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Dento-maxillofacial Abnormalities Caused by Radiotherapy and Chemotherapy

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ABSTRACT

A case of dento-maxillofacial abnormality involving a 10-year-old male patient with a history of esthesioneuroblastoma is presented. This patient had been treated with 54 Gy ^{60}Co-gamma-radiation to the nasal cavity for 6 weeks and 6 cycles of combination chemotherapy of Cyclophosphamide, Cisplatin, Adriamycin, VM-26 (Teniposide), and DTIC (Dacarbazine) when he was 16 months of age. Five years after cessation of cancer therapy, he was disease free and transferred for extensive dental care to Kyung Hee University Dental Hospital. A clinical and radiologic follow-up over last 4 years showed root stunting, premature closure of the root apices, microdontia, developmental arrest, small crowns, and partial anodontia. Maxillofacial morphology evaluated by cephalometric analysis showed deficiency of maxillary development. (***Korean J Oral Maxillofac Radiol 2000 ; 30 : 287-292***)

KEY WORDS : radiotherapy, chemotherapy, esthesioneuroblastoma

Pediatric cancer in the early year of life is the second largest cause of mortality surpassed only by accidents. Between 50 to 60% of the children diagnosed with cancer would be cured from the use of different therapies including surgery, radiotherapy (RT), and chemotherapy (CT).[1] The combination of RT and CT is used frequently on pediatric oncological patients. In this type of treatment the maxillofacial complica-tions constitute a common problems and may start anomalies in the dentomaxillofacial development. If the affected children are treated in the early life, this raises the possibility of complications.

Chemotherapy interferes with the cell cycle and with intracellular metabolism, and may cause retarded dental development, microdontia, taurodontism, and root stunting. Alteration of ameloblastic reproduction secretory function, membrane permeability and calcium exchange across the cell membrane can produce irregular enamel matrix formation and irregularities in the surface of enamel, manifested clinically by enamel radiopacities. Also altered odontoblastic activity can produce shortend, thinned, and blunted roots.[2,3] Radiation damage occurs simultaneously to the bone, tooth, periodontal ligament, and pulp.[2] Radiation effects, unlike chemotherapy sequelae, are limited to the irradiated area. Mature ameloblasts are permanently damaged by 10 Gy of radiation; 30 Gy halts tooth development at the point of maturation at which the teeth are irradiated.[4] Chemoradiation effects on facial bones result from osteocyte death, microvascular injury, periosteal damage, and fibrous replacement of marrow spaces. This changes lead to altered bone growth and development.

The nature and severity of potential side effects vary with the child's age at diagnosis, doses and schedules of treatment, and the anatomic regions treated.[2,3,5,6] Knowledge of the stage of dental development at the time of oncology treatment and the type of therapy allows the clinician to predict dento-maxillofacial effects of the chemoradiation.

Representative case illustrates the clinical and radiographic manifestations of chemoradiation on the dental and craniofacial development.

Case report

An 1-year-old male presented with a soft tissue mass of the left nasal cavity. The mass involved upper nasal cavity area. Computed tomography showed the lesion extend from the nasal cavity to ethmoid sinus. There was partial destruction of the ethmoid sinus. Biopsy revealed an esthesioneuroblastoma.

Because the tumor extension was not significant, surgical resection was excluded at this stage. This patient had been treated with RT and CT. Electron energy had been applied by means of a ^{60}Co-gamma-radiation. Radiation therapy were carried out with a total tumor dose of 5,400 cGy in 30 fractions of 180 cGy. The field of irradiation included the both side of nasal cavity and ethmoid sinus, and the size of irradiation

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field were 4 cm × 4.5 cm (frontal) and 6 cm × 4.5 cm (lateral) (Figs. 1A, B). Chemotherapy were carried out with Cyclophosphamide, Cisplatin, VM-26 (Teniposide), Adriamycin and DTIC (Dacarbazine) over 42 weeks (6 cycles).

Five years after cessation of cancer therapy, he was disease free and transferred for extensive dental care to Kyung Hee University Dental Hospital.

At age 6, a clinical examination revealed a Class III facial profile with loss of vertical dimension and severe mobility of upper incisors. Radiologic examination showed that the patient had a mixed dentition with normal primary dentition, short and tapered root of both central incisors, and delayed eruption of both lateral incisors in maxilla.

Posteriorly both premolar tooth germs were not visible and both first molars showed delayed eruption (Figs. 2A, 3A, 4A, 5A).

At age 7, radiologic examination of maxillary teeth of the patient exhibited shortening of both canines, malformation and missing of both premolars, and root stunting of both first molars (Figs. 3B, 4B, 5B).

At age 9, radiologic examination of maxillary teeth revealed early exfoliation of both deciduous molars, arrest of root development of both canines, underdevelopment and missing of both premolars, and full eruption of both first molars with root stunting. In addition, patients exhibited missing of both second mandibular premolars and delayed eruptional sequences of the mandibular teeth (Figs. 2B, 3C, 4C, 5C).

Lateral cephalometric analysis was made 5 years and 9 years after chemoradiation (Figs. 6A, B). To evaluated craniofacial growth, the sellae-nasion-A point angle (SNA), sellae-nasion-B point angle (SNB), A point-nasion-B point angle (ANB), sellae-nasion/gonion-menton angle (SN/GoMe), condylion-A point distance (midfacial length : Co-A), condylion-gnathion distance (Co-Gn), nasion perpendicular to point A, and nasion perpendicular to pont B were measured (Table 1). Cephalometric analysis revealed a normal development of mandible and a significant hypoplasia of maxilla (Figs. 7A, B).

Discussion

Esthesioneuroblastoma is an uncommon tumor arising in the nasal cavity or paranasal sinuses.[7] The treatment is controversial. Radiotherapy, alone or combined with surgery, has demonstrated to be an effective treatment in early stages. Chemotherapy, associated to radiotherapy, can improve the outcome in advanced stages and reduce the morbidity related to surgery.[8,9]

This type of intensive oncologic treatement induces a series of immediate and long-term side effects. In this type of treatment, acute side effects–neutropenia, oral mucositis, severe trismus, and pain–rendered all dental treatment impossible at that stage and led to poor nutritional intake and oral hygiene.[10] The chemoradiation-induced effect on the saliva–hyposalivation, low pH, diminished buffer capacity, and alteration of the oral microflora toward a more acidogenic flora–resulted in the development of rampant caries.[10,11] The bone marrow is

Table 1. Cephalometric values of patient vs standard norms

	Measured value (at age 10)	Norm value*
SNA	73.5°	82.48°
Nasion perpendicular to point A	−3.5 mm	−2 mm
Midfacial length (Co, Pt-A)	74 mm	83 mm
SNB	74°	80.42°
Nasion perpendicular to point B	−5 mm	−5 mm
Mandibular length (Co-Gn)	103 mm	103 mm
ANB	0.5°	2.05°
Convexity (N-A-Pog)	0.5°	2.36°

* Korean association of orthodontics (1998)

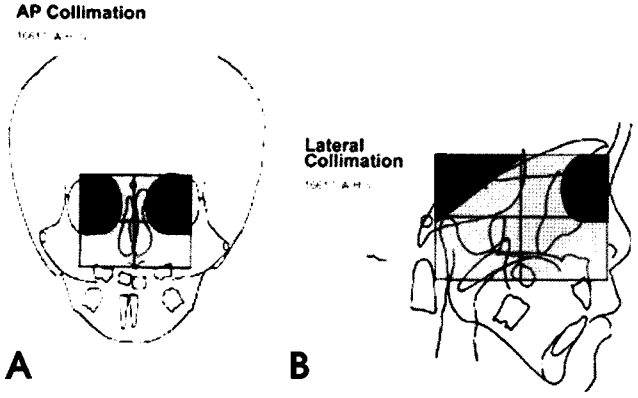

Fig. 1. Irradiation fields of lateral (A) and frontal (B) head.

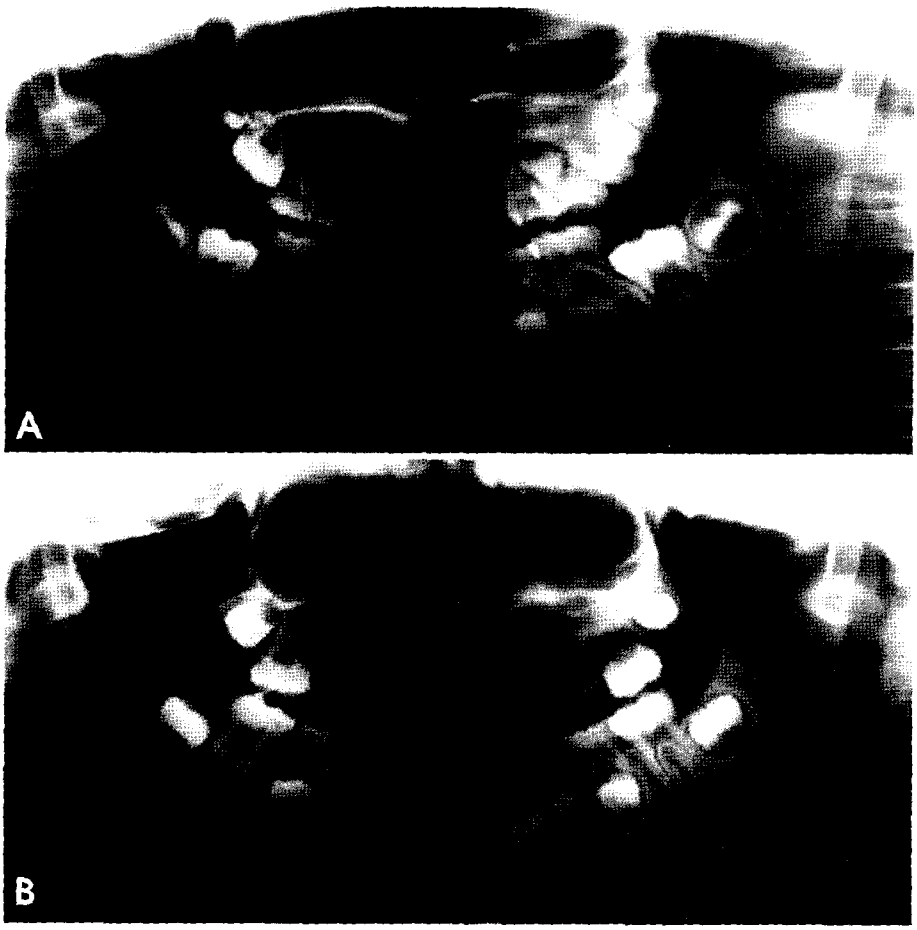

Fig. 2. Panoramic radiographs of the patient at age 6 (A), and 9 (B) showing multiple reduction in height of maxillary alveolar ridge, delayed eruption of maxillary and mandibular teeth, and multiple missing teeth.

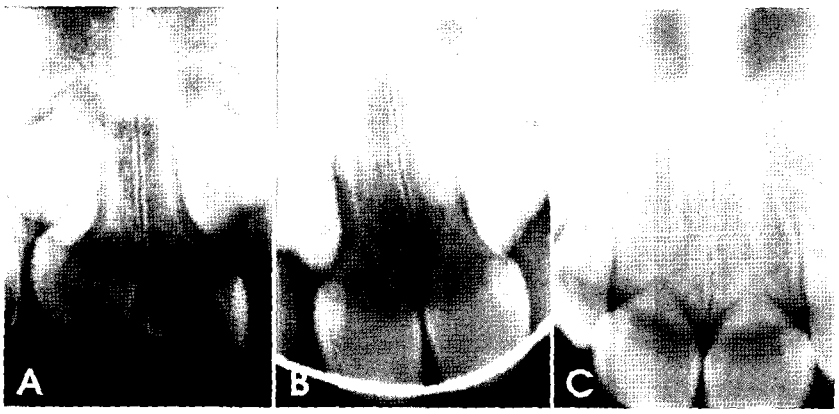

Fig. 3. Periapical radiographs of anterior teeth at age 6 (A), 7 (B), and 9 (C) showing short and tapered root of both central incisors, and delayed eruption of both lateral incisors.

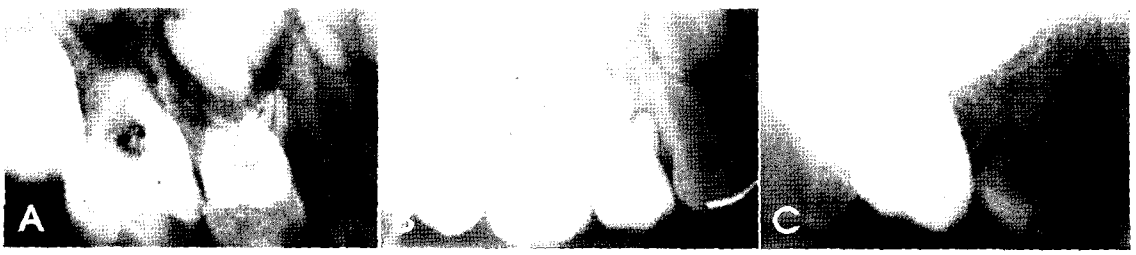

Fig. 4. Periapical radiographs of right maxillary molars at age 6 (A), 7 (B), and 9 (C) showing early exfoliation of deciduous molars, premature apical closure of canine, underdevelopment and missing of premolars, and root stunting of first molar.

Fig. 5. Periapical radiographs of left maxillary molars at age 6 (A), 7 (B), and 9 (C) showing early exfoliation of deciduous molars, premature apical closure of canine, underdevelopment and missing of premolars, and root stunting of first molar.

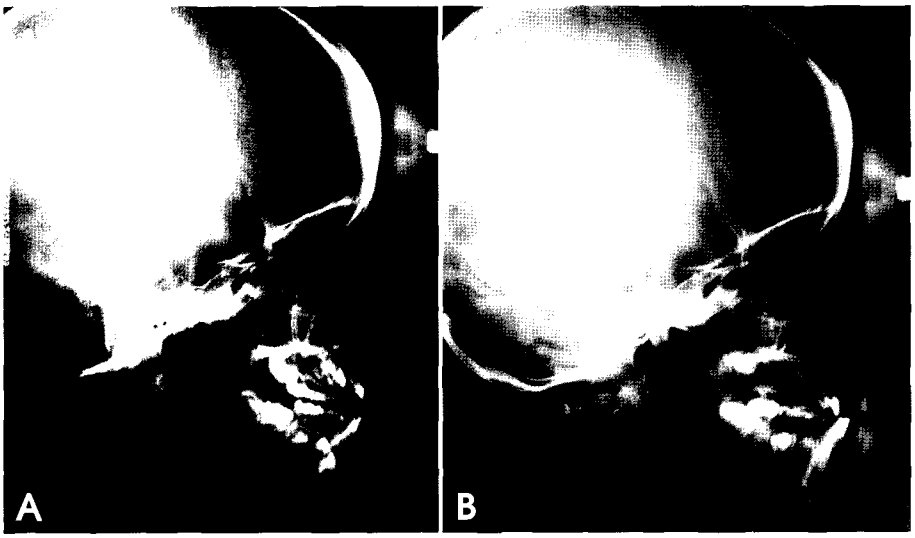

Fig. 6. Lateral cephalometric radiographs of at age 6 (A) and 10 (B) showing maxillary hypoplasia and facial disproportion.

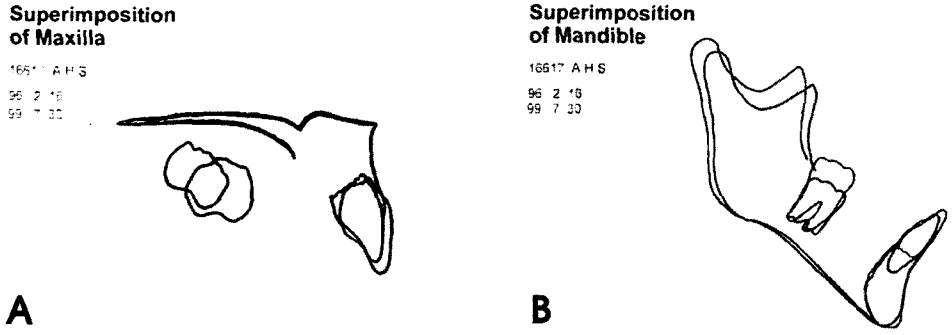

Fig. 7. Superimposition of maxilla and mandible. Mandible showing normal development (A), but maxilla shows disturbance of development (B).

significant acellular and avascular, with fibrosis and fatty degeneration. The endosteum atrophies; osteoblastic and osteoclastic activity decreases.[12] As for tooth development, if radiation occurs before calcification is complete, the tooth buds may be destroyed.[13] Exposure later in the developmental process may arrest growth and cause irregularities in enamel and dentin.

Animal models have demonstrated the marked radiosensitivity of developing teeth and facial bones.[4] Doses of 10 Gy and 30 Gy permanently damanged mature ameloblasts, arresting tooth development.[4] Case reports in the literature suggest that radiation doses in excess of 20 Gy result in significant bone growth disturbance regardless of the child's age, whereas lower doses in children 1 to 2 years old result in minor or no residual deformity.[14] Damages occurring during periods of maximum bone growth and development, that is, birth to 6 years of age and during puberty, result in particularly marked growth disturbance.[14] Radiation damage to bone, periodontal ligament, and pulp occurs simultaneously. The effects on these structures are interrelated, and it is difficult to distinguish between primary and secondary effects.[14] Our patients received 54 Gy facial radiation at 16 months of age. The

subsequent microdontia, root stunting, short and tapered root, delayed eruption, and missing teeth may have been as a result of chemotherapy, radiation therapy, or their combined effects. However, the patterns of these abnormalities were commensurate with radiation damage at an early age.

According to Scott,[15] permanent maxillary anterior and premolar tooth germ are fully formed by the 30 weeks of fetal life, and calcification begins at 3 to 4 months after birth in the central incisors, 4 to 5 months in canines and first molars, 10 to 12 months in maxillary lateral incisors, and $1^1/_2$ to $2^1/_2$ years in premolars. In our patient, maxillary central incisors showed normal crown, and short and tapered root. This period coincide with the stages of enamel formation ($1^1/_2$ months) and root development ($1^1/_2$ years). At that age of paitent, development and calcification of the crowns of permanent maxillary anterior teeth, except for the canines, is normally just about complete. Microdontia and agenesis are common features in patients receiving radiotherapy during the development of teeth; in the present case, microdontia and missing were observed in both premolar area. It could be expected because the tooth buds had not formed at the time of therapy. Hard tissue formation of both maxillary premolar begins at $1^1/_2$-$2^1/_4$ year. In our patient, marked root stunting of both maxillary first molars could be expected because the crowns had already formed at the time of therapy although the roots were still developing. But both maxillary first molars showed normal eruption. It is particularly interesting that all the teeth erupted fully even though the roots failed to form. In light of this observation, the various theories on the mechanism of tooth eruption are considered. Obviously, the theories that eruption is caused by the growth of the root are not substantiated. Baume and others[16] thought that eruption of teeth was a process of growth and differentiation of maturation influenced by growth hormone and thyroxin. Massler and Schour[17] concluded from their investigation that eruption may be related to the vascularity of the periapical tissues. Gowgiel,[18] reporting on an investigation of eruption of rootless teeth in monkeys treated with radiation, found that the degree of vascularization of the periapical tissues of the erupting tooth was within normal limits and that the main artery and most of the arterioles had arteriosclerosis that was produced by radiation. This agrees with our findings in the case presented. Currently the most convincing theory of the mechanism of tooth eruption seems to be that the process is the result of growth of the follicular sac, the alveolar bone, or both.[18,19]

In our case, we also observed the delayed development of mandibular teeth. Although the teeth are not in the field of irradiation, the small amount of scatter radiation coupled with aggressive chemotherapy affects dental development, particularly in the posterior. These defects may result from scatter radiation or synergistic effects of scatter radiation and chemotherapy. Early-age chemotherapy may retard the development of Hertwig's root sheat by interfering with epitheliomesenchymatose induction during the odontogenic process.[20] Studies[21,22] in rats have established that chemotherapeutic agents used to treat patients with cancer delay or disrupt odontogenesis, as manifested by the increased number of incremental lines and deranged production of dentinal matrix after administration of these drugs.

Cephalometric analysis of our patient revealed as maxillary hypoplasia. This disturbance of maxillary growth reflects the distribution of the radiation field (only nasal cavity area). Irradiation of only one side of the face generally results in damage to growth centers of that side only, resulting in unilateral hypoplasia.[12]

In the growing child the consequences of radiation are more conspicuous on the facial skeleton than on the soft tissues, with the effect usually more evident in the mandible than in the maxilla.[23] Growth failure of the facial bones in children treated by radiation therapy for head and neck tumors has been reported in the literature.[12,23,24] Tissues seemed to be particularly sensitive during periods of maximum growth, from birth to 6-year-old and during puberty.[14] Our cephalometric analysis, made from the lateral skull roentgenogram taken 5 year and 9 year after radiotherapy, showed that all linear measurements were some different value in comparison with the standard cephalometric norms. An examination of our values revealed that the maxilla and the midfacial length were deficient in size in the sagittal and vertical planes, and that mandibular length (Co-Gn) was normal. The sagittal angular relation of the maxilla to the anterior skull base (SNA) was more abnormal in comparison with that of the mandible (SNB), which has a relative normal relation to skull base. This results in a maxillary hypoplasia, which confirmed by angle of convexity (N-A-Pog). It is evident that the heavy radiation load, because of its direct effect on bone, soft tissue, and blood vessels, is the major causative factor in the facial growth disturbance seen in our case. We could not, however, exclude influences associated with changes in growth hormones secondary to radiation of the hypothalamic area and the pituitary gland. But we did not confirm a lack of such hormones in our cases. Several authors[25-28] have reported growth failure with documented growth hormone deficiency after radiation therapy that included the hypothalamic-pituitary

axis. In addition, systemic conditions including hypopituitarism, hypothyroidism, and Down syndrome may be associated with retarded eruption of permanent teeth, and opinions differ regarding the effect of chemotherapy on this process.

The results of this case show that oncotherapy of child cancer resulted in a higher prevalence of various malformations in teeth and adjacent structures; however further studies with larger number of cases and control subjects are needed. In addition, evaluations with respect to diagnosis and treatment protocols are necessary for a comprehensive understanding of oncotherapeutic effects on dentomaxillofacial areas. It can be speculated that inasmuch as children treated in the early years of their lives displayed the most severe dental defects, immature teeth are at a greater risk of developmental disturbances than are fully developed teeth.

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