamel pearl on the buccal

surface of the lower incisors, dental hypoplasia, caries, and the presence of hypertrophic gingiva.

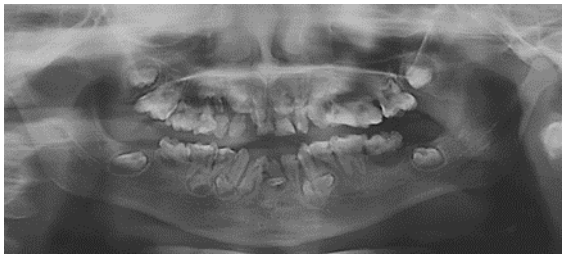

Figure 3: *Panoramic radiograph of the 7-year-old patient. The absence of teeth germs, undeveloped roots, misshapen tooth germs in the direction of eruption, and increased radio-opacity associated with increased sclerosis in the maxilla and mandible can be noted.*

In the radiographic examination when the patient was 10 years old, there was determined to be a deformed shape in the anterior teeth, insufficient root development, and abnormal pulp chambers, the right lower central tooth remained embedded, canine teeth had not developed crowns, and roots, absent second premolars except the right lower, insufficient vertical development of the alveolar bone, undeveloped root in the left lower first molar, atypical crowns in the second molars but root development was normal, and increased lamina dura thickness [Figure 4].

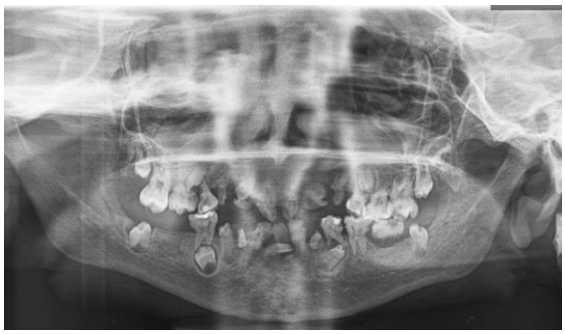

Figure 4: *Panoramic radiograph of the 10-year-old patient. Eruption abnormalities, misshapen crowns, and roots, insufficient root development, and increased lamina dura is observed.*

Dental Treatment Planning and Management in the Patient

Dental treatments were performed under the guidance of medical consultation. Fillings were checked, and fissure sealant and fluoride applications were applied. A consultation was made with the orthodontics and maxillofacial surgery department for the extraction decision and eruption disorders. Due to the abnormal osteoclastic activity of this disease and the inability to take anchor from insufficient root development any orthodontic treatment was not considered appropriate.

It was recommended that surgical interventions should not be performed unless necessary, against the risk of osteomyelitis and bone fracture. For all these reasons, the patient's clinical follow-up is still ongoing [Figures 5].

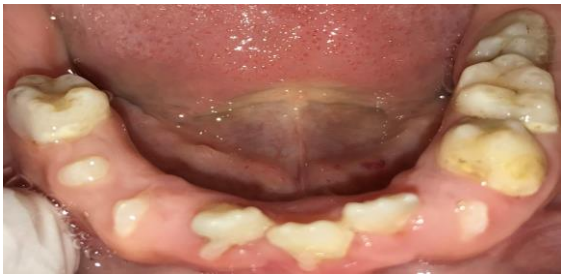

Figure 5*: Intra-oral view of the lower jaw of the patient after treatment.*

Effects Of Malignant Infantile Osteopetrosis On Primary And Mixed Dentition- Mini Review

Few studies in the literature have defined the reason for the effect on dental tissues in MIO patients [12-14]. Fried et al. [13] reported that due to the weak development of dental structures in patients with osteopetrosis, the developing dental germs were not nourished as a result of decreased bone density.

In a study of osteopetrotic rats, Philippar et al. [14] reported that in the histological and microbiological examination, the developing odontogenic epithelial tissue was affected by

osteopetrosis even if bone marrow returned to normal, and the periodontal membrane was rapidly invaded by osteopetrotic bone trabeculae in the incisors, and the process reached all molars on the eleventh day, advanced ankylosis developed in the incisors and molars, the teeth were covered by non-resorbed bone, tooth germ development was arrested and remained atrophic, and the visualization of gubernaculum dentis played no role in tooth eruption.

In studies of the mandible in the autopsy of a 10-year-old child with osteopetrosis, Younai et al. [12] determined areas of ankylosis in the dentin-bone interface of teeth that had not erupted. The failure of the eruption was reported to be due not only to mechanical obstruction but also to ankylosis.

In a study of 4 Iranian children with MIO, there was observed be anemia, hepatospleno-megaly, visual disorders, hearing loss, increased bone density, skeletal and mental retardation, short stature, increased distance between the eyes, frontal protrusion, exophthalmos, and a typically broad face [9]. In another MIO patient diagnosed at the age of 4 months, there was reported to be sight and hearing loss, as well as developmental retardation. Despite regular blood transfusions until the age of 3, the patient died at 10 years of age [12].

In a 7-year-old Moroccan MIO patient with consanguineous parents, Droz Desprez et al. [15] suggested that no teeth erupted following bone marrow transplantation. It was also reported that a gubernaculum dentis was present above the level of the left second molar.

In a 3-year-old patient who had undergone bone marrow transplantation at 6 months, Jalevik et al. [16] reported that the development of all the teeth was normal, but there were several decay lesions, the teeth were of small dimensions, there was hypoplasia in the enamel, atypical crown shape, the roots of the deciduous incisors were short, and there was not full root development in the first molars.

Bjorvatn et al. [17] examined 4 children with MIO born between 1967 and 1975. All the permanent teeth were partially or fully embedded and misshapen, there was a little vertical alveolar crest and the periodontal attachment was weak.

In another case report of a patient diagnosed at 6 months, the permanent anterior incisors were misshapen, there was thickened lamina dura in the permanent small molars, the mandibular second premolars were missing, there was insufficient root development in the first molars, and there were reported to be lost teeth associated with mobility [18].

An 8-year-old patient with MIO was reported to have cone-shaped permanent incisors, small v-shaped roots, hypoplasia, and hypomineralization in the first permanent molars, the second molars were of normal mineralization and size but had atypical enamel formation, the trabecular structure of the mandible, in particular, was thinner and there were several missing permanent teeth [16].

Discussion

The dentition of MIO patients is greatly affected by the course of the disease [15]. The patient received regular blood transfusions in infancy and a bone marrow transplantation at the age of 3, hence he had normal blood values at the age of 10. In the present case, growth retardation was observed in terms of age, vision, and hearing loss as well as typical facial and ocular findings of MIO. This patient's teeth were observed to erupt after bone marrow transplantation.

In the present case, findings similar to other studies were observed in the dentition period of primary teeth [16]. There was determined to be dental hypoplasia, atypical crown shapes, abnormal pulp chambers and caries in some deciduous teeth, and no root development in the lower first molar. In addition to these, it was observed that all second premolars, except the right lower second premolar, did not have permanent tooth germs and the tooth germ was not in the eruption direction, especially in the right lower central tooth.

Similar findings were seen in other studies on the dentition of permanent teeth [16-18]. There was determined partially embedded, and misshapen in the permanent anterior teeth, some permanent premolars were missing, insufficient root development and abnormal pulp chambers, little vertical alveolar crest, hypoplasia and hypomineralization in the first molar, atypical crowns in the second molars but root development were normal, and increased lamina dura thickness. In addition, teeth remained embedded in a different direction to eruption.

As the mortality rate in infancy is high in these patients, there are no cases in the literature of long-term dental follow-up in paediatric MIO patients, and case presentations are usually of osteomyelitis developing after extraction. Imani et al reported 4 cases of MIO and stated that in 2 patients aged 6 and 7 years, no teeth had erupted but there were embedded teeth. One of those patients presented with osteomyelitis associated with tooth extraction, while the other one had an extra-oral fistula because of infection [9]. In 2 cases with MIO, Bjorvatn et al. [17] reported that osteomyelitis had developed as a result of infection leading to extra-oral mandibular fistula, the necrotic bone was surgically removed, and to control recurrent infections, high doses of antibiotics were administered, yet with a poor outcome as the advanced osseous destruction could not have been treated.

Lam et al. [19] reported that because of defective osteoclast function and associated impaired wound healing, MIO patients were referred to specialists by dentists and complications could develop even in non-complicated dental extraction in this high-risk group. In an 8-year-old patient evaluated by Bedi et al. [20], it was reported that in cases of segmental mandibulectomy of the necrotic bone developing after tooth extraction with reconstruction applied using a reconstruction plate, the importance was stated of the need for prophylactic dental treatment as sequestrum and cysts could develop rapidly in the bone, the careful application of oral hygiene procedures, chlorhexidine mouth-wash, and fluoride application. In this respect, the fact that the current case was kept under follow-up, and due to the preventative procedures applied, no conditions developed which could threaten the health of the patient such as infection or osteomyelitis, hence it suggests that follow-up examinations by dentists are important.

A systematic dental recommendation is not yet recommended for osteopetrosis. In these patients, osteomyelitis is triggered by tooth infection. Taking preventive measures, regular dental examinations, and protecting the teeth are very important. Fluoride therapy can be applied to prevent cavities. Extraction should be performed by specialists under antibiotic prophylaxis by providing appropriate bone preservation conditions. At the end of the surgical procedure, the wound site should be carefully monitored [21].

Complications such as fractures and osteomyelitis can occur in the jaws during dental treatment in these patients. Oral aspects of this disease have become more evident and preventative dental treatments

have become important in recent years due to the increase in survival expectancy of MIO patients following bone marrow transplantation. At every follow-up examination of the current patient, preventative applications were made, caries were restored, the decision for extraction was made for teeth with mobility and follow-up decisions were made as a result of consultations with orthodontists and surgeons. In addition, treatment was applied for hypertrophic gingivitis which was thought to have formed due to the pearl enamel formation present in the lower anterior teeth. The clinical follow-up of the patient is still ongoing.

As a result of the 3-year follow-up of this patient with MIO, the general dental findings were seen to be that the deciduous teeth erupted in the normal time frame, but there were eruption disorders in the permanent dentition. Eruption of the teeth was determined to have continued after bone marrow transplantation. This case report can be considered to contribute to the literature in respect of the dental development of MIO patients.

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The authors report no conflict of interest.

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Data analysis and interpretation: **EA, YP, YY**
Collection and/or assembly of data: **EA, YP, YY**
Writing the article: **EA, YP, YY**
Critical revision of the article: **EA, YP, YY**
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