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Orthodontic management of a patient who underwent anti-cancer therapy for acute myelogenous leukemia: A case report

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Abstract

Survivors of childhood cancer are at risk for disturbance of craniofacial growth and dental development as a result of the side-effects of their therapeutic protocols. For this reason, special considerations are required when oral management is planned for these children. We herein report the successful 2-stage orthodontic treatment of a girl who was diagnosed with acute myelogenous leukemia（AML） and who underwent multiple therapeutic protocols, including total body irradiation（TBI）, bone marrow transplantation（BMT）, and chemotherapy during adolescence. She showed skeletal Class III malocclusion with a low mandibular plane angle, anterior crossbite, crowding, and severely disturbed dental development, including tooth agenesis, and arrested root development, and enamel hypoplasia at 12 years of age, when she first visited our clinic. Growth modification in adolescence period with functional appliances followed by treatment with a fixed appliance was performed to correct her malocclusion. The aim of this case report is to show the long-term outcome of orthodontic treatment in a patient who underwent multiple anticancer therapies that influenced craniofacial growth and dental development.

INTRODUCTION

Due to the progress of medical care in recent decades, the survival rate of patients with childhood cancer has dramatically improved[1]. With the improvement of the survival rate, the quality of life（QoL）after childhood cancer treatments received increased attention[2]. We currently have more chances to encounter survivors of childhood cancer who request orthodontic treatment for the correction of malocclusion[3].

Childhood cancer treatment, including chemotherapy, radiotherapy, surgery, and additional care can cause various late side effects, including neurotoxicity, growth impairment, and hormone disorder[4,5]. In the craniofacial and oral region, disturbances of craniofacial growth and dental development are frequently reported[6,7]. Growth retardation of the cranial base, facial sagittal and vertical dimensions are seen in survivors who receive craniofacial radiotherapy and/or chemotherapy[8]. Disturbances of dental development, such as agenesis[9], root stunting[10], enamel defect[11], hypodontia[12], delayed/arrested eruption of tooth, and microdontia[13], are also commonly seen after radiotherapy and/or chemotherapy. Especially in patients who receive bone marrow transplantation（BMT）with pre-transplant total body irradiation（TBI）, such

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disturbances in the craniofacial and oral region are more likely to be frequent and severe[8,14]. Further, dental caries, lesion, mucositis, xerostomia, and cariogenic microflora are also observed after cancer treatment[15]. Malocclusion and impairment of the oral health-related quality of life may be seen among survivors of childhood cancer[6]. However, when orthodontic treatment is performed for survivors of childhood cancer, special considerations are required. Orthodontists should understand their primary disease, its treatment protocols, and its effects on the craniofacial and oral region, and orthodontic tooth movement[16], since survivors of childhood cancer have great potential risks, which are associated with complications of orthodontic treatment, such as root resorption and caries[17].

We herein report the successful 2-stage orthodontic treatment of a 12-year-old girl who was diagnosed with acute myelogenous leukemia (AML) and who underwent BMT with pre-transplant TBI and chemotherapy during early childhood. She had chronic graft-versus-host disease (GVHD), hypothyroidism, hyperinsulinemia, hypoglycemia, hypogonadism, and short stature after cancer treatment. She showed skeletal Class III malocclusion with a low mandibular plane angle, crowding, and severely disturbed dental development, including tooth agenesis, arrested root development, V-shaped root, and enamel hypoplasia. In the present case, we show the long-term outcomes of orthodontic treatment in a childhood cancer survivor with disturbed craniofacial growth and dental development after cancer treatment.

CASE HISTORY

A Japanese 12-year-old girl first visited our hospital with chief complaints of anterior crossbite and crowding of the maxillary anterior teeth. She had been diagnosed with AML at 6 months of age and underwent BMT at 1 year of age. High-dose chemotherapy (cyclophosphamide; CPA) and TBI (12 Gy) were performed for preconditioning, followed by BMT. After these treatments, she exhibited chronic GVHD, hypothyroidism, hyperinsulinemia, hypoglycemia, hypogonadism; thus, multiple medications were prescribed, including carcinostatic substances (methotrexate), a hypoglycemic agent (voglibose), a digestive enzyme preparation (excelase), and a thyroid hormone preparation (levothyroxine sodium hydrate). She also showed short stature (131.6cm, -2.9 S.D.). She did not receive growth hormone treatment.

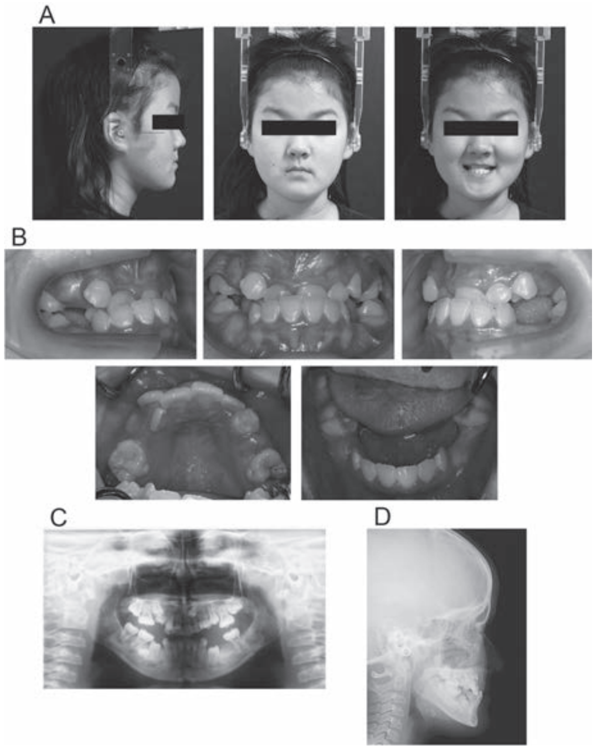

Figure 1. Pre-treatment records (age: 12 years and 4 months). A, Facial photographs. B, Intraoral photographs. C, Panoramic radiographs. D, Lateral cephalograms.

An extraoral examination showed a concave type facial profile with a large nasolabial angle and retruded lips with midfacial deficiency. She also exhibited long lower facial height and mild lip incompetency with an asymmetrical facial profile (Figure 1A). An intraoral examination revealed negative anterior overjet, large overbite with blocked out upper right canine and an Angle Class I molar relationship. The right upper and lower first molars were medially localized in comparison to the contralateral side (Figure 1B). A panoramic radiograph showed impacted upper left canine and both second premolars on the right side (Figure 1C). The predicted arch length discrepancy of the upper dental arch was -26.9 mm, while that of the lower

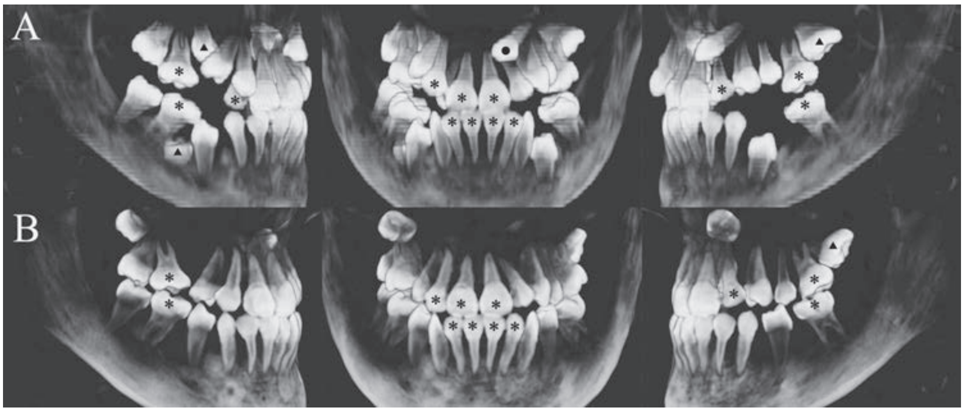

Figure 2. Cone-beam computed tomography. A, pre-treatment(age: 12 years and 4 months). B, Post-active treatment (age: 19 years and 11 months). *= short V-shaved root, ▲=impaired root development, ●=impacted tooth.

Table 1: Lateral cephalometric measurements.

	T1（12Y4M）: Pre-treatment			T2（17Y8M）: Pre-edgewise			T3（19Y11M）: Post-treatment					
		Norm（12Y F）			Norm（18Y F）			Norm（18Y F）				
	Measure	Mean	SD	Measure	Mean	SD	Measure	Mean	SD	T2-T1	T3-T2	T3-T1
Angular (deg.)												
SNA	82.5	80.7	0.5	82.3	80.8	0.4	82.3	80.8	0.4	−0.2	0.0	−0.2
SNB	85.5	77.6	1.9	84.7	77.9	1.5	85.4	77.9	1.6	−0.8	0.7	−0.1
ANB	−3.0	3.0	2.7	−2.4	2.8	2.2	−3.1	2.8	2.4	0.6	−0.7	−0.1
MP-FH	24.9	29.6	1.4	26.9	30.5	1.7	26.5	30.5	1.9	2.0	−0.4	1.6
U1-FH	104.6	112.2	1.0	111.2	112.3	0.1	116.5	112.3	0.5	6.6	5.3	11.9
L1-MP	80.3	92.5	2.3	73.1	93.4	3.0	67.5	93.4	3.8	−7.2	−5.6	−12.8
IIA	150.2	125.4	2.5	148.9	123.6	2.4	149.5	123.6	2.4	−1.3	0.6	−0.7
Linear（mm）												
S-N	62.8	66.9	1.2	62.8	67.9	1.4	62.8	67.9	1.4	0.0	0.0	0.0
N-Me	105.5	120.9	3.5	114.4	125.8	2.3	114.9	125.8	2.2	8.9	0.5	9.4
N/PP	48.5	54.7	2.2	51.1	56.0	1.9	51.1	56.0	1.9	2.6	0.0	2.6
Me/PP	56.6	64.8	2.3	62.8	68.6	1.6	63.5	68.6	1.4	6.2	0.7	6.9
Ptm-A/PP	43.1	46.4	1.4	41.7	47.9	2.2	41.7	47.9	2.2	−1.4	0.0	−1.4
Go-Me	71.0	69.2	0.5	74.9	71.4	0.9	74.9	71.4	0.6	3.9	0.0	3.9
Ar-Go	40.7	44.2	1.1	44.2	47.3	0.9	47.7	47.3	0.1	3.5	3.5	7.0
Ar-Me	101.4	102.3	0.2	109.3	106.6	0.5	110.8	106.6	0.7	7.9	1.5	9.4
OJ	−3.3	3.2	6.5	0.5	3.1	2.4	1.9	3.1	1.1	3.8	1.4	5.2
OB	5.5	3.6	1.0	0.1	3.3	1.7	0.6	3.3	1.4	−5.4	0.5	−4.9
U6/PP	14.9	22.1	3.5	19.5	24.6	2.5	19.9	24.6	2.3	4.6	0.4	5.0
U1/PP	24.7	29.5	2.2	25.4	31.0	2.4	25.4	31.0	2.4	0.7	0.0	0.7
L6-MP	25.3	30.8	2.3	26.4	32.9	2.6	26.6	32.9	2.5	1.1	0.2	1.3
L1/MP	34.9	42.1	3.1	34.1	44.2	3.8	34.2	44.2	3.7	−0.8	0.1	−0.7

*For Japanese normative mean (Wada K. A study of the individual growth of maxillofacial skeleton by means of lateral cephalometric roentgenograms. J Osaka Univ Dent Sch. 1977; 22: 239–269.)
A=subspinale; Ar=articulare; B=supramentale; Cd=condyle; FH=Frankfort horizontal; Gn=gnathion; Go=gonion; IIA=interincisal angle; MP=mandibular plane; Me=menton; N=nasion; PP=palatal plane; Ptm=pterygomaxillary; S=sella.

dental arch was −8.2 mm. The anterior ratio was 74.6% due to the large size of the upper anterior teeth. There was a discrepancy between centric occlusion and centric relation; thus, there was an end-to-end incisor relationship. A panoramic radiograph and cone-beam computed tomography revealed either short or thin roots throughout the dentition (Figures 1 and 2).

In comparison to the Japanese norms[18], a lateral cephalometric analysis indicated a skeletal Class 3 jaw base relationship due to a deficient maxilla and anti-clockwise rotation of the mandible(point A-N-point B angle[ANB]=−3.0°, SNA= 82.5° SNB= 85.5°, mandibular plane[MP]-Frankfort horizontal plane[FH]=24.9°) (Figure 1D and Table1). The cranial base and maxilla length were short (sella [S]-nasion [N]=62.8 mm, pterygomaxillary [Ptm]-A/Palatal plane [PP]=43.1

mm) while the mandibular ramus height and length were within the normative range (gonion [Go] -menton [Me]=71.0 mm, articulare [Ar]-Go=40.7 mm, Ar-Me=101.4 mm). The upper and lower incisors were lingually inclined (upper incisor [U1]-FH=104.6°, lower incisor [L1]-MP=80.3°) which resulted in retruded lips. The postero-anterior cephalogram showed 1.0 mm mandibular deviation toward the left side from the facial midline.

TREATMENT OBJECTIVES

Based on these findings, we diagnosed this patient with a skeletal Class III relationship with an anterior crossbite, low mandibular plane angle, and severe crowding. Special consideration was required due to her medical history of anticancer therapy and malformed dentition.

Extraction of the blocked-out upper right lateral incisor and impacted upper left canine was planned for aligning the incisors, followed by the use of a functional appliance to correct the anterior crossbite and counterclockwise rotation of the mandible. The use of a fixed edgewise appliance was planned with further extraction of the upper left and lower left second bicuspids.

TREATMENT ALTERNATIVES

With regard to the impacted dentition, orthodontic retraction could have been considered with the extraction of other dentition. Reverse headgear treatment could have been applied instead of the removable functional appliance to correct the anterior reverse overjet. Double jaw surgery could have been considered to improve her concave-type facial profile with mid-facial deficiency and retruded lip. For this particular case, we avoided surgical intervention for her low bone density and thin root which resulted from her medical treatment history.

TREATMENT PLAN AND PROGRESS

Extractions of upper right lateral incisor and upper left cannie were performed under local anesthesia at 12 years and 8 months of age. After the extractions, a removable functional appliance was used for 17 months in order to correct anterior reverse overjet by retracting lower incisors and clockwise rotation of the mandible. After obtaining positive anterior overjet and puberty growth at 16 years and 4 months of age, extractions of the upper and lower second bicuspid were performed. After the extraction, fixed edgewise appliances were placed at 17 years 8 months of age (Figure 3). Pre-adjusted edgewise appliances (0.022-inch slot) with 0.012-inch nickel-titanium wires were placed in both dental arches to initiate leveling. Round wires were mainly used for the alignment of both arches and 0.016 stainless steel archwires were utilized for detailing. After 19 months of the second phase of treatment, all appliances were removed (Figure 4). Begg-type retainers were placed on both arches for retention.

TREATMENT RESULTS

The first phase of orthodontic treatment was initiated with a functional appliance after extracting the upper right canine. This improved the patient's anterior crossbite by proclination of the upper incisors and inclination of the lower incisors, together with clockwise rotation of the mandible (Figure 3B, 3D and 5). Between 12 years of age and 16 years of age, the upper incisors were inclined labially by 6.6° and extruded by 0.7 mm. The lower incisors were inclined lingually by 7.2° and intruded by 0.8 mm. The upper molars and the lower molars were extruded by 4.6 mm, and 1.1 mm, respectively. As a result, the overjet was increased from -3.3 mm to 0.5 mm, and the overbite decreased from 5.5 mm to 0.1 mm (Figure 3D, 5 and Table 1). The straight downward growth of the mandible was observed, while a skeletal class III relationship remained with almost the same degree of ANB angle (Figure 3D, 5 and Table 1). The root of the lower right second bicuspid showed arrested development, while the root of the contralateral tooth formed normally. The upper and lower right second bicuspids were still impacted and medial drift of the first molars resulted in a lack of space on the right side in both the maxilla

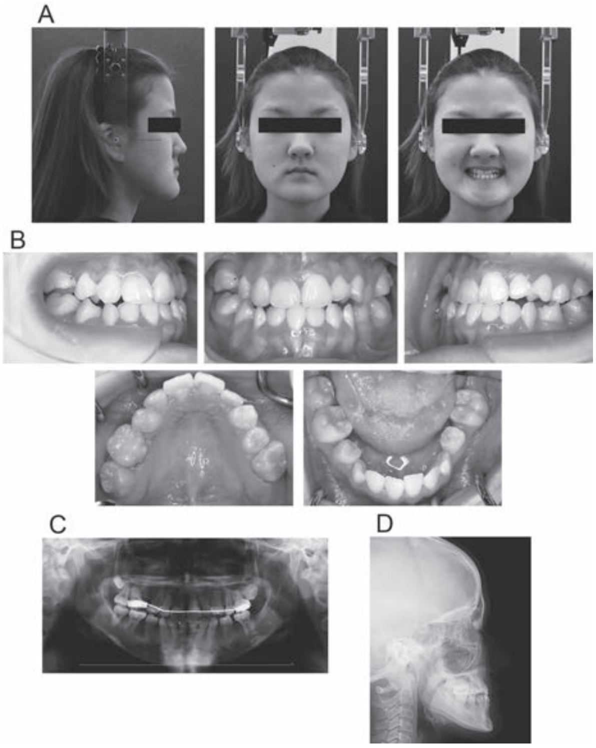

Figure 3.　Records at the initiation of the second phase treatment（age: 17 years and 8 months）. A, Facial photographs. B, Intraoral photographs. C, Panoramic radiographs. D, Lateral cephalograms.

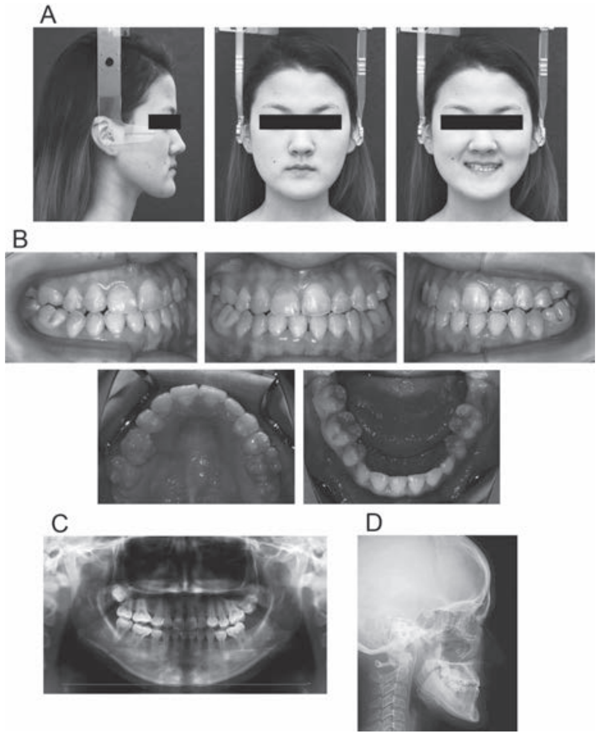

Figure 4.　Post-active treatment records（age: 19 years and 11 months）. A, Facial photographs. B, Intraoral photographs. C, Panoramic radiographs. D, Lateral cephalograms.

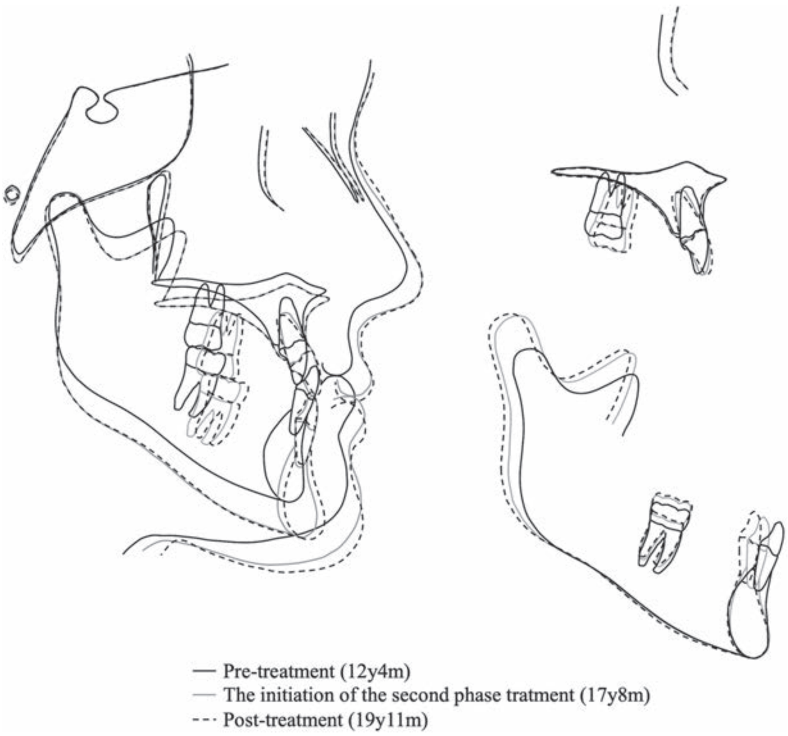

Figure 5.　Superimposed lateral cephalometric tracings on the SN plane at S: pre-treatment（black）, the initiation of the second phase of treatment（gray line）and post-treatment（dashed line）.

and mandible.

The second phase of orthodontic treatment was performed with the extraction of the impacted upper and lower second bicuspids. Although the occlusion was not established as an ideal Class I relationship between the canines and molars, a proper overbite and overjet were obtained without any orthodontic complications, such as root resorption (Figure 2B, 4B, 4C, and 4D). Between 16 years of age and 19 years of age, the SNB angle increased by 0.7°, with mandibular anticlockwise rotation. The upper incisors were inclined labially by 5.3° and the lower incisors were inclined lingually by 5.6°. Finally, an overjet of 1.9 mm and an overbite of 0.6 mm were achieved (Figure 4D, 5, and Table 1). A panoramic radiograph showed no root resorption and adequate root alignment (Figure 4C).

DISCUSSION

The advancement of cancer therapy significantly improved the survival rate of pediatric cancer patients[19]. It has also been reported that chemotherapy and radiotherapy could influence the development of multiple organs, including craniofacial structures[20]. This case report presented the long-term outcomes of 2-stage orthodontic treatment in a survivor who had received BMT during childhood and discussed the precautions during orthodontic treatment for childhood cancer survivors. In order to facilitate the provision of better comprehensive treatment for malocclusion in patients who have received cancer therapy at a young age, it is important to continuously report the clinical outcomes of orthodontic treatment.

Craniofacial growth

Several studies demonstrated that therapeutic irradiation for treating cancer in growing patients contains a growth-suppressive effect on the craniofacial skeleton[20]. Among children with acute lymphocytic leukemia who were treated with craniofacial irradiation (24 Gy), the cranial base, and facial vertical and sagittal dimensions were short at 5 years after cancer treatment[21]. This growth retardation of the craniofacial skeleton was prominent, especially in children who received irradiation before 6 years of age. In addition, pretransplant TBI is considered to have a significant growth-suppressive effect on the craniofacial skeleton[8]. According to Dahllöf[8], the cephalometry of anterior facial height (N-Me) and mandible length (Condyle [Cd]-Gnathion [Gn]) was much shorter in children with acute leukemia who had received stem cell transplantation (SCT) with TBI in comparison to sex-and age-matched controls. The study reported that the height of the upper anterior and posterior alveolar processes in children treated by SCT with TBI were reduced by 50% in comparison to the control, which suggested that the reduction of the alveolar processes is caused by the adverse effect of irradiation on normal dental development.

The present case exhibited a shorter length of cranial base (S-N=62.8 mm), mandible length (Cd-Gn=122.3 mm), maxilla length (Ptm-A/PP=41.7 mm), and lower anterior facial height (N-Me=114.9 mm) (Figure 4D and Table1). The height of the anterior alveolar processes in the maxilla (Porosthion [Pr] -PP=13.8 mm) and the mandible (Infradentale [Id] -Mp=23.3 mm) was also short (Figure 4D). Between 12 and 16 years of age, the ramus height and mandibular body length increased 1.2 mm and 1.3 mm per year respectively (Figure 5 and Table1).

Disturbances in dental development.

A number of studies have reported developmental disturbances in dentition after cancer therapy[12,22]. The severity of dental defects seems to be associated with the timing, protocols, and duration of cancer treatment[23]. According to the latest systematic review and meta-analysis, dental defects were significantly associated with the combination of chemotherapy and radiotherapy[7]. The study concluded that younger age at the diagnosis, higher radiation dose, and TBI are associated with a higher prevalence of dental defects. A previous study revealed dental abnormalities, such as tooth agenesis and impaired root development were seen in the group who received BMT at<6 years of age[14]. A study showed that chemotherapy without radiation could also result in tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, and premature apical closure[24]. Animal experiments with mice revealed a negative effect of an anticancer agent（CPA） on developing dentition by showing congenital missing teeth and truncated roots. Interestingly, the severity of the dental defects was associated with the developmental stages of the tooth germs at the time of CPA administration[25].

In the present case, tooth agenesis of lower left second premolar and second molar, arrested root development of upper right second molar and lower right second premolar, impaction of upper right cannie, and V-shaped the root of almost all teeth were observed （Figure 2）. The severity of each dental disturbance appears to be associated with the dental development of each permanent tooth.

Orthodontic treatment

In the orthodontic treatment of patients with a history of anticancer therapy, it is advisable to reduce the duration of treatment when possible and to use a light force in order to minimize the risk of damage to the root[17]. Simple mechanics should also be chosen to prevent infection, caries, and oral ulcers. A previous study[26] demonstrated that longer usage of fixed appliances is a risk factor for root resorption. Additionally, the probability of external root resorption was less in patients who received 2-stage treatment with removable appliances followed by the use of a fixed appliance in comparison to those who received single-stage treatment with fixed appliances. For these reasons, we used removable appliances for the first phase of treatment and an edgewise appliance for the second phase of treatment. In this way, we tried to minimize the duration of edgewise treatment and finished the treatment in 19 months after the placement of the fixed appliances. At the end of active orthodontic treatment, her occlusion and oral health showed good improvement without major complications, such as further root resorption （Figure 4）.

Cancer treatment often results in decreased resistance to infection and atrophy of the oral mucosa, and even minor irritation from orthodontic treatment can cause severe ulceration[17]. In terms of such irritation, removable appliances also appeared to be suitable for the present patient who had chronic GVHD after BMT. In the present case, we mainly used round wires for the alignment of both arches in fixed appliance therapy. Root resorption during orthodontic treatment was monitored by obtaining X-ray films every 6 months.

CONCLUSION

We described the successful 2-stage orthodontic treatment of a Japanese girl with a history of BMT for the treatment of AML during childhood, who showed skeletal Class III malocclusion with negative overjet, low mandibular plane angle, crowding, and severe disturbance of dental development, including tooth agenesis and impaction. As a result, improved occlusion and oral health were achieved. Our case report provides useful information for understanding the etiology, progress, and precautions of orthodontic treatment for childhood cancer treatment.

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