Case Report

Surgical-orthodontic treatment for severe malocclusion in a patient with osteopetrosis and bilateral cleft lip and palate: *Case report with a 5-year follow-up*

Jin-Kyu Kim[a]; Jun-Young Kim[b]; Hwi-Dong Jung[c]; Young-Soo Jung[d]

ABSTRACT

Orthognathic surgery in patients with craniofacial osteopetrosis, a condition associated with osteoclast dysfunction, is usually avoided because of the risk of osteomyelitis. A 19-year-old woman presented with the chief complaint of severe malocclusion and anterior crossbite. After radiographic evaluation, craniofacial osteopetrosis was diagnosed. Surgical-orthodontic treatment was performed after meticulous history taking and verification of normal bone turnover using bone-metabolism markers for endocrine evaluation. Favorable esthetic and functional outcomes were achieved. (*Angle Orthod.* 2021;91:555–563)

KEY WORDS: Osteopetrosis; Surgical-orthodontic treatment; Bone turnover marker; Orthognathic surgery; Malocclusion

INTRODUCTION

Osteopetrosis is a rare bone disease characterized by a marked increase in bone density caused by osteoclast dysfunction.[1–3] The German radiologist, Heinrich Albers-Schönberg, first described the disease in 1904.[4] The prevalence of the disease is 1 in every 100,000 to 500,000 individuals.[5] Poorly or non-functioning osteoclasts lead to reductions in bone resorption and remodeling, resulting in the formation of sclerotic bone. All the bones in the patient's body gradually become denser, with decreased cellularity and vascularity.[6] Nerve compression, owing to the compromised resorption-remodeling cycle of the bone, and neurological symptoms such as hearing loss, visual disturbances, and facial palsy, may occur. Systemic bone pain, frequent fractures, anemia, and thrombocytopenia are typical symptoms. The genetic variability of the disease is responsible for a variety of phenotypes, which can range from asymptomatic to fatal. There are three clinical subtypes.[6]

Autosomal recessive infantile malignant osteopetrosis is usually diagnosed during early infancy. It presents with diffuse skeletal sclerosis, bone marrow failure, frequent fractures, cranial nerve compression, and growth impairment. Untreated children usually die before school age from severe hepatosplenomegaly, infections, and pancytopenia. Bone marrow transplantation is the only reliable treatment for this condition.[7,8] The autosomal recessive intermediate type (marble-bone disease) is diagnosed in childhood and can cause neurological complications and dental anomalies.[9] Autosomal dominant adult (Albers-Schönberg disease) osteopetrosis is diagnosed later in life. It is characterized by less severe symptoms, and the survival rate is the best among the three types of osteopetrosis. Symptoms may not be evident in 40% of patients, and marrow failure is rare.[10–12] The typical features of this type of osteopetrosis are clearly visible on panoramic tomograms. Cortical bone trabeculation throughout the jaw bones, except the inferior alveolar nerve canal, is the principal characteristic feature. Additionally, tooth agenesis, delayed eruption, enamel hypoplasia, and tooth malformations are common diagnostic features of osteopetrosis. Severe malocclu-

The first two authors contributed equally to this work.

[a] Fellow, Department of Oral and Maxillofacial surgery, College of Dentistry, Yonsei University, Seoul, Korea.

[b] Clinical Assistant Professor, Department of Oral and Maxillofacial surgery, College of Dentistry, Yonsei University, Seoul, Korea.

[c] Associate Professor, Department of Oral and Maxillofacial surgery, College of Dentistry, Yonsei University, Seoul, Korea.

[d] Professor, Department of Oral and Maxillofacial surgery, College of Dentistry, Yonsei University, Seoul, Korea.

Corresponding author: Young-Soo Jung, DDS, PhD, Professor, Department of Oral & Maxillofacial Surgery, Yonsei University College of Dentistry, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Korea
(e-mail: ysjoms@yuhs.ac)

Accepted: November 2020. Submitted: August 2020.
Published Online: January 25, 2021

Figure 1. Pretreatment clinical photographs.

sion and dentofacial deformities occur in addition to the dental anomalies caused by mandibular prognathism and unerupted teeth.

Few reports have documented active treatment modalities for dentofacial deformities and malocclusion in patients with osteopetrosis, owing to the high probability of osteomyelitis of the jaw bones, especially the mandible.[13] Anemia and neutropenia may result in poor healing. However, maxillofacial deformities and dental problems should be treated since they cause several psychological and social problems. This case report describes the successful surgical-orthodontic treatment of an adult osteopetrosis patient with severe malocclusion and bilateral cleft lip and palate. The current case report is of surgical-orthodontic treatment performed in a patient with osteopetrosis, after confirming normal bone turnover using markers, that showed successful bone healing without any evidence of infection.

CASE REPORT

Diagnosis and Etiology

A 19-year-old woman visited the Department of Oral and Maxillofacial Surgery with the chief complaint of severe malocclusion and anterior crossbite (Figures 1 and 2). She also had unrepaired bilateral alveolar clefts, and the maxillary left central incisor showed ectopic eruption in the premaxilla. She reported a history of primary repair for bilateral cleft lip and palate before 1 year of age, and scars of the surgery were evident on the philtrum. Intraoral examination showed loss of multiple teeth, severe crowding, transverse maxillary collapse, and dental caries in multiple remaining teeth. After a thorough radiographic evaluation for dentofacial deformity, she was diagnosed with a Class III skeletal malocclusion with maxillary retrusion and mild mandibular prognathism through a cephalometric analysis (Figure 3). Panoramic tomogram observations of abnormal bone pattern, overall thickening of the cortical bone, and sclerosis of the cancellous portion led to computed tomography (CT) scanning. Bony sclerosis was observed in the medullary portion of the majority of the bones of the skull, including the temporal, frontal, parietal, occipital, zygomatic, maxillary, and mandibular bones, and discontinuity of alveolar segments was observed due to unrepaired bilateral alveolar clefts (Figure 4). The findings were collated, and the patient was diagnosed with autosomal dominant adult (benign) type 1 osteopetrosis.

The patient also reported a history of posterior fixation for thoracolumbar scoliosis at the age of 13

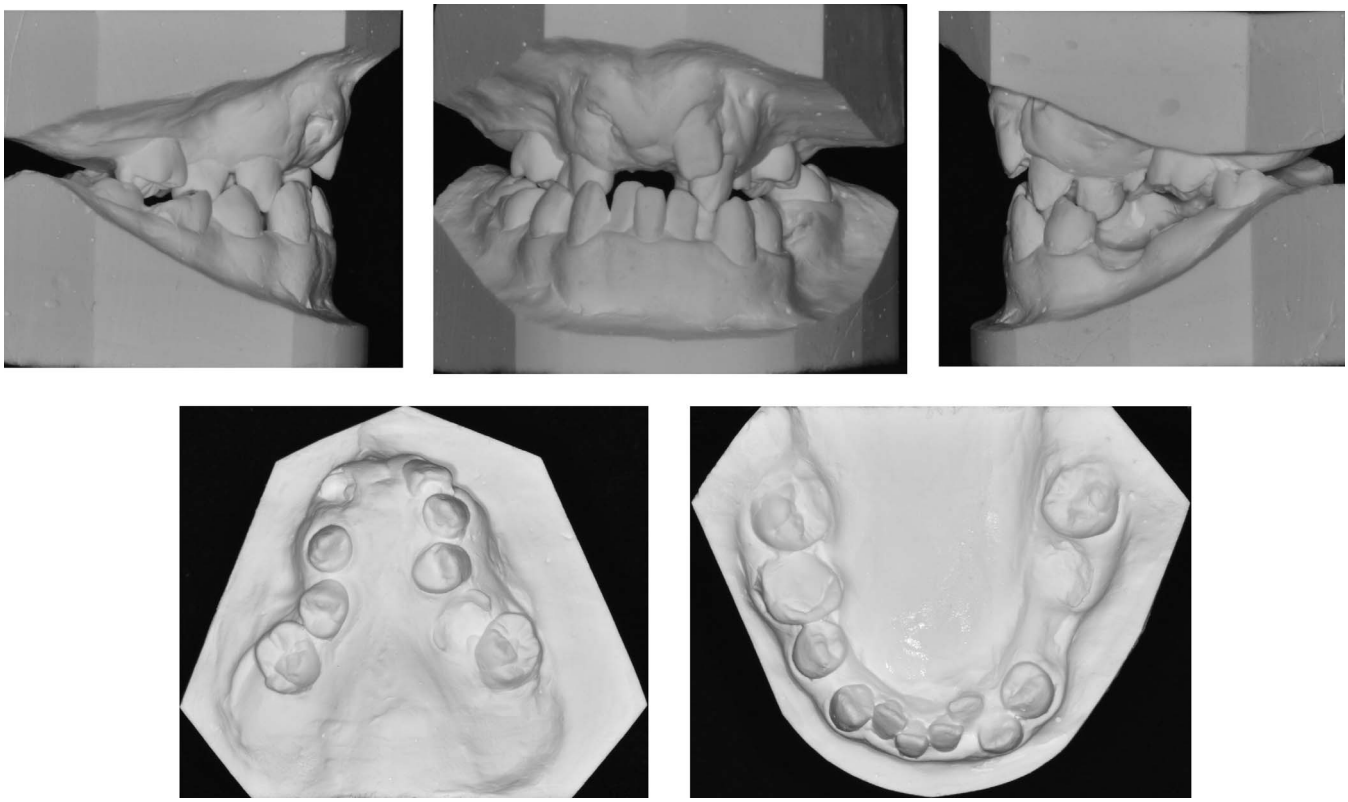

Figure 2. Pretreatment dental casts.

years. There was no other history of surgery. However, she wore hearing aids for her impaired hearing. Impaired hearing, caused by sclerosis of the otic canal, is a typical feature of patients with osteopetrosis.

Treatment Objectives

The objectives of treatment were: (1) to improve the skeletal pattern and soft tissue profile, (2) to achieve normal overjet and overbite after the correction of the anterior crossbite, (3) to relieve the crowding of teeth, and (4) to achieve an ideal occlusion.

Treatment Alternatives

The following three treatment options were considered: (1) presurgical orthodontic treatment, followed by simultaneous bimaxillary orthognathic surgery and bilateral alveolar cleft repair, (2) bilateral alveolar cleft repair with iliac bone graft, followed by maxillary horizontal expansion and camouflage orthodontic treatment; (3) camouflage orthodontic treatment with prosthodontic treatment, excluding any bone surgeries.

The first option included bimaxillary orthognathic surgery and genioplasty for improvements in the skeletal and soft tissue profiles. Simultaneous alveolar cleft repair with three-piece Le Fort-I osteotomy to reduce the overall duration of treatment would follow. This option enabled maxillary advancement to improve maxillary hypoplasia due to bilateral cleft lip and palate, but potential complications such as postoperative osteomyelitis related to the osteopetrosis could occur.

The second option included maxillary horizontal expansion after alveolar cleft repair. However, the prognosis would be unpredictable owing to the severe collapse of the maxillary arch. Additionally, though occlusal correction would be possible, correcting the skeletal deformity would not, and this option had the possibility of postoperative osteomyelitis related to alveolar cleft repair as in the first option.

The third option did not include bone surgery, thereby minimizing potential complications associated with osteopetrosis. However, this approach had the most therapeutic limitations because the treatment results were not guaranteed.

To achieve ideal skeletal and occlusal relationships, the first option was selected. However, it was decided that possibility of complications associated with osteopetrosis would be evaluated prior to the initiation of treatment.

Treatment Progress

A combination of surgical-orthodontic treatment was selected to treat the patient's chief complaint. As patients with osteopetrosis show a higher tendency for

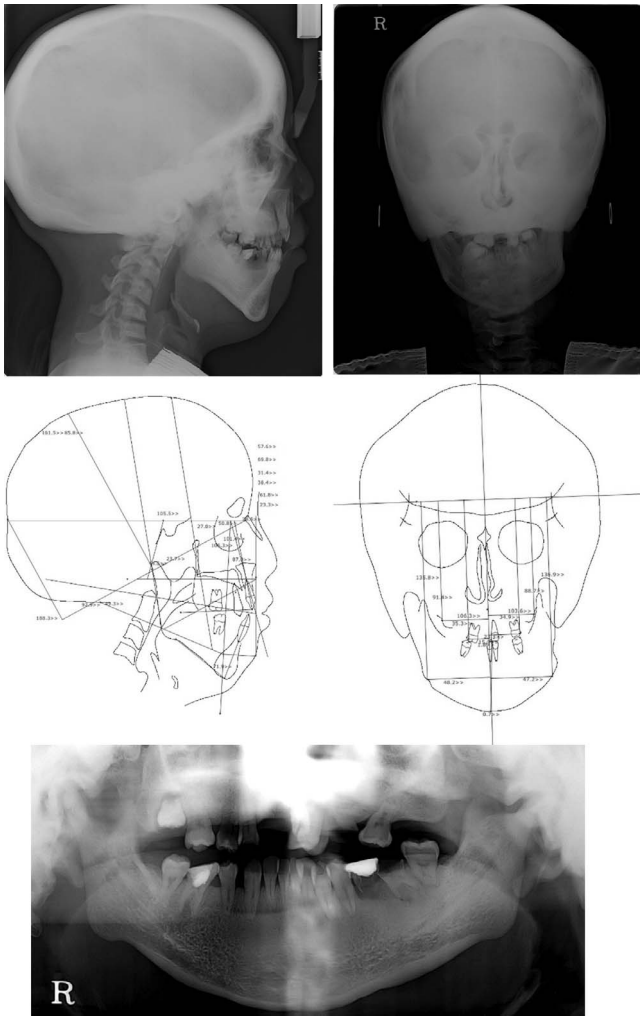

Figure 3. Pretreatment lateral and posteroanterior cephalograms, tracings, and panoramic tomogram.

complications such as osteomyelitis owing to decreased bone-turnover rate, the patient was referred for endocrine evaluation, specifically systemic bone-turnover examination, before the commencement of treatment. Bone density evaluation showed a Z-score of 3.2 in the femoral neck, 2.6 in the tibial neck, and 2.0 in the lumbar spine. These results corresponded to normal bone density. The level of C-telopeptide, a bone resorption marker, was 0.556 ng/mL. The levels of osteocalcin and bone alkaline phosphatase (bone formation markers) were 35.05 ng/mL and 13.6 μg/mL, respectively. The examination demonstrated a normal bone turnover rate (Table 1).

The patient did not report any history of pathologic fracture of the femur, pelvis, or any other bone, or failure of healing after tooth extraction, which is commonly observed in patients with osteopetrosis. Secondary osteomyelitis is the most common complication of tooth extraction in patients with osteopetrosis, which did not occur in this patient. Based on this history and the normal bone turnover rate of the patient, presurgical orthodontic treatment was decided to be initiated.

All teeth with hopeless prognoses were extracted before presurgical orthodontic treatment, and normal bone healing patterns were observed. Thereafter, leveling and alignment of teeth for decompensation was performed for 24 months without any problems, and the patient's dentition responded to normal orthodontic forces (Figure 5).

The patient underwent bimaxillary orthognathic surgery and alveolar cleft repair with iliac bone grafting under general anesthesia after presurgical orthodontic treatment. A three-piece Le Fort-I osteotomy and alveolar cleft repair with iliac bone graft were performed for expansion of posterior maxillary width, impaction (2 mm), and maxillary advancement (3 mm). Mandibular setback surgery with intraoral vertical

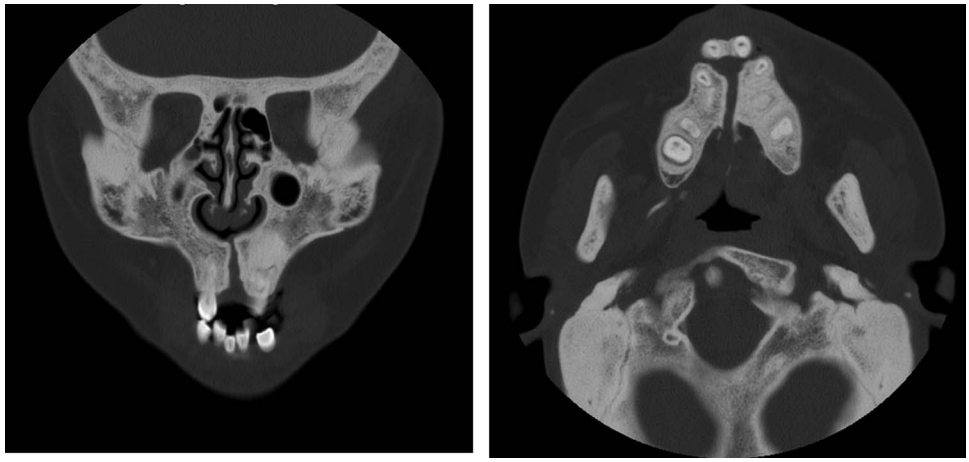

Figure 4. Pretreatment computed tomography.

Table 1. Pretreatment Serum Level Results for the Evaluation of Bone Remodeling Function

	Serum Level	Unit	References
Estradiol (E2)	101	pg/mL	Multi-reference
Thyroid-stimulating hormone	3.96	μIU/mL	0.35∼4.94
Luteinizing hormone	11.45	mIU/mL	Multi-reference
Follicle-stimulating hormone	4.4	mIU/mL	Multi-reference
Parathyroid hormone	65.3	pg/mL	15∼65
Insulin-like growth-factor-1 (Somatomedin-C)	185.3	pg/mL	179.9∼777.6
Bone alkaline phosphatase	13.6	μg/mL	Multi-reference
b-CrossLaps (C-telopeptide)	0.556	ng/mL	Premenopausal: $\leq$ 0.573
Osteocalcin	35.05	ng/mL	Premenopausal: 11-43
25-hydroxy-vitamin D	11.92	ng/mL	Multi-reference
Calcium	9.1	mg/dL	8.5∼10.5
Inorganic phosphate	3.7	mg/dL	2.8∼4.5

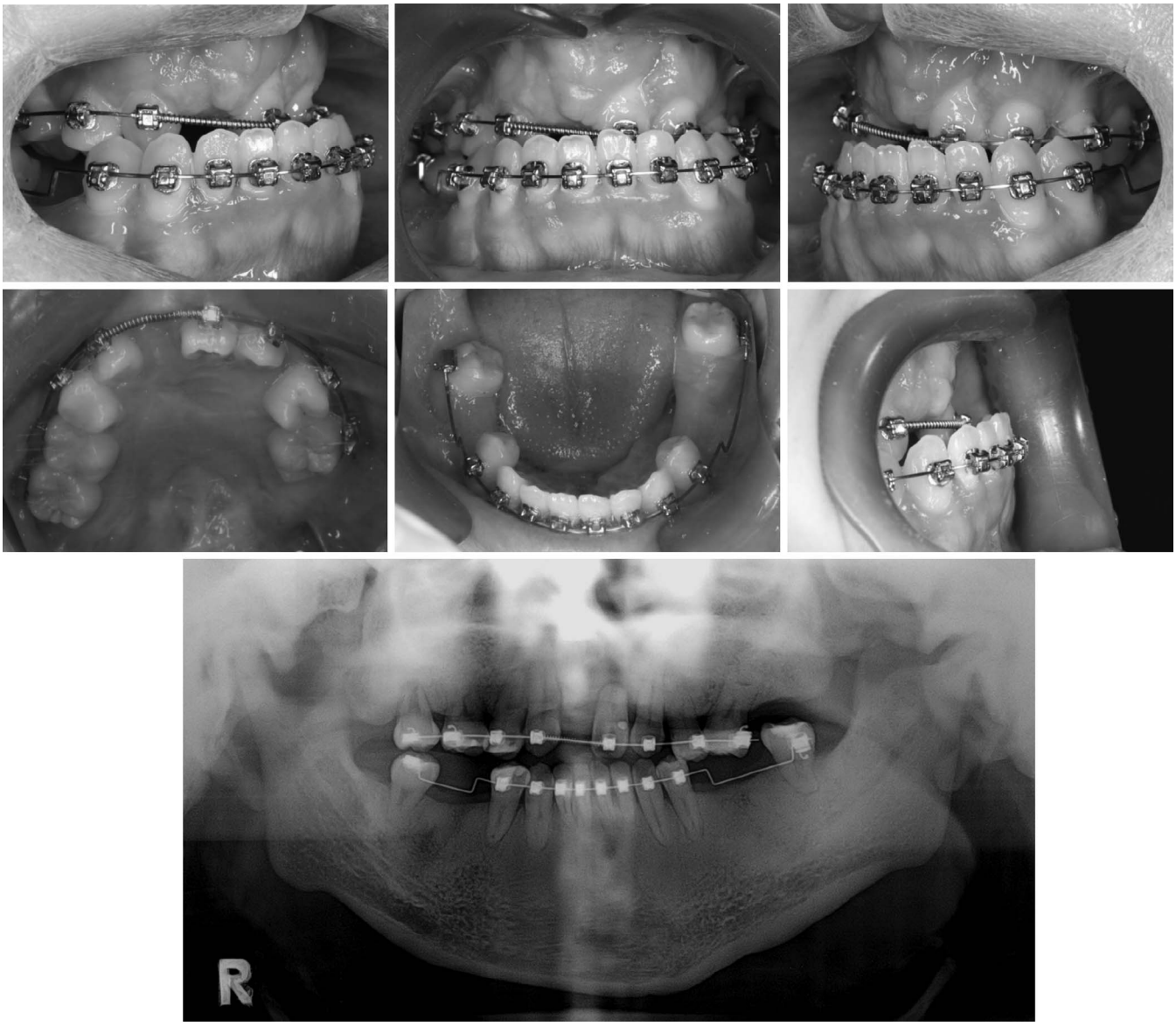

Figure 5. Intraoral photographs and panoramic tomogram after presurgical orthodontic treatment.

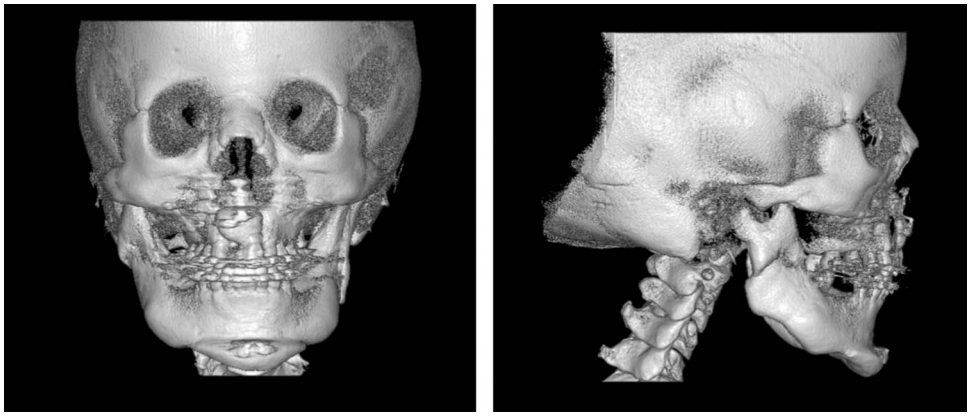

Figure 6. 3D computed tomography images taken 1 year after the orthognathic surgery.

ramus osteotomy was performed for the mandible, and advancement (8 mm) and reduction (5 mm) genioplasty was performed to improve the chin profile. While performing the surgical procedures, difficulty in sawing was noted due to the lack of bone marrow associated with the increased bone density in osteopetrosis. Intermaxillary fixation was performed 2 days after surgery and was maintained for 10 days. After the removal of intermaxillary fixation, active physiotherapy was performed in the outpatient department and functional recovery was achieved. The bony healing process was checked periodically and normal bone recovery was radiographically confirmed by computed tomography scanning 1 year after surgery (Figure 6). Skeletal changes and maintenance through the surgery were confirmed on the cephalometric superimpositions (Figure 7).

Postsurgical orthodontic treatment was performed for approximately 15 months to complete the treatment and establish stable occlusion (Figures 8 and 9). After the removal of the fixed orthodontic appliances, dental implants were placed and prosthetic rehabilitation were performed for the replacement of missing teeth. The total treatment duration was approximately 45 months, including the prosthetic phase of the treatment.

Treatment Results

After the surgical-orthodontic treatment and prosthetic rehabilitation, significant improvements in facial esthetics and occlusion were evident in clinical photographs (Figure 10). The alveolar cleft repair was successful, and considerable maxillary advancement was accomplished. There was no complication related to osteopetrosis. The patient was followed for 5 years. The patient desired to remove the titanium miniplates and screws used in the previous orthognathic surgery.

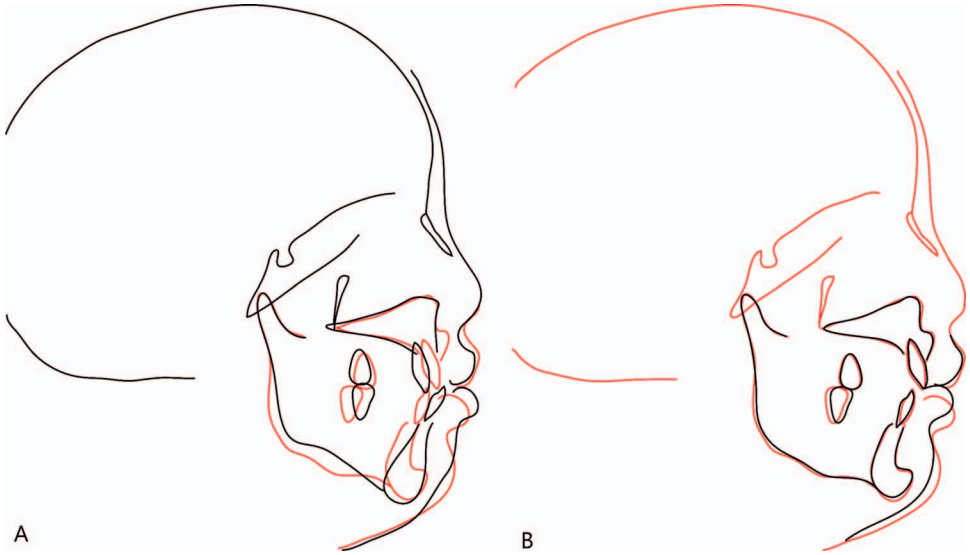

Figure 7. Superimposition of the lateral cephalogram tracings. (A) preoperation and postoperation. Black, preoperation; red, postoperation; (B) postoperation and 1 year after operation. Red, postoperation; black, 1 year after operation.

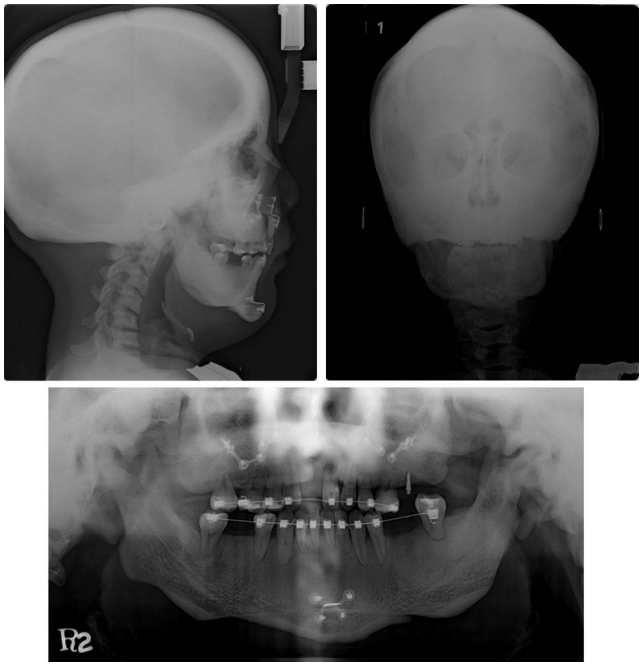

Figure 8. Lateral and posteroanterior cephalograms, tracings, and panoramic tomogram after postsurgical orthodontic treatment.

Successful bone union was confirmed during the surgical removal of the titanium miniplates (Figure 11).

DISCUSSION

Treatment of osteopetrosis involves stimulating the osteoclasts or providing alternative sources of osteoclasts.[10] Bone marrow transplantation is the primary mode of treatment for infantile osteopetrosis, and hormonal therapy such as corticosteroid and parathyroid hormones can be used.[14] Few reports of treatment for dentofacial deformities in the craniofacial region or for malocclusion have been reported, due to the high prevalence of osteomyelitis. The principal strategy for the treatment of osteopetrosis includes avoiding and limiting bone surgery whenever possible.[13] Therefore, the only treatment guideline that has been reported suggests that supportive therapy should be performed, without active treatment.[15] However, because dentofacial deformities or malocclusions may cause several social and psychological problems, active treatment may sometimes be essential for improving a patient's quality of life.

This is the first report to describe the protocol of surgical-orthodontic treatment for severe skeletal malocclusion in a patient with autosomal dominant osteopetrosis. In addition, this case was particularly rare, as bilateral cleft lip and palate accompanied the

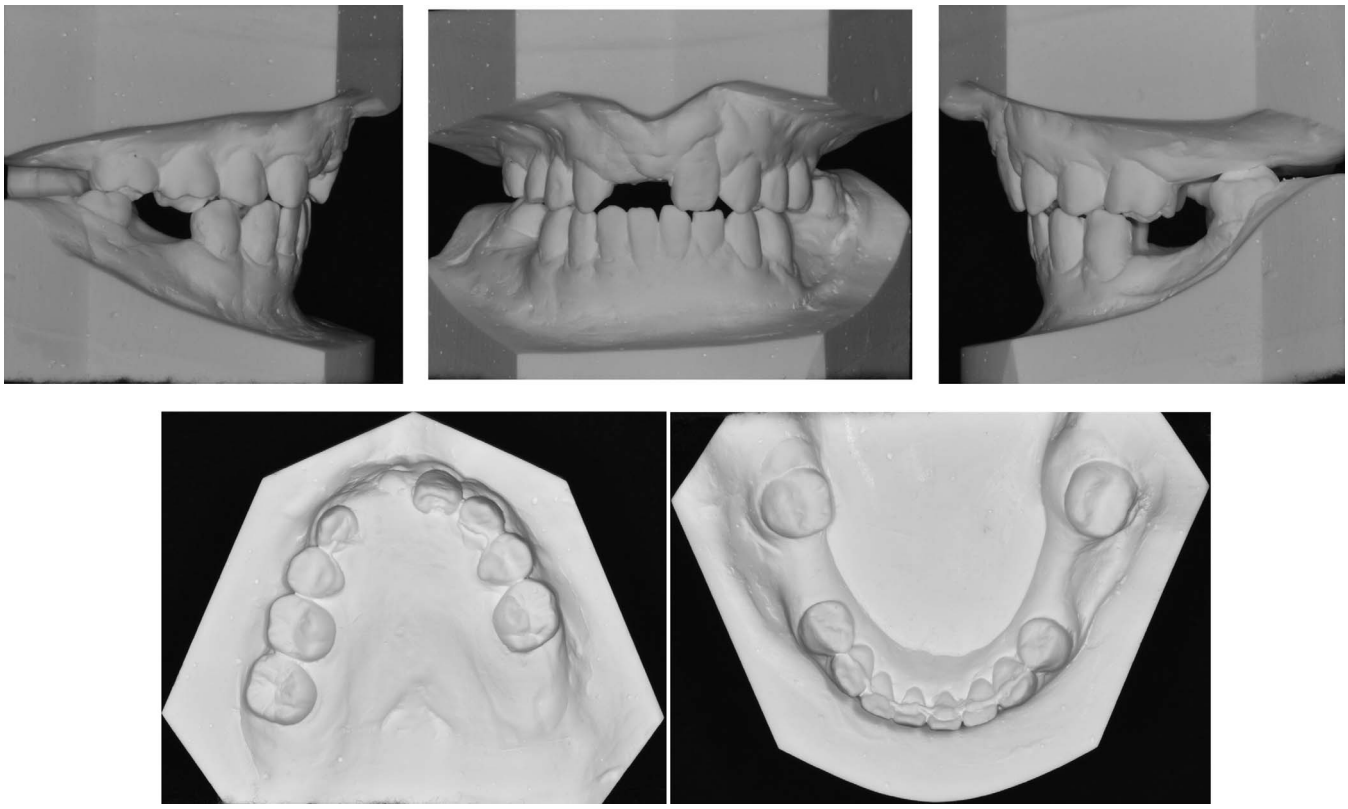

Figure 9. Dental casts after postsurgical orthodontic treatment.

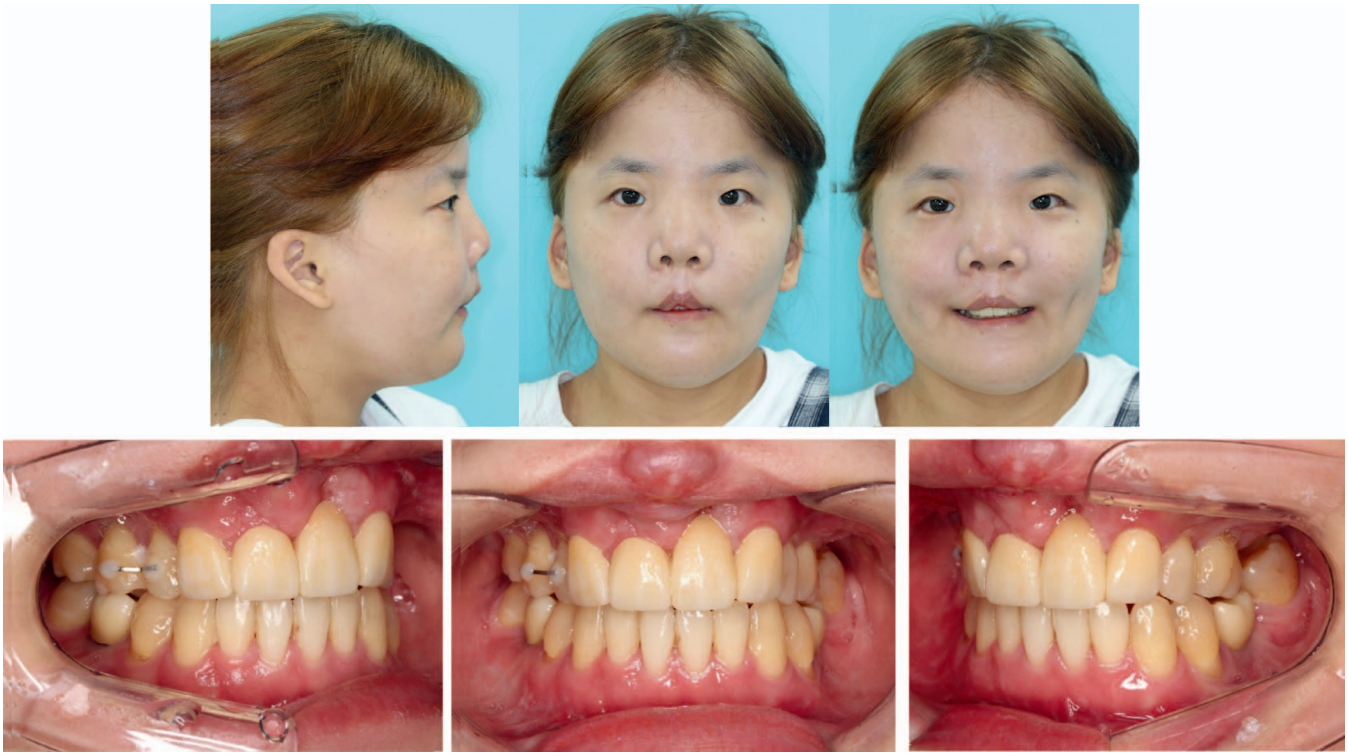

Figure 10. Post-treatment clinical photographs.

osteopetrosis. This patient could not receive alveolar cleft repair due to osteopetrosis, and unrepaired alveolar clefts place significant limitations on treating the patient with orthodontic therapy alone. Therefore, surgical-orthodontic treatment was chosen as the optimal treatment from the available alternatives.

Several dentists argue that treatments such as dental implants, tooth extractions, maxillofacial surgery, and orthodontic treatment should be avoided in patients with osteopetrosis, because of the increased susceptibility to osteomyelitis, which also occurs in medication-related osteonecrosis of the jaw (MRONJ) in patients on bisphosphonate therapy.[16] However, because the pathogenesis of osteomyelitis in patients with osteopetrosis is believed to be similar to that of MRONJ caused by antiresorptive drugs (ie, osteoclast deterioration),[17] recent experiences with MRONJ have led to the recognition of the importance of bone-turnover rate in the treatment of osteopetrosis patients. As dental extractions, implant placements, and other surgical procedures are usually performed after restoring the bone-turnover marker levels for prevention of MRONJ, bone surgeries such as orthognathic surgery, orthodontic treatment, and placement of dental implants may be possible if bone-turnover rate is normal in patients with osteopetrosis.

Fortunately, preoperative examination of bone-remodeling markers in this patient revealed normal bone-remodeling functions, evident by uneventful healing after previous extractions. These findings were en-

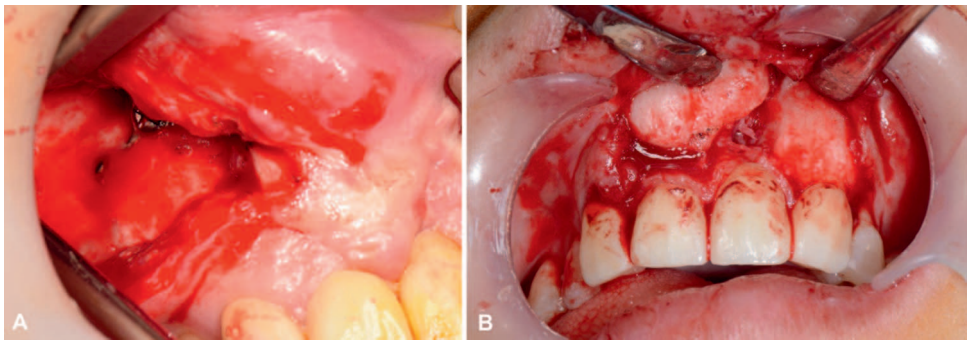

Figure 11. Intraoperative photographs showing complete bone healing at the osteotomy sites, 5 years after orthognathic surgery.

couraging for the initiation of surgical-orthodontic treatment. If the results of the preoperative examination of bone-remodeling markers had been abnormal, surgical-orthodontic treatment was to have been postponed, pending drug therapy to normalize bone-turnover rate by using teriparatide, a recombinant parathyroid hormone.[18]

Although this case report suggests the possibility of orthodontic treatment accompanying bone surgery for craniofacial osteopetrosis patients and the results supported the chosen treatment protocol, evidence provided by case reports has limitations and may be misleading. Clinical case-control studies are required in the future as few such studies have been conducted.

CONCLUSIONS

- Orthognathic surgery in patients with craniofacial osteopetrosis, a condition associated with osteoclast dysfunction, is generally avoided because of the risk of osteomyelitis. This case report showed that a favorable surgical-orthodontic treatment outcome could be achieved when bone turnover is normal, even in patients with adult osteopetrosis. This case report highlights the possibility of active bone surgery in osteopetrosis patients, after endocrine evaluation.

ACKNOWLEDGMENTS

We would like to thank Editage for language editing. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Barry CP, Ryan CD. Osteomyelitis of the maxilla secondary to osteopetrosis: report of a case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;95(1):12–15.
2. Khullar SM, Tvedt D, Chapman K, Herlofson BB. Sixty cases of extreme osteonecrosis and osteomyelitis of the mandible and maxilla in a West African population. *Int J Oral Maxillofac Surg*. 2012;41(8):978–985.
3. Helfrich MH, Aronson DC, Everts V, et al. Morphologic features of bone in human osteopetrosis. *Bone*. 1991;12(6): 411–419.
4. Burr DB, Martin RB. Errors in bone remodeling: toward a unified theory of metabolic bone disease. *Am J Anat*. 1989; 186(2):186–216.
5. Bakeman RJ, Abdelsayed RA, Sutley SH, Newhouse RF. Osteopetrosis: a review of the literature and report of a case complicated by osteomyelitis of the mandible. *J Oral Maxillofac Surg*. 1998;56(10):1209–1213.
6. Wu CC, Econs MJ, DiMeglio LA, et al. Diagnosis and Management of Osteopetrosis: Consensus Guidelines From the Osteopetrosis Working Group. *J Clin Endocrinol Metab*. Sep 1 2017;102(9):3111–3123.
7. Coccia PF, Krivit W, Cervenka J, et al. Successful bone-marrow transplantation for infantile malignant osteopetrosis. *N Engl J Med*. 1980;302(13):701–708.
8. Solh H, Da Cunha AM, Giri N, et al. Bone marrow transplantation for infantile malignant osteopetrosis. *J Pediatr Hematol Oncol*. 1995;17(4):350–355.
9. Lam DK, Sandor GK, Holmes HI, Carmichael RP, Clokie CM. Marble bone disease: a review of osteopetrosis and its oral health implications for dentists. *J Can Dent Assoc*. 2007; 73(9):839–843.
10. Drake MT, Collins MT, Hsiao EC. The Rare Bone Disease Working Group: report from the 2016 American Society for Bone and Mineral Research Annual Meeting. *Bone*. 2017; 102:80–84.
11. Junquera L, Rodriguez-Recio C, Villarreal P, Garcia-Consuegra L. Autosomal dominant osteopetrosis and maxillo-mandibular osteomyelitis. *Am J Otolaryngol*. 2005;26(4): 275–278.
12. Bollerslev J, Andersen PE, Jr. Radiological, biochemical and hereditary evidence of two types of autosomal dominant osteopetrosis. *Bone*. 1988;9(1):7–13.
13. Naval L, Molini MS, Herrera G, Naval B. Dental implants and osteomyelitis in a patient with osteopetrosis. *Quintessence Int*. 2014;45(9):765–768.
14. Kocher MS, Kasser JR. Osteopetrosis. *Am J Orthop (Belle Mead NJ)*. 2003;32(5):222–228.
15. Balan A, Girija KL, Ranimol P. Osteomyelitis of maxilla in infantile osteopetrosis: a case report with review of literature. *Int J Clin Pediatr Dent*. 2011;4(2):125–128.
16. da Silva Barbirato D, Fogacci MF, Arruda M, Rodrigues MO, Neto LV. Periodontal profile and radiographic characterization of the jaws in a patient with autosomal dominant osteopetrosis. *Endocrinol Diabetes Metab Case Rep*. 2017; 2017:16–0106.
17. Goss A, Bartold M, Sambrook P, Hawker P. The nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in dental implant patients: a South Australian case series. *J Oral Maxillofac Surg*. 2010;68(2):337–343.
18. Hasegawa T, Kawakita A, Ueda N, et al. A multicenter retrospective study of the risk factors associated with medication-related osteonecrosis of the jaw after tooth extraction in patients receiving oral bisphosphonate therapy: can primary wound closure and a drug holiday really prevent MRONJ? *Osteoporosis Int*. 2017/08/01 2017;28(8):2465–2473.