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Dental Abnormalities in a Patient Treated for Neuroblastoma

Zaburzenia rozwojowe uzębienia u pacjenta leczonego z powodu rozpoznania nerwiaka zarodkowego

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Long-term cancer survivors require additional diagnostics and care due to the late effects of the neoplasm and its treatment. The type and intensity of the dental pathological changes can be determined among others by the type and dose of the cytostatic drug applied as well as the duration of oncological treatment. Most abnormalities occur in the period of intense development of tooth buds, i.e. before 5 years of age.

Neuroblastoma is a solid tumor arising from neural crest cells. It occurs most often in the retroperitoneum and is diagnosed very early, at approximately 2–3 years of age. Chemotherapy administered at that stage of life may subsequently affect dental development.

This paper presents a case report of a 13-year-old male patient with microdontia of the four first premolars. The patient was treated with long-term chemotherapy at the time of the first premolar crowns' development. The treatment of neuroblastoma probably caused these adverse effects. Moreover, clinical examination has revealed enamel anatomical abnormalities of the permanent incisors, canines and first molars (**Dent. Med. Probl. 2015, 52, 3, 356–362**).

Key words: neuroblastoma, chemotherapy, dental abnormalities, microdontia, late effects.

Słowa kluczowe: nerwiak zarodkowy, chemioterapia, zaburzenia zębowe, mikrodoncja, późne następstwa.

Long-term cancer survivors require additional diagnostics and care due to the late adverse effects of the disease and its treatment. In the past, conventional chemotherapy was predominantly combined with radiotherapy and the injurious effects were attributed mainly to irradiation. Chemotherapy-induced abnormalities are only beginning to be currently described [1–5]. The presence of potential disturbances depends on the type and dose of the cytostatic drug and the duration of treatment. However, reports still include a large number of patients subjected to preventive radiotherapy. Subsequently, there are no explicit opinions on the effect of chemotherapy on odontogenesis [1–3, 6]. The severity of the discussed pathological changes varies with the patient's age at diagnosis, i.e. the stage of dental development. Most abnormalities are observed in the period of intense development of tooth buds, i.e. before 5 years of age. Fewer complications are noted in older children [2, 6, 7]. Some authors, however, do not observe such a correlation [8, 9].

Experimental research has confirmed the toxic effects of vincristine, cyclophosphamide or doxorubicin applied in current treatment protocols [10–13]. Being sensitive to environmental agents, dental tissues manifest dose-dependent changes in histological and anatomical structure due to cyclically applied chemotherapy [4]. These abnormalities are caused by an inhibition of mitotic division and cell secretion. This may lead to changes in tissue laminar structure and the production of irregular enamel and dentin, even with the inhibition of tissue formation [8, 10–12]. Chemotherapeutics, similarly to irradiation, damage precursor cells and have a toxic effect in the early stages of tooth formation. From an early age, they can cause tooth agenesis, microdontia, changes in the anatomical structure of teeth, hypoplasia and arrested root development, which occurs at a later age [1, 2, 5, 8, 9, 14–17]. There are no reports of a large number of patients treated solely with chemotherapy, so its adverse effects remain unknown. Moreover, therapy administered at different stages of odontogenesis creates difficulties in reliable statistical evaluation.

Neuroblastoma is a solid tumor arising from neural crest cells, which can occur as primary everywhere in the body but most commonly in the retroperitoneum [1, 18]. This tumor is diagnosed at an early age (ca. 2–3 years of age) and usually at the moment of diagnosis its metastases are already present [1, 15, 18]. In Poland approximately 70–80 cases of neuroblastoma are noted annually, which accounts for ca. 6.5% of all childhood neoplasms. In the USA the prevalence under 15 years of age is 8% [15, 19]. It is the most common solid extracranial childhood tumor [1, 19, 20]. Neuroblastoma can have various clinical behaviors and, depending on severity, requires different kinds of treatment. Patients suffering from a low-risk disease, due to favorable prognosis, are subjected to surgery, which in some cases is supplemented with cytostatic treatment. The medium- and high-risk disease, apart from surgical treatment, requires chemotherapy, sometimes also radiotherapy, and in some cases bone marrow transplantation (see International Neuroblastoma Staging System classification) [1, 20, 21]. The stage of the neoplasm and the early age at diagnosis result in a potential risk of pathological changes in all the developing structures, including odontogenesis.

The aim of the study is to evaluate the late effects of chemotherapy in the dentition of a patient treated for neuroblastoma at a very early age.

Case Report

A 13-year-old boy first appeared at the age of 10 years at the Children's Dentistry Outpatient Clinic of the Department of Pediatric Dentistry at the Medical University of Silesia in Katowice to have his teeth checked before orthodontic treatment. The interview revealed that the patient had had neoplasm at a young age.

Medical History

At the age of 12 months (weight 10 kg, height 80 cm), the patient was diagnosed with neuroblastoma – a 70 × 58 mm tumor located near the upper pole of the right kidney, without metastases (stage I according to INSS classification). Chemotherapy based on vincristine (VCR) and actinomycin (ACT) was administered immediately and, after approximately 1 month, surgery was performed, resulting in a complete removal of the tumor with right-sided nephrectomy. Cytostatic treatment was continued for 13 months, i.e. until the boy's 26th month of age. The patient also received etoposide (ETHIO), Vumon® (VM-26), Cardioxane® (CRDX), cyclophosphamide (CTX), Adriblastin® (ADM), cisplatin (CDDP), dacarbazine (DTIC) and ifosfamide (IFO). During the treatment, the patient suffered immediate cytotoxic therapy side effects: anemia, leucopenia, thrombocytopenia, pancytopenia and their consequences. After 14 months of treatment, his weight was 12 kg and height 87 cm. A USG and CT examination did not reveal any abnormalities and no pathological foci of enhanced radiotracer uptake were noted in the check-up scintigraphy of the osseous system. The patient, in very good general condition, is still subjected to regular check-ups. Due to the applied antineoplastic therapy, the boy suffers from bilateral hearing loss and stage 2 renal insufficiency of the remaining kidney.

Physical Examination

The patient, having a correct constitution, is currently 166 cm tall and weighs 55 kg (a standard for 13 years of age). On the belly skin there is a visible horizontal 20-cm scar, resulting from the surgery performed as part of the antineoplastic treatment. On the chest skin, in the vicinity of the heart, the patient has a scar due to a port applied during hospitalization. Other deviations from the standard have not been found. The patient's psychomotor development is correct.

Intraoral Examination

There are no active carious lesions in the boy. The teeth in the third cervical part are covered in thin yellow-brown debris, although the oral cavity hygiene is very good. The patient prophylactically brushes his teeth with a paste containing 1450 ppm of fluoride on a daily basis and is regularly subjected to a debris cleaning procedure. Moreover, clinical examination has revealed a microdontia of all first premolars, which do not have a regular shape of premolar teeth and their size reaches less than half of the physiological size (Fig. 1–3). The enamel of the incisors and canine teeth is marked by regular transverse corrugation of the surface (Fig. 4). There was no family history of similar dental abnormalities.

a)
b)
c)


Fig. 1. Conditions in the time of first premolars eruption. 20.10.2012 (patient 11 years of age): a) microdontia 34 and 44; b) microdontia 34 and unerupted 24; c) eruption of 14

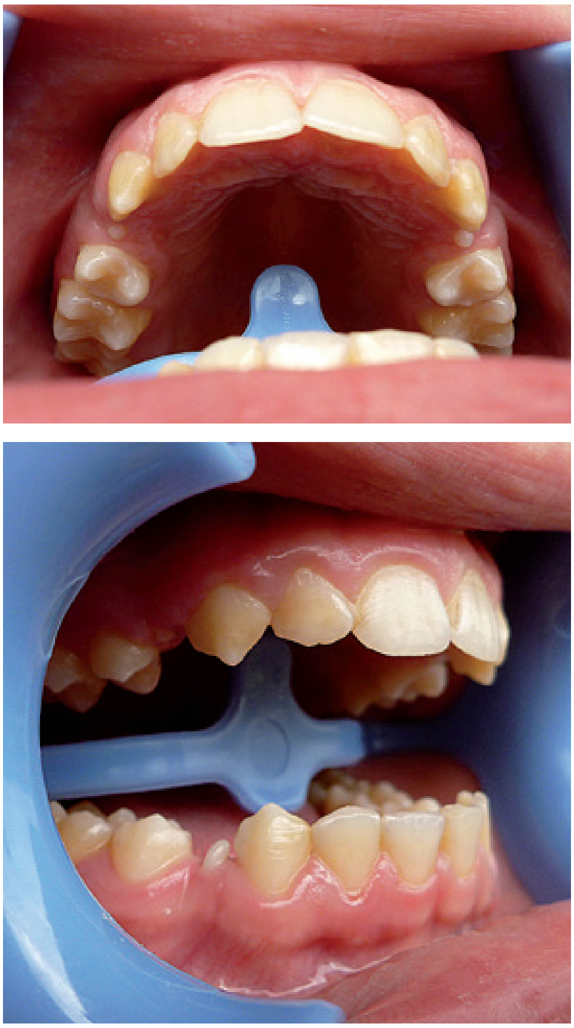
a)
b)


Fig. 2. Conditions after eruption of all first premolars. 1.06.2013 (patient 12 years of age): a) maxillary teeth; b) the distance between 43 and 45 is getting smaller

Fig. 3. Conditions after extraction of 14, 24, 34, 44. 29.03.2014 (patient 13 years of age)

Radiological Examination

Over several years of dental care provided to the patient, we have collected extensive radiological documentation, which gives an overview of the subsequent stages of the conservative and orthodontic treatment applied. The radiograms show teeth 14, 24, 34 and 44 with a considerably reduced size of the crown and root in relation to the other teeth (Fig. 5, 6).

Fig. 4. Enamel abnormalities – horizontal lines on the surface (valleculae)

Examination and Conservative--Orthodontic Treatment

In the patient aged 10, the following were found: brachycephaly, cis-frontal profile and well-formed dental arch symmetrical in relation to the face. Complete distoclusion and supraclusion with visibly ground lower incisors were diagnosed, with a suspicion of microdontia in teeth 14, 24, 34 and 44 (Fig. 5). In the following year, complete resorption of the roots and exfoliation of teeth 74 and 84 were observed. Another radiogram confirmed microdontia in the four first premolars (Fig. 6). Teeth 54 and 64 were extracted and treatment with elasto-positioner Multi P (RMO, Denver, USA) was begun. Next, a block device was modified in order to further reduce the above-mentioned malocclusions. When the orthodontic devices were used, the spaces corresponding to first premolars decreased and then extraction of these teeth was performed (Fig. 2, 7). The patient is still treated with the block device. Further drifting of the surrounding teeth to close the spaces is observed (Fig. 3).

Discussion

The diagnosis of microdontia in a 10-year-old survivor with undisturbed general development comes as a surprise. Microdontia occurs when the size of a dental crown is smaller than or equal to half of its physiological dimension. The form of the crown is ordinary or conical, also called peg-shaped [6, 14]. The photographs present the patient's extracted teeth compared with ones having a physiological structure (Fig. 7).

One can find opinions that both the size and shape of a dental crown are programmed in prenatal life and any stimuli after the birth cannot disturb its development [8]. Oguz et al. [9] noted microdontia in only 1 of 36 examined patients subjected to antineoplastic therapy. This result is similar to the conditions of the healthy population, where the prevalence of microdontia reaches 2.5% [17]. Moreover, in the above-quoted research, the diagnosis was made when the patient was five years old, so a correlation to chemothera-

Fig. 5. Panoramic radiograph – patient 9 years of age

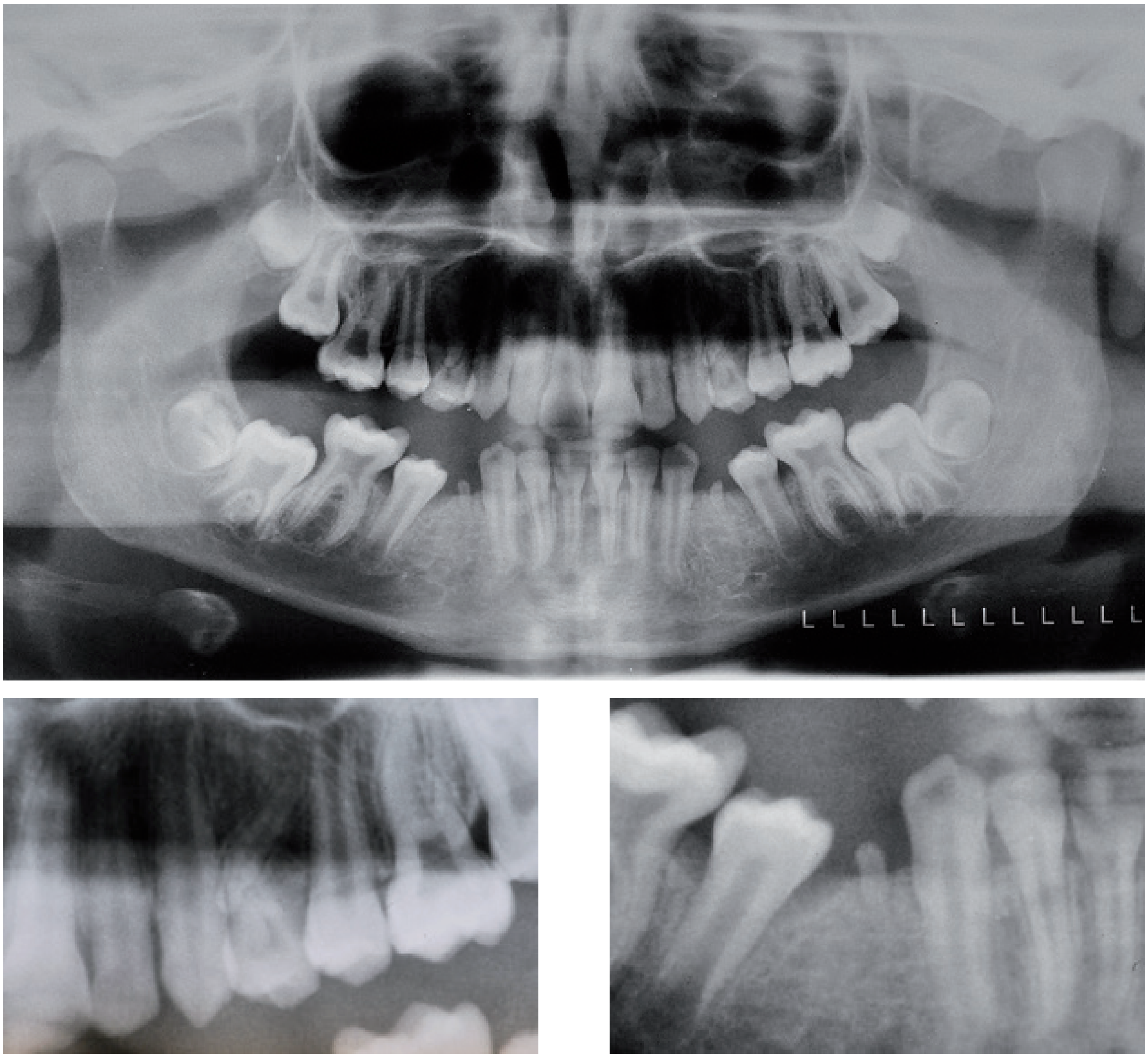
a)
b)
c)


Fig. 6. Panoramic radiograph of patient aged 11: a) whole dentition; b) magnification of region 64 (24); c) magnification of region 44

py seems doubtful. Other researchers, however, diagnose microdontia in a larger number of patients treated with radio- and chemotherapy – 38% and 18%, respectively [3, 15]. Holtta et al. [14] found microdontia in as many as 80% of children who were subjected to chemo- and radiotherapy, and in 85.7% of children treated solely with chemotherapy. In another study, the same authors found microdontia in 44% of children [6]. A definitely lower percentage of patients with microdontia, 5.2%, was observed in research carried out by Avsar et al. [8]. This number was not statistically significant, but all the cases of microdontia were found in children below 5 years of age. In this group, the percentage of patients with the disorder reached 11.1% [8]. The investigations conducted by Maguire et al. [17] revealed that microdontia occurred in as many as 38% of children subjected to treatment in the first three years of life.

Fig. 7. Extracted permanent teeth in comparison with undisturbed first premolars

The average age at which neuroblastoma is diagnosed is approximately 2–3 years, when there is a real risk of disturbing the odontogenesis. The development of primary teeth begins around the sixth week of embryonic life and finishes with the full development of roots at around 3 years of age. There is a limited probability of therapy-induced developmental injuries. In the case of permanent teeth, development starts in the prenatal period and is completed around 15 years of age (excluding third molars), so a disturbance is likely to occur. The toxic effects of cyclophosphamide and vincristine administered to the presented patient on the development of enamel and dentin has been proved in research using an animal model [8, 10, 12]. The earlier this harmful influence occurs in the process of tooth development, the more serious the disorder of its structure is expected [2, 17]. However, despite the proved detrimental effects of chemotherapy on tooth buds, in some studies the prevalence of microdontia is statistically insignificant. The authors point to the fact that the half-life period of cytostatic drugs is very short and, therefore, they cause only temporary and localized injuries [8]. This fact may account for the correct development of most teeth in the examined patient. Chemotherapy was administered to him very early, in the 12^{th} month of life, and continued for another 13 months. The period before this time marks the beginning of mineralization of first molars, incisors and canines, and at the latest – lateral incisors in the mandible, in approximately the 11^{th} month of life [22, 23]. Usually, no microdontia is found in the above-mentioned teeth in patients who have received antineoplastic treatment. However, Remmers [1] demonstrated a neuroblastoma survivor who not only had all the first premolars affected, but also maxillary lateral incisors, though to a lesser extent. The patient received one cycle of chemotherapy in the third month of her life and the author suggests that the applied treatment probably induced abnormalities. The subsequent 6 cycles of cytostatic treatment began in the 11^{th} month of the girl's life, when disease relapse was diagnosed, which might be correlated with the disorder in the above-mentioned premolars. The development of these teeth starts at birth, whereas the beginning of mineralization falls to 1.75 – 2 years of age [22, 23]. The time before and the beginning of the mineralization of these teeth in the presented patient coincides with the period of chemotherapy treatment. As the calcification of the remaining teeth begins in later years, the complication affects all the teeth in one group and there is no family history, it can be presumed that microdontia was caused by the antineoplastic therapy. An analysis of the time of the beginning of particular teeth's development and mineralization makes it possible to conclude that cytostatic drugs did not have a detrimental effect on the buds of the permanent teeth in the early period between the initiation of odontogenesis and the beginning of calcification in the studied patient. No abnormalities have been observed in the second premolars and second molars, which were at an early stage of development at the time of chemotherapy, and their mineralization usually starts between 2 and 2.5 years of age [22, 23]. The buds of the first premolars at the time of the patient's treatment were probably at a high-sensitivity developmental stage. On the basis of average data regarding the whole population, it may be presumed that the treatment occurred in the period ranging from a few months before to a few months after the beginning of calcification.

Of course, this observation needs to be confirmed by research conducted on a larger group of patients, although a thorough analysis of the circumstances described in this work makes it hard to believe that this is a question of coincidence. Remmers [1] also points to chemotherapy as the probable cause of pathological changes in the girl he examined, although the duration of her treatment was shorter than that applied for the patient discussed in this work. It should be considered whether the changes might have been influenced by the type and dose of the cytostatic drug administered.

Changes in the enamel of the patient's incisors, canines and in the cervical parts of the first molars are not observed in other teeth, which began to mineralize in the period following completion of the oncological therapy. The beginning of the calcification of incisors and canines falls into the period around 3–5 months of age, except for the maxillary lateral incisor (11 months of age), whereas the complete development of incisor crowns finishes around 4–5 years of age, and canines at 6–7 years of age. The period of first molar mineralization, which starts at birth and finishes in the area of the crown around 2.5–3 years of age, also partially coincides with the time of the cytostatic treatment applied. The enamel covering the previously calcified nodules of the chewing surface is smooth and shiny, as opposed to the cervical part of the crown, which mineralizes at a later time. The above-mentioned changes might have been caused by chemotherapy administered to the patient. Vincristine and cyclophosphamide disrupt the calcium transport mechanism in ameloblasts, thus leading to enamel hypomineralization [8]. In animal experiments, as early as 24 hours following the administration of cyclophosphamide, a complete disintegration of enamel cells and their necrosis in some areas was observed [10]. There are also reports of disturbances related to the secretory function of ameloblasts and cell membrane permeability, which, combined with changes in the membrane transport of calcium, may cause abnormalities on enamel surface due to the production of irregular matrix [16].

In the examined patient, no isolated alterations of dental root development have been found. Chemotherapy was completed at a very young age, when the crown was not fully developed in any of the teeth groups. The small size of the first premolars' roots was determined by the relatively smaller size of their crowns.

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