Developmental Dental Defects Linked with Chemoradiotherapy: A Case Report

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Developmental orofacial dentoalveolar complications associated with chemoradiotherapy in an 8 year old child with a history of rhabdomyosarcoma are reported. This report details, clinically and radiographically, these effects in a child diagnosed at 3 years of age with a lesion primary to the left buccinator. Early evaluation is vital to determine potential dentoalveolar complications and long-term consequences.
Keywords*: chemotherapy, radiotherapy, dental defects, case*
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INTRODUCTION

Rhabdomyosarcoma (RS), the most common soft tissue sarcoma of childhood, is a quickly growing, highly malignant soft tissue neoplasm of skeletal muscle origin formally described in 1854.[1, 2] As a solid, RS is the third most common extracranial tumor of childhood after neuroblastomas and Wilms' tumor.[2] Roughly 250 new cases of RS are diagnosed in the US each year[3] with an yearly incidence of four to seven per million children 15 years of age or younger. The majority (65%) of cases are diagnosed in children less than six years of age with remaining cases noted in the age group of 10 to 18 years. There is also a slight gender predilection for males, with a male-to-female ratio of 1.3:1.5.[4, 5] While the incidence in males is similar for both groups, the incidence in African-American females is half that of Caucasian females in the US.[3]

Significant features appear to cluster around the primary tumor site, age at diagnosis, and also histological subtype of the tumor. For example, the most common site of the neoplasm in children is the head and neck (35%), followed by the genitourinary tract (23%) and extremities (17%).[6] In the head and neck region, the predominant sites excluding the orbits, are the nasopharynx, paranasal sinuses, middle ear and mastoid, and facial soft tissues.[6-11] Tumors of the oral cavity, which account for approximately 10% of all head and neck RS, appear most frequently in the tongue, palate, and cheeks.[12-14] Clinical appearances of RS in the head and neck region range from a small cutaneous nodule on the face to a rapidly developing facial enlargement. These swellings may be painless or associated with pain, trismus, paresthesia, facial palsy, and aural or nasal discharge.[15-16] Diagnosis is commonly confirmed by a combination of light microscopic examination and various adjunctive techniques including electron microscopy, cytogenetic analysis, and immunohistochemistry.[17-21]

With regards to its pathogenesis, identification of viral particles in malignant RS tissues may indicate viral involvement as a possible cause. Further cytogenetic and molecular studies have pinpointed chromosomal translocations and mutations in oncogenes but have not yet been well-established.[22,23] Overall; RS is associated with high rates of recurrence and generalized metastases through hematogenic and/or lymphatic routes as a result of the cells' aggressive neoplastic behavior. Nonetheless, childhood RS in the head and neck region has a better prognosis when compared to those at other anatomical sites, perhaps due to the early evolutive stage of the tumor at the time of the detection.[24]

Treatment modalities for RS include surgery, radiation therapy, and chemotherapy. The primary tumor may be removed or resected surgically. Further radiation therapy controls local microscopic or gross residual disease by directly or indirectly ionizing the atoms that make up the DNA of the cells. Systemic chemotherapy may also be used to inhibit the growth of rapidly dividing malignant cancer cells and therefore is effective in primary cytoreduction as well as eradication of gross and micrometastatic disease. The prognosis of the disease is associated with the location, evolutive stage, and histological type of the tumor,[25] and the cancer therapy for pediatric head and neck tumors may often be linked with significant oro-dentofacial morbidity. This case report details the long-term developmental consequences associated with chemoradiotherapy in a child with a history of RS.

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CASE REPORT

An 8-year-old male patient with a history of alveolar RS, hypothyroidism, and sickle cell anemia presented to the Columbia University Medical Center pediatric dental residency clinic for routine dental care. The child patient had undergone radiation therapy on the left side of the head and neck region at the age of 3.6 years for his cancer treatment, and the cancer is in remission at the present time. Initially before the diagnosis of his cancer, he developed a proptosis of the left eye and left submandibular mass. The mass was first noted during a routine visit to the Hematology Clinic. Computed axial tomography (CT) imaging revealed a 2 x 2.4 x 2.5 cm mass at the angle of the mandible on the left side. In addition, magnetic resonance imaging indicated an enhancing lesion in the region of the left ethmoid air cells, extending into the left anterior cranial fossa and epidural extension along left frontal lobe. Biopsy confirmed an alveolar rhabdomyosarcoma (2:13 translocation). Further evaluation of the lung CT and bone revealed no metastasis.

Following the diagnosis, he received 50.4 Gy radiation to the head and neck region including the ethmoid and sphenoid sinuses and completed the chemotherapy in 12/03. When a CT evaluation revealed a new lytic bony abnormality in the midline of his frontal bone extending to the ethmoid bone, in 6/04, he was re-examined for a cancer relapse. Additional examinations, including bone scan and chest CT, demonstrated no other evidence of a relapse and hence the biopsy was deferred. The imaging study in 6/05 reported the lesion as stable, and it is presently believed to be related to sickle cell disease or infarct.

Complications during the patient's cancer treatments included fever, neutropenia, and infections that ranged from G-tube cellulites to facial cellulitis. He also developed an episode of leg pain that after extensive evaluation, was felt to be consistent with a sickle pain crisis. He previously had several episodes of significant life threatening epistaxis but currently presents no significant problems with epistaxis for more than 2 years. His growth that was falling below normal for his age may be due to endocrine abnormalities that may have occurred after cranial irradiation. Currently, his growth is improving on growth hormone and carefully monitored by his endocrinologist. His prognosis is now excellent as he has been free of the cancer and off treatments and he continues to be followed with semi-annual scans.

The patient is currently taking folic acid, growth hormone, synthroid, and penicillin. When initially examined at age 5, he presented with poor oral hygiene and visually evident rampant dental caries and dental abscesses. Comprehensive dental treatment was accomplished under general anesthesia at Children's Hospital (New York City, New York). No complications followed the procedure and wounds healed uneventfully. The child was placed on routine oral hygiene maintenance visits.

The parent and patient never followed up regularly and returned to the clinic 3 years later with a chief complaint of unerupted teeth. He was free from any signs of facial swelling or lymphadenopathy. Intra-oral examination (Figure 1A) revealed normal soft tissue with an absence of any soft tissue pathology or gingival inflammation. Spacing in the dentition was consistent for the child's age and the occlusal relationship was within normal limits. Although the child's overall oral hygiene was excellent with no clinical evidence of caries, he presented some enamel hypoplasia. While the remaining dentition was free from any other signs of mobility, the central incisors exhibited two degrees of mobility. Furthermore, radiographic evaluation (Figure 1B and Figure 2), now at age 8 demonstrated multiple developmental dental defects. The patient exhibited tooth agenesis of permanent maxillary second premolars and partial odontogenic deficits, including generalized moderate root

Table 1. Dental and Oral Complications Secondary to Chemoradiotherapy*

Complication	Signs/Symptoms	Treatment
Abnormal Dental Development *Chemotherapy:* Vincristine, actinomycin D, cyclophosphamide, 6-mercaptopurine (6-MP), procarbazine, nitrogen mustard (HN_2) *Radiation:* Generally 10 Gy can obliterate developing roots)	• Microdontia • Hypoplastic or hypomineralized enamel • Underdeveloped roots • Delayed eruption • Premature exfoliation of primary teeth • Hypoplasia of jaws	• Dental examination every 6 months with attention to early caries, periodontal disease, and gingivitis, and baseline panoramic and bitewing radiographs (age 5-6 years) • Careful evaluation before tooth extraction, endodontics and orthodontics, topical fluoride, antibiotics as needed for patients at risk for infection
Xerostomia, Stomatitis *Radiation:* >40 Gy and >50% of gland irradiated	• Decreased salivary flow • Xerostomia • Altered taste perception • Caries • Candida	• Dental examination, salivary flow studies, attention to early caries, periodontal disease • Encourage meticulous oral hygiene, saliva substitution, prophylactic topical fluorides, dietary counseling regarding avoidance of fermentable carbohydrates, nystatin for oral candidiasis, pilocarpine

**Adapted from Schwartz et al.* [33]

stunting, root agenesis of permanent first molars for both arches, root tapering of lower right permanent canines, and microdontia for permanent premolars and maxillary second molars. Radiographically, underdeveloped jaws were also noted. Future treatment options were discussed and the patient continues to be monitored through his routine dental examinations.

DISCUSSION

RS is a rapidly growing, aggressive neoplasm in children, and the peak age for the occurrence in the head and neck region is between the ages of two to six.[26] Over the last 25 years, treatment has evolved to multidisciplinary protocols made up of surgery, radiation, and systemic chemotherapy regimens. The selected cancer treatment is risk adapted and is based on the tumor stage and its clinical group. Chemotherapy and radiation therapy inhibit the growth of rapidly dividing cells, such as cancer cells. Chemotherapy should only destroy the malignant cells without affecting normal cells. However, many drugs are not sufficiently specific and may damage other high turn-over tissues, such as hair, skin, mucous membrane and the hematopoietic system. In the case of radiotherapy regimens, cranial irradiation can eradicate malignant white cells in the central nervous system that are protected from chemotherapy by the blood-brain barrier. When cranial radiation is conducted, irradiation of the eyes and orodental structures must be minimized.[26-27]

Tooth development begins at approximately 6-8 weeks of

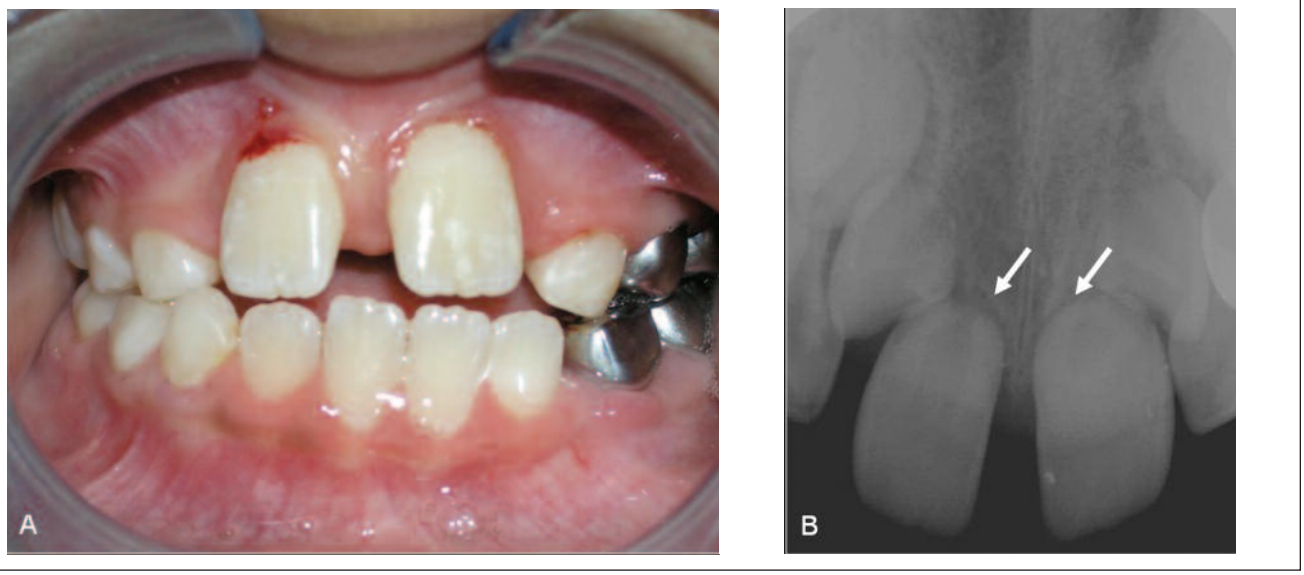

Figure 1. (A) Intraoral photo demonstrating splaying of incisor teeth, and (B) a periapical radiograph revealing root agenesis on incisor teeth resulting in delayed eruption.

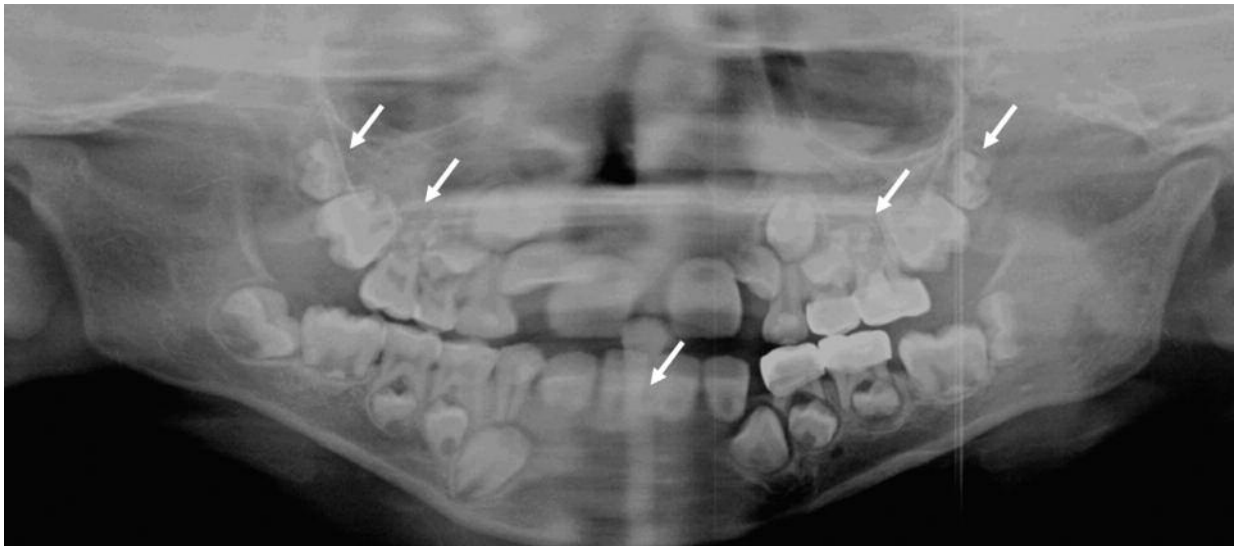

Figure 2. Panoramic radiograph. Note advanced root stunting of incisor teeth, microdontic premolars and second molars, root stunting of the 6 year molars, and root tapering of lower right permanent canine.

intrauterine life and continues into early adolescence when permanent crowns and roots are fully formed.[29] Children who have been treated in the early years of their lives demonstrate the most severe dental defects since immature teeth are at a greater risk of developmental disturbances than are fully developed teeth. Table reviews dental and oral complications secondary to chemoradiotherapy. Regimens during dental development may cause various cosmetic and functional abnormalities of dentition. More than 85% of survivors of head and neck RS who receive radiation doses greater than 40 Gy may have significant dental abnormalities, including increased dental caries, mandibular or maxillary hypoplasia, hypodontia, microdontia, root stunting, and xerostomia.[30, 31] Doses of 20 Gy to 40 Gy may lead to root shortening or abnormal curvature, dwarfism, and hypocalcification.[32]

In the case of radiation therapy, tooth agenesis is one of the associated dental sequelae that results from destruction of ameloblasts, odontoblasts, and non-proliferating odontogenic precursor cells. Additionally, pulp mesenchyme may form osteoblast-like cells that alter ability to initiate dentinogenesis, and the event could result in odontogenic anomalies, such as shortened, thin, tapered roots. An alteration in mineralization process may also lead to defects such as enamel hypoplasia. Overall, the therapy may lead to interferences with growth of the craniofacial skeleton, trismus, microdontia, hypoplastic or hypomineralized enamel, underdeveloped roots, delayed eruption, premature exfoliation of primary teeth, and dental caries.[33] Osteocyte death, microvascular injury, periosteal damage, and fibrous replacement of marrow spaces from the radiation therapy may also lead to altered bone growth and development including jaw hypoplasia.[34] The present case illustrates many features that are characteristics of a patient with a history of alveolar RS and past radiation therapy. Clinically, the patient presented root agenesis, microdontia, underdeveloped roots, and rampant dental caries that resulted from the retarding effect of the radiation therapy on oral and perioral tissues.

Acute side effects of chemoradiotherapy include stomatitis, xerostomia, trismus, and dysphagia, and long-term effects include radiation caries. Because of potential oral complications, strict supportive therapy and oral hygiene, adherence to a non-cariogenic diet, use of fluorides, trismus prevention and treatment, and primary caregiver education on oral care and probable acute and long-term effects of therapy in the craniofacial complex are recommended. Any existing or potential sources of oral/dental infections and/or soft tissue trauma may further compromise the medical treatment and hence should be addressed.

In addition, late effects of cranial irradiation treatment for childhood cancer include endocrine abnormalities, such as growth hormone deficiency, delayed or precocious puberty, and hypopituitarism.[35, 36] Hypothalamic dysfunction is most commonly noted while pituitary insufficiency may also occur. The present case exhibits the impaired growth that is a common complication following the radiotherapy to the head. To ensure that he will reach his optimal growth potential, it is important to conduct a timely therapy of the endocrine sequelae of cancer treatment and long-term endocrine follow-up visits.

Regards to the patient's sickle cell anemia, oral manifestations were nonspecific. In general, the mucous membranes often exhibit jaundice due to hemolysis and pallor that are caused by the low hematocrit. Delayed tooth eruption may also be noted, although dental shape and size are not affected.[37,38] Radiographic findings for the condition include a reduced radiodensity of bone and formation of a coarse trabecular pattern that are due to the erythroblastic hyperplasia and medullary hypertrophy with consequent loss of trabeculae and increased marrow spaces.[39] Lateral skull radiographs often show widening of diploic space, with thinning of the outer table of the calvarium and vertical trabeculations, also known as the "hair-on-end" appearance.[37, 40] Thinning of the inferior border of the mandible, loss of alveolar bone height, pronounced lamina dura, hypomineralization of the dentin, interglobular dentin in the periapical area, inclusion in the peripulpal dentinal tubules, abrupt interruption of dentinogenesis, calcified bodies in the pulp chamber, and hypercementosis may also be exhibited in these patients.[39, 41] In addition, patients may present with orofacial pain without odontogenic etiology since sickling crises within the microcirculation of the facial bones and dental pulps and small areas of necrosis in the bone marrow may lead to pulpal necrosis.[42]

When treatment planning, a dentist should consider timing of cancer treatment and prioritizing dental treatment in relation to the cancer treatment. Some hematological considerations in dental care include use of antibiotic therapy for low absolute neutrophil counts, platelet transfusions for low platelet counts, and other coagulation tests. Dental professionals play a considerable role in the early identification and treatment of dental problems that may compromise the child's quality of life before, during, and after cancer treatment. Unfortunately, clinical establishment of the differential diagnosis of RS is yet difficult.[20] Children with RS may present signs and symptoms, including pain, paresthesia, loss of teeth, and trismus, as a result of advanced tumor stage, infiltrative growth and tumor location.[43] Because of the difficulty in the diagnosis of RS, it is important to aid in establishing an appropriate treatment plan in a timely manner that are aimed at improving prognosis and patient survival as soon as it is detected.

In addition, it is necessary for the dentist to be aware of the oral manifestations of the patient's underlying medical condition and the necessary modifications in treatment protocol of patients undergoing chemotherapy and/or radiotherapy and incorporate medical considerations so that their individual risk for oral complications are addressed. Abnormal dental development secondary to chemoradiotherapy from childhood malignancy present a treatment challenge as a future prosthodontic rehabilitation may be necessary to due to shortened roots with poor long-term prognosis.

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