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REVIEW ARTICLE

Abnormal Odontogenesis following Management of Childhood Cancer (Retinoblastoma): Review and a New Variant

Karthik Venkataraghavan, Shankargouda Patil, Sowjanya Guvva, Sandhya Karthik, Shilpa Bhandi

ABSTRACT

A young child being diagnosed with cancer naturally generates a pretty melancholy reaction. Each cancer can be managed with a vast array of treatment options that are available either individually or as a combination, the final goal of which is total eradication of the condition in the affected individual. Since, most of these treatments are administered during the age of tooth formation, they may affect stages of odontogenesis. Most common treatment of childhood cancers includes – chemotherapy and radiotherapy. With recent advancements in cancer therapy additional treatment options like laser therapy, radiation in the form of brachytherapy or teletherapy, cryotherapy, thermochemotherapy, etc. are available. As treatment of childhood cancers starts at a very young age coinciding with dental development, a number of dental malformations have been reported in childhood cancer survivors. The most common ocular cancer in children is retinoblastoma. This is the first such reported case and unique one where microdontia has affected all the first premolars.

Keywords: Chemotherapy, Radiation, Dental abnormalities, Microdontia, Retinoblastoma, Childhood cancer.

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INTRODUCTION

A young child being diagnosed with cancer naturally generates a pretty melancholy reaction. Although substantial progress has been made in both fighting and curing the disease, in the end, cancer is still cancer, and if left untreated, progress can quickly turn fatal.[1]

Once any form of childhood cancer has been diagnosed the management starts almost immediately after careful diagnosis of the condition has been completed. Each cancer can be managed with a vast array of treatment options that are available either individually or as a combination, the final goal of which is total eradication of the condition in the affected individual.

Since most of these treatments are administered during the age of tooth formation, they may affect stages of odontogenesis. Most common treatment of childhood cancers includes—chemotherapy and radiotherapy. With recent advancements in cancer therapy additional treatment options like laser therapy, radiation in the form of brachytherapy or teletherapy, cryotherapy, thermo-chemotherapy, etc. are available. As treatment of childhood cancers starts at a very young age coinciding with dental development, a number of dental malformations have been reported in childhood cancer survivors.

It has been reported that the incidence of dental visits for childhood cancer survivors falls below the American Dental Association's recommendation that all adults visit the dentist annually thereby giving health care providers further impetus to encourage routine dental and dental hygiene evaluation for survivors of childhood treatment.

The Problem

Ten million individuals in the United States are living with a cancer diagnosis today, three times the number of survivors in 1971. The 5-year survival rate for adults with cancer is 60 to 65%, and for children it is 80 to 85%. In the near future, one of every 450 individuals in the population will be a long-term survivor of childhood cancer: Presently 1 in 640 individuals between 20 and 39 years of age is a childhood cancer survivor.[2] The long-term morbidity of childhood cancer survivors was determined in a landmark Childhood Cancer Survivor Study (CCSS). Based on this

the following late effects of cancer therapy have been documented and they include those affecting:

- Heart
- Vasculature
- Lung
- Gastrointestinal tract
- Spleen liver
- Kidney
- Bladder
- Skeletal
- Muscle
- Thyroid
- Growth and development
- Gonads
- Central nervous system
- Eye
- Ear
- Teeth and gums

RETINOBLASTOMA

The most common ocular cancer in children is retinoblastoma.[3] This is a rare cancer of the retina (the innermost layer of the eye, located at the back of the eye that receives light and images necessary for vision) and accounts for 3% of childhood cancers.[4] In 1986, the gene mutation at fault for retinoblastoma, the Rb 1 gene (located on chromosome #13) was finally discovered by cancer research scientists. Since then, retinoblastoma research has shifted from discovering a cause, to discovering what can further be done to prevent and more effectively treat that cause;[1] this is an autosomal dominant gene where both the sexes are equally affected and there is a 50/50 chance, with each pregnancy, for a parent to transmit the gene to the child.[4]

CAUSES

In almost all cases, it affects children under the age of 5 with the average age of diagnosis being 2. In the earliest stages of eye development, cells known as retinoblasts form, multiply, and eventually stop growing and mature into actual retinal cells of the eye. Sometimes this process will be disrupted, however, and retinoblasts grow out of control and change into cancer cells. The Rb gene's duty is to be a tumor suppressor gene, or to keep the cell process controlled so that cancer does not develop. Whenever, there is the slightest glitch in this retinoblastoma protein, though, retinoblastoma occurs.[1]

Two mutations (or gene changes) are necessary to 'knockout' this gene, and cause uncontrolled cell growth. In inherited retinoblastoma (40% of cases), the first mutation is inherited from a parent, while the second occurs during the development of the retina. In sporadic retinoblastoma (60% of the cases), both mutations occur during development of the retina.

SYMPTOMS[4]

The most common symptoms of retinoblastoma include:

- Leukocoria – a white reflex that occurs at certain angles when light is shown into the pupil
- Strabismus (also called 'wandering eye' or 'cross-eyes') –a misalignment of the eyes
- Pain or redness around the eye(s)
- Poor vision or change in child's vision.

DIAGNOSIS

Although retinoblastoma is found early in many children due to evident symptoms, a standard retinoblastoma screening test does not exist. Even though a blood test capable of testing for the Rb gene mutation is available; it is usually only used for those children which have a family history of the gene abnormality.[1] For the latter, in addition to a complete medical and physical examination, other diagnostic procedures like:[4]

- Complete eye examination
- Fundoscopic examination – with the child under general anesthesia, the pupils are dilated so the entire area can be viewed and examined
- Ultrasound exam of the eye
- Computed tomographic scan
- Magnetic resonance imaging
- Lumbar puncture (spinal tap)
- Tests of the fluid surrounding the tumor
- Genetic and/or DNA testing.

When the condition has been diagnosed, tests will be performed to determine the size, number, location of the tumors, and if the tumors have spread to the other parts of the body. This is called staging and is an important step toward proper treatment planning.

Stages of Retinoblastoma[4]

Although there are various staging systems can be used for, the Reese-Ellsworth stages of retinoblastoma is commonly used for staging tumors that have not spread beyond the eye:

- *Group I:* Either one or more tumors that are less than 4 disk diameters (DD) in size and located at or behind the equator.

- *Group II:* Either one or more tumors that are 4 to 10 DD in size located at or behind the equator.
- *Group III:* Any lesion in front of the equator or one tumor larger than 10 DD behind equator.
- *Group IV:* Multiple tumors with some or all greater than 10 DD in size or any lesions that extend beyond the back of the eye.
- *Group V:* Very large tumors involving more than half of the retina or that have spread into the vitreous (the gelatinous material that fills the eye).

The 'equator' is an imaginary line that divides the eye into equal parts.

Treatment of Retinoblastoma

The best initial and subsequent treatments are based on whether the child has unilateral or bilateral disease, the stage of the disease, and the age of the child.[3] The choice of treatment is also based on the risk of metastases, the diameter and location of the tumor, the age of the patient, the heredity and the visual prognosis.[5]

The cure rates are high in children when the tumor is confined to the eye and has not spread systemically or into the orbit or brain.[3]

To sum it up, the treatment may include one or more of the following:[4]

- Enucleation (surgical removal of the eye or eyes involved with the tumor)
- Chemotherapy
- Radiation therapy
- Laser therapy or photocoagulation
- Thermal therapy
- Cryotherapy (uses freezing process to destroy the tumor)
- Bone marrow or peripheral blood stem cell transplantation
- Fitting and training for a prosthesis
- Blind or decreased vision adaptation training
- Supportive care (for the side effects of treatment)
- Antibiotics (to prevent/treat infection).

As with any cancer, prognosis and long-term survival can vary greatly from child to child. Every child is unique and treatment and prognosis is structured around the child's needs. Prompt medical attention and aggressive therapy are important for the best prognosis.[4]

CASE REPORT

An 8-year-old girl visited, The Kids Clinic at Vibha Dental Care Center, Bengaluru, India, with the purpose of having an opinion about a dental problem suggested to them by another dental practitioner.

During the first visit initial examination was carried out and was found to be potentially uncooperative and the appointment was kept short. Upon discussing the history with the parents it was revealed that the child is a cancer survivor. She had been diagnosed with unilateral macular retinoblastoma (group II) in the right eye, at the age of 1 year for which she had undergone multiple treatment combinations including, fundoscopic examination, transpupillary thermotherapy, chemotherapy, radiation, peripheral and transconjunctival cryotherapy. All the procedures were carried out under general anesthesia owing to the age of the child and also under the effect of antiemetics. After five cycles of chemotherapy (using injection carboplatin 180 mg, injection etoposide 50 mg and injection vincristine 0.5 mg) calcific residue with chorioretinal atrophic patches surrounding the calcific mass was noted along with few inactive vitreous seeds—features of regressed retinoblastoma. The right eye was completely enucleated. A careful family history was recorded to know the pattern of inheritance which turned out to be negative indicating that this was a sporadic case. The child is on periodic check up and on prescribed medications.

As fallout of these procedures over the years the child has become extremely timid and shy and as noticed during the course of here initial examination needed a lot of coaxing to get her oral cavity examined which revealed the presence of crowding in the mandibular anterior region and a mixed dentition (Fig. 1), which was normal for her age. The extraoral examination revealed the presence of an opaque spot (Fig. 2) in the right eye upon exposure to bright light (like photographic flash) probably due to the enucleation.

Based on the clinical examination and owing to the good oral health status of the child a routine orthopantomograph

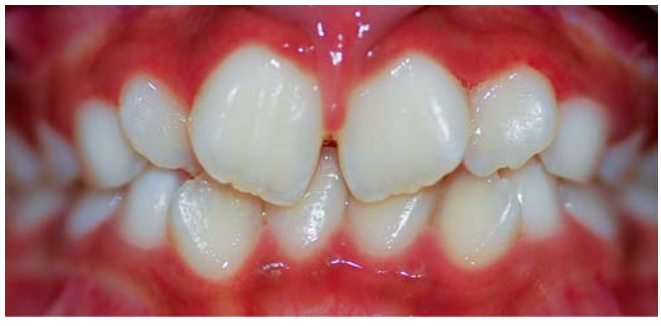

Fig. 1: Crowding in the mandibular anterior region and a mixed dentition

Fig. 2: Presence of opaque spot in the right eye

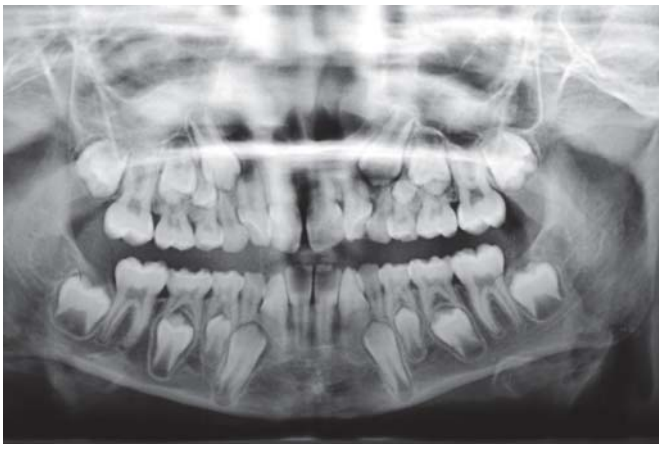

Fig. 3: OPG showing microdontic first premolars in maxillary and mandibular arc

(OPG) (Fig. 3) was advised to aid in future treatment planning. The OPG revealed a normal mixed dentition with the presence of all succedaneous teeth. Upon careful examination of all the teeth present a rather unique and rare finding was noticed. All the first premolars in both the arches bilaterally were microdont whereas all the other teeth appeared to be normal. Based on this unique finding and owing to the condition of the child (she was apprehensive about all dental procedures) and the age it was planned to defer the treatment. This was decided based on the unique finding of microdontia and the space that will be available after the child attains puberty. The extraction of the microdontic premolars will aid in orthodontic treatment to align the teeth properly by which time the child would have grown out of her fears.

DISCUSSION

Retinoblastoma is the most frequently occurring primary intraocular malignant tumor in children. Early detection is important for the chance of survival.[5] Enucleation, chemotherapy, and various forms of radiotherapy, etc. along with local ophthalmic therapies can be used in the treatment.[3] Retinoblastoma usually affects children under the age of 5 years with the average age being 2 years. In this period, odontogenesis occurs beginning in the 4th week of uterine life and finishing around the age of 21 years. Chemotherapy and radiation therapy are commonly used treatment options.

The radiosensitivity of developing teeth has been demonstrated in animal models. The nature and severity of the potential side effects of radiation on developing teeth vary with the child's age at diagnosis, the stage of tooth development, the doses and schedules of treatment and the anatomic region treated. The principal dental abnormalities caused by radiation include destruction of the tooth germ with failure of tooth development, stunted growth of the whole tooth or root, incomplete calcification, tapering roots, etc.[6,7]

Chemotherapy interferes with the cell cycle and with intracellular metabolism and in the teeth may thereby cause retarded dental development, microdontia, enlarged pulp chamber and root stunting.[7]

Histological studies have shown changes in dental morphology induced by high dose chemotherapy and total irradiation inpatients. They have also shown that chemotherapy mainly induces qualitative disturbances in dentine and enamel, whereas total body irradiation induced both qualitative and quantitative changes.[8]

Teeth with higher incidence of abnormalities were the first and second upper and lower premolars, in isolation.[1] Our finding is the first of its kind to be reported where in a unique dental abnormality *viz* microdontia has affected only the first premolars both in the maxilla and mandible bilaterally in a child who has undergone a combination of treatment for the management of retinoblastoma.

CONCLUSION

It can be suggested that dental abnormalities are related to the stage of dental development, which may be directly related to the age of the child at the beginning of the therapy, as well as to the type, intensity and frequency of the drugs administered.[9] Microdontia has so far not been reported in patients treated for retinoblastoma. This is the first such reported case where only the first premolars have been affected by the condition.

It becomes all the more important for dentists to understand about the dental abnormalities arising as a result of cancer therapy and as well as learn how to handle them to help provide the patients with a better quality of life.

What this paper adds:

- A rare case of abnormal odontogenesis
- Childhood cancer management can cause oral/dental malformations
- Thorough screening of childhood cancer survivors in all aspects to rule out any malformations.

Why this paper or case report is important to pediatric dentists:

- Microdontia affecting both maxillary and mandibular first premolars bilaterally
- Childhood cancer survivors should be examined carefully so as to rule out any defects that might arise as a result of the treatment taken for its treatment
- Pediatric dentists need to carefully assess such situations and initiate appropriate treatment options at suitable time at the same time keeping in mind the psychological status of the child.

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ABOUT THE AUTHORS

Karthik Venkataraghavan (Corresponding Author)

Professor and Head, Department of Pediatric and Preventive Dentistry College of Dental Sciences and Research, Ahmedabad, Gujarat, India e-mail: veekart@yahoo.co.in

Shankargouda Patil

Lecturer, Department of Oral Pathology, MS Ramaiah Dental College Bengaluru, Karnataka, India

Sowjanya Guvva

Reader, Department of Periodontics, SVS Institute of Dental Sciences Mahabubnagar, Andhra Pradesh, India

Sandhya Karthik

Dental Surgeon, The Kids Clinic, Vibha Dental Care Centre, Bengaluru Karnataka, India

Shilpa Bhandi

Lecturer, Department of Conservative Dentistry and Endodontics, MS Ramaiah Dental College, Bengaluru, Karnataka, India