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Nevoid basal cell carcinoma syndrome: a review of the literature and a report of a case

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Summary. The purpose of this paper is to report the development of multiple odontogenic keratocysts (OKCs) in a 15-year-old female with nevoid basal cell carcinoma syndrome (NBCCS) and review the literature pertinent to NBCCS. Although more than 100 abnormalities have been reported in NBCCS, the development of OKCs is one of its principle features. In view of this, the patient was subjected to further medical, dermatological and radiographic investigation. Multiple basal cell naevi and skeletal anomalies associated with NBCCS were found. Because of the autosomal dominant inheritance of this syndrome, the patient's family was then investigated. The patient's father was found to have multiple OKCs. The report highlights the need for vigilance in considering the diagnosis of NBCCS in all cases of OKCs, particularly those affecting young patients.

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), which is also referred to as Gorlin–Goltz syndrome, basal cell nevomatosis, hereditary cutaneous mandibular prolyncosis and the fifth phacomatosis, is transmitted as an autosomal dominant trait with high penetration and variable expression [1,2]. It is an ecto-mesodermal polydysplasia with numerous manifestations that affect multiple organs. The NBCCS is characterized by: cutaneous anomalies, including multiple basal cell naevi, benign dermal cysts, and palmar or planter pits; dentofacial anomalies, including multiple odontogenic keratocysts (OKCs), a broad nasal bridge and increased head circumference; skeletal anomalies, including frontal and parietal bossing, mandibular prognathism, and rib and vertebral anomalies; ophthalmologic anomalies, including hypertelorism, congenital blindness and strabismus; and neurological anomalies, including calcifications of the falx cerebri, bony bridging of the sella turcica and medulloblastoma [3]. Less well-described complications include uterine and ovarian calcification or fibromas, cardiac fibroma, facial nerve palsy, nerve deafness, cleft lip and palate, and learning difficulties [4].

This paper reviews the literature on NBCCS, and reports the development of multiple OKCs in a 15-year-old female followed for 3·5 years at the Department of Oral Surgery, Oral Medicine, Oral Pathology and Periodontics, Jordan University Hospital, Amman, Jordan.

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Literature review

Case reports of NBCCS go back more than a century. In 1894, White [5] published a case of multiple jaw cysts associated with skeletal abnormalities and basal cell naevi. Gorlin and Goltz [6] catalogued the known abnormalities thought to be associated with the syndrome in 1960, after analysing 150 cases from the literature. Nevoid basal cell

carcinoma syndrome is uncommon, but not rare: the annual incidence of the syndrome is one per 1 600 000 live births [3]. The syndrome occurs with equal frequency in both sexes, and has both a sporadic and a familial incidence [3]. Autosomal dominant inheritance mediates the familial type, while the sporadic type may occur by spontaneous mutation [7].

A defective gene has been found in the familial and sporadic forms, and it has been mapped to the long arm of chromosome 9q22.3-q31 [8]. This has been confirmed by many studies utilizing linkage and loss of heterozygosity [9,10]. Approximately 50% of cases of NBCCS have allelic losses that include the 9q22.3-q31 site [9]. By positional cloning, the gene has been isolated and shown to be the human homologue of the drosophila 'patched' gene (PTCH), which is part of the hedgehog-signalling pathway that is important in determining embryonic patterning and cell fate in the developing embryo [11–14]. Data suggest that the product of this gene acts as a tumour-suppressor [10], and the typical malformations in NBCCS suggest that the gene's main function is to control growth and development. Basal cell carcinoma (BCC) is associated with mutations that activate the proto-oncogene 'smoothened' or that inactivate the tumour-suppressor 'patched'. Smoothened and patched mediate the cellular response to the hedgehog-secreted protein signal, and oncogenic mutations affecting these genes cause excess activity of the hedgehog response pathway [15]. The mutations in human patched result in the loss of control of several genes known to play a role in both organogenesis and carcinogenesis, and this may explain both the congenital anomalies and cancer predisposition seen in NBCCS [12,16,17].

Syndromic basal cell naevi can arise in patients as young as 2–5 years of age, with 80% of these patients developing at least one BCC by the age of 20 [18–22]. The naevi are rarely congenital, with most appearing in increasing numbers around the time of puberty. After puberty, naevi can become aggressive and locally invasive [19]. The lesions, unlike non-syndromic BCCs, occur in both sun-exposed and unexposed areas of the body, and may vary from a few to several hundred [23]. They are commonly found on the neck and upper trunk, but the periorbital area, eyelids, nose, upper lip and malar region constitute the most commonly affected areas [24]. Cutaneous manifestations of NBCCS include palmar or planter pits. These nearly pathognomic pits affect up to 75% of patients [3] and represent areas of defective keratinization that form holes of 2–3 mm in diameter and 1–3 mm in depth. They are sometimes accompanied by underlying erythema so that they appear as red spots at a distance [25]. The pits become more evident when patients' hands or feet are placed in warm water for several minutes [2]. Other reported cutaneous anomalies include epithelial cysts, lipomas, fibromas and small whitish spots, or milia, particularly around the eyes [24].

About 75% of patients with NBCCS have skeletal anomalies. These include costal anomalies such as bifid, splayed or synostotic ribs, and ribs associated with the cervical spine. Vertebral anomalies such as spina bifida occulta, scoliosis, kyphoscoliosis and imperfect segmentation of cervical vertebrae can also be found. Brachymetacarpalism (short fourth metacarpal bones) may be present, but this anomaly is generally so subtle it is diagnosed radiographically rather than clinically [15,22,26].

Multiple OKCs are the most constant and common anomaly in NBCCS, occurring in 65–100% of patients, and usually appearing by the second or third decade of life [3,27]. The dentists' diagnostic role surfaces when considering the fact that OKC development frequently antedates the syndromic basal cell naevi [2,7], thereby allowing an earlier diagnosis. The cysts occur three times more frequently in the mandible than the maxilla and can cross the midline in both jaws [3,28]. Jaw swelling, dull pain, and intraoral drainage of cystic contents are common signs and symptoms [26,29]. Syndromic OKC patients frequently experience the development of new and recurrent OKCs until the fourth decade, when the rate of development tends to slow [3,30]. A 60% recurrence rate was reported following enucleation in one published report [31]. Furthermore, the OKCs associated with NBCCS have been known to transform into ameloblastomas or squamous cell carcinoma [3]. Other reported oral manifestations in NBCCS include: malocclusion (i.e. displaced, impacted or missing teeth); mandibular prognathism; ameloblastoma; cleft lip and/or palate; and hyperplasia of the mandibular coronoid process [2,22,32–34].

Patients with this syndrome share a rather distinctive physical appearance. There may be frontal and parietal bossing coupled with prominent supraorbital ridges and heavy and fused eyebrows, giving a sunken appearance to the eyes [24,26]. The nasal bridge may be broad, and there may be ocular

hypertelorism and pouting lips [12]. The size of the calvarium can be relatively large with a head circumference (occipto-frontal) of 60 cm or more in 25% of cases [3,26,35]. Patients are often tall and marfanoid [5].

Neurological involvement is variable. Commonly cited afflictions include calcification of the falx cerebri, which can present in up to 92% of patients with NBCCS (normally in up to 5% of patients without the syndrome) [26]. Bridging of the sella turcica is also common [22], and calcification of the tentorium cerebelli and other parts of the dura have been reported [21,26]. These intracranial anomalies are occasionally accompanied by medulloblastomas [6,36], mild learning difficulties, facial nerve palsy, nerve deafness, congenital hemiparesis and epilepsy [7,37]. Ophthalmic abnormalities such as chalasions, internal strabismus, cataract and congenital blindness have been described [2,19,24,29].

Affected individuals are prone to develop benign tumours in addition to the aforementioned malignancies in early life. Females may develop benign uterine or ovarian fibromas that can represent the initial manifestations of the syndrome and cardiac fibromas have been found in some patients affected by NBCCS [19]. Furthermore, NBCCS patients have developed malignancies after being subjected to high doses of ionizing radiation usually intended to address multiple BCCs or medulloblastomas [16,37–39]. A form of cellular instability or at least increased sensitivity to ionizing radiation has been postulated to account for the clinical behaviour towards radiotherapy. However, *in vitro* studies have produced inconsistent results [40]. Some have shown abnormal induction of DNA synthesis in fibroblasts taken from NBCCS lesions after being irradiated [16,41]. Consequently, omitting or at least limiting radiation therapy to patients with this syndrome has been advocated [16,42,43].

Racial variations in the expression of the features of NBCCS have been found. When NBCCS occurs in black individuals, there is minimal expression of the BCCs and full expression of the other components of the syndrome. In a study of 11 NBCCS cases in two African-American families, it was found that only 44% developed BCCs [44], as opposed to the commonly cited 90% in white races. It was concluded that the relative lack of these tumours in African-Americans is partly because of increased skin pigmentation that confers protection against ultraviolet (UV) light [37,44]. This is in agreement with the finding of a relatively lower percentage of BCCs (30%) in Italians with NBCCS [21], and an earlier appearance of BCCs in Australian patients with NBCCS [20].

There is no specific laboratory test to diagnose NBCCS, although affected patients may have high levels of cyclic adenosine monophosphate and alkaline phosphatase, and impaired phosphate diuresis upon parathormone challenge [2]. The diagnosis is made clinically by using the major and minor criteria suggested by Evans *et al*. [19] and Kimonis *et al*. [22]. The diagnosis is achieved upon finding any two of the major criteria, or one major criterion together with two minor criteria (Tables 1 and 2).

The definitive treatment of NBCCS has not been established; however, early diagnosis is very important. Periodic follow-up to detect transformation in skin lesions and recurrence of OKCs is essential. It is recommended that patients with NBCCS have dermatological examinations every 3–6 months with the removal of basal cell naevi showing growth, ulceration or haemorrhage [21]. Patients should be advised to avoid or reduce their exposure to UV light (direct sunlight), this may lessen their risk of developing BCCs [2,22]. Radiation therapy should be avoided as well. Patients presenting with a medulloblastoma early in life should be investigated for the stigmata of NBCCS [7]. The risk of developing a medulloblastoma is greatest between 2 and 3 years of age [22]. Therefore, a neurological examination every 6 months is recommended for children with NBCCS. From 3

Table 1. Diagnostic criteria for nevoid basal cell carcinoma syndrome (NBCCS) taken from Evans *et al*. [19].

Major criteria
More than two basal cell carcinomas (BCCs), one BCC in patients younger than 30 years of age or more than 10 basal cell naevi
Any odontogenic keratocyst (proven by histology) or polyostotic bone cyst
Three or more palmar or planter pits
Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification)
A positive family history of NBCCS
Minor criteria
Congenital skeletal anomaly (e.g. bifid, splayed, fused or missing rib, or bifid, wedged or fused vertebra)
Occipital-frontal circumference greater than the ninety-seventh percentile, with frontal bossing
Cardiac or ovarian fibromas
Medulloblastoma
Lymphomesenteric cysts
Congenital malformation, such as cleft lip/palate, polydactylism or eye anomaly (e.g. cataract, coloboma or microphthalmos)

Table 2. Diagnostic criteria for nevoid basal cell carcinoma syndrome (NBCCS) taken from Kimonis *et al*. [22].

Major criteria
More than two basal cell carcinomas (BCCs) or one BCC in patients younger than 20 years of age
Odontogenic keratocysts of the jaw (proven by histological analysis)
Three or more palmar or plantar pits
Bilamellar calcification of the falx cerebri
Bifid, fused or markedly splayed ribs
A first-degree relative with NBCCS
Minor criteria
Macrocephaly
Congenital malformations (e.g. cleft lip or palate, frontal bossing, coarse facies, and moderate or severe hypertelorism)
Other skeletal abnormalities (e.g. Sprengel deformity, marked pectus deformity and marked syndactyly of the digits)
Radiological abnormalities (e.g. bridging of the sella turcica, vertebral anomalies, modelling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet)
Ovarian fibroma or medulloblastoma

to 7 years of age, the neurological examination can be done annually. After this age, the occurrence of medulloblastoma is very unlikely [19]. Children diagnosed with this syndrome should also undergo full cardiac evaluation, and genetic counselling is recommended for those of childbearing age [43]. Multiple OKCs should alert the dentist to the possibility of this syndrome and trigger a thorough investigation. An annual dental panoramic radiograph has been suggested between the ages of 8 and 40 years for the potential detection of OKCs [22].

Case report

A 15-year-old female with no significant past medical history presented to the Department of Oral Surgery, Oral Medicine, Oral Pathology and Periodontics, Jordan University Hospital, Amman, Jordan, in September of 1999 complaining of a swelling on the left side of her mandible. The patient was 1·7 m in height. Extraoral examination revealed a prominent forehead, a slightly prognathic mandible and a hard, non-tender swelling in the left body of the mandible. Intraorally, the patient had several retained primary teeth. A firm and non-tender swelling approximately 2 cm in diameter obliterated the buccal sulcus in the mandibular left premolar region, and an expansile lesion was evident on the lingual aspect of the anterior mandible.

A radiographic examination (Fig. 1) disclosed three well-defined, well-corticated cystic lesions. The largest

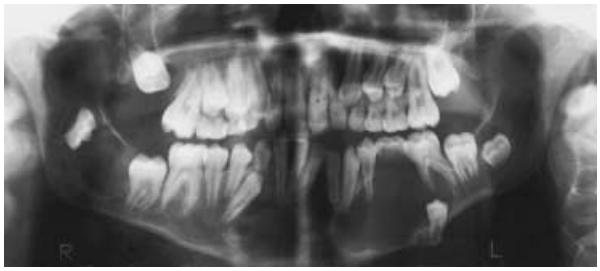

Fig. 1. Panoramic radiograph taken on the subject's initial presentation showing three cystic lesions.

was located in the left mandibular body extending from the canine to the distal root of the first permanent molar. The second cyst was 3·0 × 2·0 cm in diameter, developing in the anterior region of the mandible and extending from the right canine to the left lateral incisor. The third one was 3·0 × 2·0 cm in the right angle of the mandible surrounding and displacing the unerupted third molar into the ramus. The unerupted left second premolar was displaced to the inferior border of mandible and the root of the lower right unerupted canine was displaced distally. A provisional diagnosis of multiple OKCs was made.

Under intravenous (IV) sedation and local anaesthesia, the mandibular left second primary molar was extracted, and the underlying cyst was marsupialized in an attempt to save the unerupted lower second premolar. An incisional biopsy was taken from the cyst lining to determine its histopathology. The decompressed cyst was then packed with tetracycline-impregnated ribbon gauze, and the patient was dismissed to be reviewed for daily irrigation and replacement of the ribbon gauze. Two weeks later, the two other cysts were treated by enucleation and curettage under IV sedation and local anaesthesia. The impacted lower right canine was left *in situ* and the flap was replaced in such a fashion as to leave its crown uncovered.

Tissue samples from the three cystic lesions were histopathologicaly shown to be OKCs. The lining of each cyst was composed of a thin, uniform layer of parakeratinized stratified squamous epithelium with a corrugated surface and a prominent palisaded basal cell layer. The epithelium appeared mature with no evidence of atypia. Areas of separation of the epithelial lining from the supporting connective tissue wall were seen. The epithelial lining was supported by a thin, fibrous connective tissue wall containing a mild chronic inflammatory cell infiltrate; however, no daughter cysts in the walls of the three cysts were

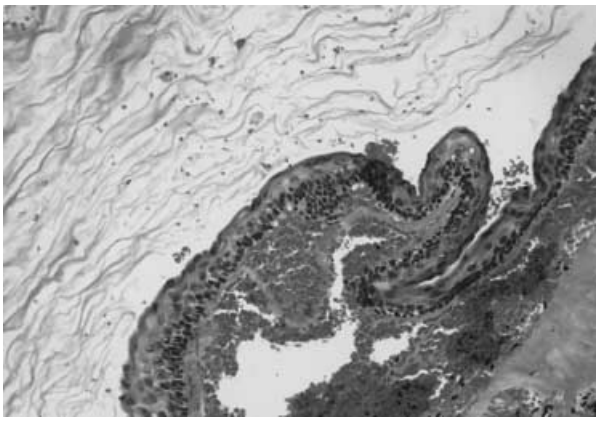

Fig. 2. The lining epithelium and the thin fibrous wall of an odontogenic keratocyst (H&E, original magnification × 200).

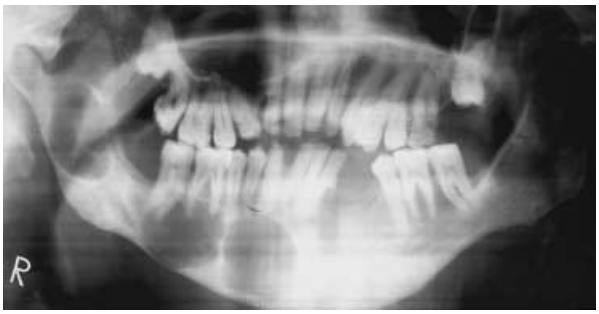

Fig. 3. Panoramic radiograph of the subject's 40-year-old father showing multiple odontogenic keratocysts.

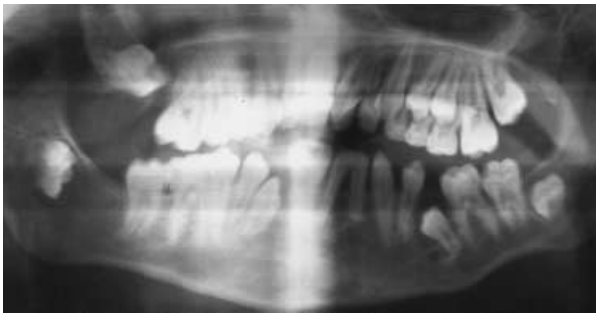

Fig. 4. Panoramic radiograph of the subject taken 19 months after the initial presentation.

seen. The cysts were filled with eosinophilic flakes composed of keratin (Fig. 2).

In view of the occurrence of three OKCs in this adolescent patient, the possibility of NBCCS was investigated. Dermatological examination of the patient disclosed multiple basal cell naevi on the forearms and back. The largest was approximately 2 cm in diameter on the right thigh. No epidermal cysts or dyskeratotic skin pits were seen. Although a radiological examination of the chest failed to reveal rib abnormalities, cranial radiographs revealed a slight opacification of the falx cerebri and bridging of the sella turcica. Using the diagnostic criteria of Evans *et al*. [19] (Table 1) and Kimonis *et al*. [22] (Table 2), the patient was diagnosed with NBCCS.

Because of the autosomal dominant inheritance of this syndrome, the patient's family was then investigated. Her 40-year-old father had a documented history of being diagnosed and treated for an OKC that affected the left side of the body of the mandible at the age of 25, so a panoramic radiograph was taken to rule out novel or recurrent lesions. Interestingly, three well-defined, well-corticated cystic lesions were discovered in the right side of the mandible: one affecting the anterior region, another the molar region and the third the ramal region (Fig. 3). The three cysts were treated by enucleation and curettage under IV sedation and local anaesthesia. A fourth, ill-defined radiolucency was noticed around the roots of the left first molar; however, it was not clear at that time if this represented a recurrence, a new lesion or an artefact, and it remained untreated. The histopathologic reports confirmed the OKC diagnosis. Six sisters and one brother, all of whom are younger than the patient, had no clear signs or symptoms of the syndrome. Follow-up appointments were arranged for all members of the family.

The daughter and father returned for follow-up and panoramic radiography 19 months later. The radiograph of the daughter showed healing of the anterior mandibular cystic lesion. The cystic lesion in the right ramus and the angle of the mandible was reduced to a small radiolucency surrounding the crown of the unerupted third molar. The lower left second premolar remained impacted, but displaced from the lower border of the mandible and close to the alveolar crest. Dilaceration of its root and a small radiolucency mesial to its crown were seen however (Fig. 4). An appointment to extract the tooth and to enucleate the lesion mesial to its root which may represent an early recurrence was arranged. The radiograph of the father showed uneventful healing of the three excised cystic lesions. Further follow-up appointments for the father were arranged. Unfortunately, the two patients again missed their arranged appointments. The daughter presented 23 months later complaining of pain associated with her lower right canine, which was partially erupted

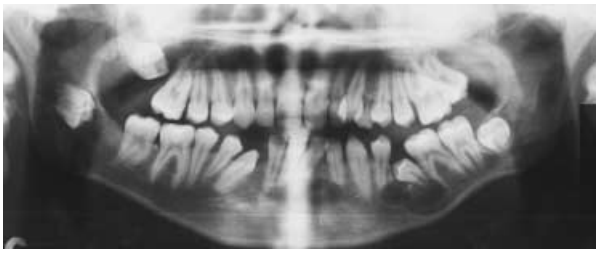

Fig. 5. Panoramic radiograph of the subject taken 42 months after the initial presentation.

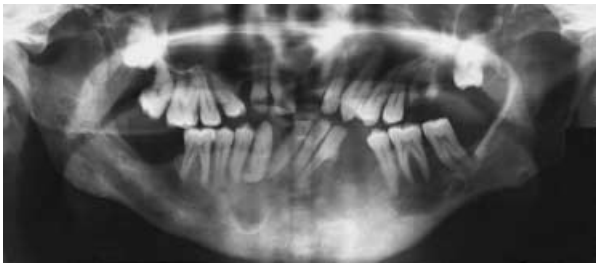

Fig. 6. Panoramic radiograph of the subject's father taken 42 months after the initial presentation.

and rotated. The gingiva associated with the tooth was erythematous and oedematous, so curettage was accomplished and oral hygiene instructions were given. A radiographic examination revealed recurrent anterior mandibular cystic lesion and that involving the left second premolar (Fig. 5). The father's panoramic radiograph revealed a recurrence of the anterior cystic lesion on the right side of the mandible and healing of the two others. The questioned area in the left mandibular body that was not treated during the father's previous surgery revealed an obvious progression extending from the second premolar to the distal aspect of the first permanent molar (Fig. 6). Enucleation and curettage of both patients' recurrent OKCs were accomplished and follow-up appointments were arranged. Extraction of the daughter's lower left second premolar was carried out because of the dilaceration of its root. The daughter's need for prosthodontic and possible orthodontic treatment was explained; however, up to the present time, the patients have not returned for follow-up.

Discussion

This case report describes a clinical scenario whereby a complaint of intraoral swelling disclosed a rare syndrome with multiorgan involvement. The diagnosis of multiple OKCs in an adolescent female suggested the possibility of NBCCS, and further dermatological and radiological examination, in addition to parental and family interviews, confirmed the diagnosis of the syndrome based on the presence of multiple OKCs, basal cell naevi, skeletal anomalies and a family history positive for OKCs affecting one of the parents.

OKCs are often the first sign of NBCCS and arise earlier in patients with the syndrome than in patients unaffected by the syndrome [21]. The presence of even one OKC in a patient younger than 20 years should alert the dentist to the possibility of NBCCS [2]. The dentist should consider NBCCS in all cases of OKCs, particularly multiple OKCs occurring simultaneously or one after the other. The NBCCS should also be considered whenever an OKC recurrence is encountered in that; syndromic OKCs have a higher recurrence rate than non-syndromic cysts [31]. In this report, the young patient had three OKCs occurring simultaneously at the age of 15 and had recurrence of two of these cysts during the 3·5 years she was followed. The father had one OKC at the age of 25 in the left side of the mandible, and four at the age of 40: three new cysts in the right side of the mandible, and a recurrent or novel cyst on the left side. One of the three cysts in the right side recurred during the 3·5 years of follow-up. Previous studies have shown a continued development of new and recurring OKCs up to about 30 years of age, at which time the development rate tends to decrease [30].

Some histopathological features may also help in the diagnosis of NBCCS: budding of the basal cell layer of the lining epithelium and the presence of high number of daughter cysts in the connective tissue wall of keratocysts were found to be more associated with syndromic OKCs [45]. Also, immunohistochemistry has been reported to be of some value. Different immunohistochemical markers have been used in an attempt to find one that can differentiate syndromic from non-syndromic OKCs [46]. It has been discovered that staining for cytokeratin 17 could help in the diagnosis of patients not previously known to have NBCCS. Staining for cytokeratin 17 in syndromic patients appears to be stronger and more uniform than non-syndromic patients [46].

It can be valuable for patients and their families when dentists assist in the early diagnosis of NBCCS. Since regular and close follow-up of NBCCS patients can allow early diagnosis of new OKCs, an annual dental panoramic radiograph is suggested between the ages of 8 and 40 years [21]. Cautious treatment of syndromic OKCs is needed because of the reported

high recurrence rate (up to 60%). The modality of treatment used here, i.e. enucleation and curettage, could, therefore, have contributed to the patients' high rate of recurrence and seems to be an insufficient ablative modality. Some reports have suggested that the standard of care for large OKCs involves the insertion of polyethylene drainage tubes with up to 6 months of decompression [47]. During this period, the cyst typically shrinks toward the tube opening. In addition, daily irrigation results in an alteration of the thin, fragile cystic wall into a thick, solid wall that does not adhere to adjoining structures and dramatically reduces the prevalence of recurrence. This modality of treatment needs a lot of cooperation from patients. Unfortunately, the patients described in this paper were uncompliant. For smaller cysts, the best treatment seems to be surgical removal with adjunctive therapy such as peripheral ostectomy, the use of Carnoy's solution or chemical cautery of the surrounding bone [48].

Early diagnosis is also of supreme importance for the general health of the patient since affected patients are prone to develop cancer early in life. Because the syndrome is inherited as an autosomal dominant trait, every family member should be investigated to allow early detection of any syndromic features. In the present case, all family members were seen. Except for the patient's father, all of the examined relatives were shown to be free of NBCCS. Nevertheless, arrangements were made for annual examinations for each family member to include panoramic radiography. A multidisciplinary approach to management, together with periodic follow-up, are advocated for the general well-being of all NBCCS patients and their families.

Résumé. Le propos de cet article est de rapporter le développement de kératokystes odontogènes multiples (OKCs) chez une jeune file de 15 ans avec syndrome de carcinome cellulaire basale naevoïde (SBCCS) et de passer en revue la littérature se rapportant au NBCCS. Bien que plus de 100 anomalies aient été rapportées concernant le NBCCS, le développement de OKCs est l'une des principales caractéristiques. La patiente a été soumise à des examens médicaux, dermatologiques et radiographiques plus poussés. Des naevi baso-cellulaires et des anomalies squelettiques associés au NBCCS ont été trouvés. En raison de la transmission autosomique dominante de ce syndrome, la famille de la patiente a été examinée. Le père présentait de multiples OKCs. Ce rapport illustre la nécessité de vigilance concernant le diagnostic de NBBCS dans tous les cas de OKCs, particulièrement ceux touchant les jeunes patients.

Zussamenfassung. Ziel dieser Arbeit ist es, die Entstehung multipler dentogener Keratozysten zu berichten bei eine 15jährigen Patientin mit Basalzellnävussyndrom und eine Literaturübersicht diesbezüglich zu erstellen. Auch wenn über 100 verschiedene Anomalien in Zusammenhang mit diesem Syndrom berichtet wurden gilt die Keratozyste als ein Hauptmerkmal. Die patientin wurde medizinisch, dermatolofgisch und röntgenologisch durchuntersucht. Dabei wurden multiple Basalzellnävi und mit diesem Syndrom vereinbare skelettale Veränderungen entdeckt. Aufgrund des autosomal dominanten Erbgangs wurde eine Familienuntersuchung veranlasst, dabei wurden beim Vater der Patientin multiple Keratozysten entdeckt. Dieser Fall verdeutlicht die Bedeutung des Basalzellnävussyndroms bei Patienten mit Keratozysten, insbesondere bei jüngeren Patienten.

Resumen. El propósito de este artículo es informar sobre el desarrollo de múltiples queratoquistes odontogénicos (QQOs) en una chica de 15 años con síndrome de carcinoma basal celular nevoide (SCCBN) y revisar la literatura pertinente al SCCBN. Aunque se ha informado de más de 100 anomalías en el SCCBN, el desarrollo de QQOs es una de las características principales. Como consecuencia, la paciente fue sometida a más investigación radiográfica, dermatológica y médica. Se encontraron múltiples células basales nevosas y anomalías esqueléticas asociadas con SCCBN. Debido a la herencia autosómica dominante de este síndrome, se investigó luego la familia de la paciente. Al padre de la paciente se le encontraron múltiples QQOs. El informe subraya la necesidad de vigilancia y a la vez considerar el diagnóstico de SCCBN en todos los casos de QQOs especialmente en aquellos que afectan a los pacientes jóvenes.

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