Treatment of Keratocystic Odontogenic Tumors in Nevoid Basal Cell Carcinoma Syndrome

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Abstract

Nevoid basal cell carcinoma syndrome (NBCCS) is inherited as an autosomal dominant trait with variable conditions, including multiple basal cell carcinoma, numerous keratocystic odontogenic tumors (KOTs) in the jaws, ectopic calcification of the falx cerebri, bifid ribs, macrocephaly, kyphoscoliosis, cleft palate, frontal and temporal bossing, mild ocular hypertelorism, mild mandibular prognathism, vertebral fusion, and so on. A 16-year-old boy visited the Dong-A University Medical Center, requiring diagnosis and treatment of multiple cystic lesions. He presented with many conditions related to NBCCS, including multiple KOTs, bifid rib, cleft lip, frontal bossing, mild ocular hypertelorism, and mild mandibular prognathism. No characteristic cutaneous manifestations (nevoid basal cell carcinoma) were observed in this patient. We report on a case of multiple KOTs associated with NBCCS with a review of the literature.

Key words: Basal cell nevus syndrome, Multiple keratocystic odontogenic tumors, Multiple odontogenic keratocysts

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) was first reported by Jarish in 1894; a detailed description of its features was reported in the 1960s by Drs. Robert Gorlin and Robert Golz[1-4].

NBCCS presents with a broad range of clinical symptoms, including multiple basal cell carcinoma, numerous keratocystic odontogenic tumors (KOTs) in the jaws, ectopic calcification of the falx cerebri, palmar and/or pits, and so on; therefore, this multidisciplinary disorder constitutes a true challenge for medical specialists[5-9]. In particular, dentists may be the first to encounter and identify this

syndrome when multiple cyst like radiolucencies are discovered on radiographs of the jaws[8,10-12].

This syndrome begins to appear early in life, usually after five years of age and before 30 years of age[9], and the average age for diagnosis of NBCCS is 13 years, while the average age for detection of basal cell carcinoma is 20 years[2,5]. Jaw cysts associated with this syndrome usually appear earlier in life than solitary KOTs, also earlier than other manifestations of this syndrome, and their recurrence is greater than that reported for solitary KOTs[9]. Histopathologically, the cysts of this syndrome are always odontogenic keratocysts or keratogenic odontogenic tumors[13].

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Fig. 1. Clinical photos. Intraoral photos.

Fig. 2. Preoperative panoramic radiography (arrows: cystic lesions).

Considering the rarity of this syndrome, we report on a young subject affected by NBCCS. A review of the literature is also included.

Case Report

A 16-year-old boy, who had been diagnosed with multiple cysts of the jaws in another tertiary medical center, visited the Dong-A University Medical Center, requiring re-diagnosis and treatment for multiple cystic lesions. There were no subjective symptoms and a full body clinical examination revealed frontal bossing, unilateral cleft lip on the left side, ocular hypertelorism, and mild mandibular prognathism (Fig. 1). Panoramic radiography showed six large radiolucent lesions on bilateral posterior sites of maxilla and mandible involving third molars and the right mandibular canine site (separately adjacent lesions) (Fig. 2). According to these findings, we suspected multiple jaw cysts associated with NBCCS and we took a skull posteroanterior (PA) view and chest radiography. Skull PA view showed no specific features. Chest PA radiograph showed two bifid formations of the right third rib and left fourth rib (Fig. 3).

Facial computed tomography showed bony expansion

Fig. 3. Chest posteroanterior radiograph (arrows: bifid rib).

of the right maxillary sinus, left maxillary tuberosity, and right mandibular ramus. Even the orbital wall of the right maxillary sinus was expanded and more than two thirds of the right mandibular ramus was occupied by cystic lesion. All third molars were involved to cystic lesions (Fig. 4). On the right mandibular canine site, two cysts were adjacent separately. Characteristic cutaneous manifestation (nevroid basal cell carcinoma) was not observed in this patient. In addition, his younger brother and mother did not show specific abnormalities.

The presence of minor and major criteria allowed the diagnosis of NBCCS. We had a plan to eliminate the cysts, including involved third molars, under general anesthesia, and performed cyst enucleation on the right maxillary sinus, left maxillary tuberosity, left mandibular third molar, and right mandibular canine area, and marsupialization was performed on the right mandibular ramal area (Fig. 5).

According to the histopathologic features, the mass

Fig. 4. Facial computed tomography. (A) Axial view. (B) Coronal view.

Fig. 5. Surgical specimen.

showed a cystic appearance composed of a fibrocollagenous wall and the inner surface of the cyst was lined by wavy, corrugated epithelium (Fig. 6). On high magnification, squamous epithelium with parakeratosis composed of a palisaded layer of cuboidal or columnar epithelial cells and regimentation of the basal layer was identified, and the interface of epithelium and connective tissue was flat and the thin fibroma wall was devoid of any inflammatory infiltration. These histological features were consistent with KOT (Fig. 6).

Fig. 6. Histopathologic view. (A) Histologic section (H&E, x20). (B) Histologic section (H&E, x200).

Fig. 7. Postoperative panoramic radiography. (A) One-month after operation. (B) Three-months after operation. (C) Six-months after operation. (D) Fourteen-months after operation.

Because of a higher recurrence rate of KOT in this syndrome, compared with solitary KOT, aggressive treatment is necessary. Yearly examination of the patient for evaluation of new and recurrent cysts is reasonable.

We performed follow-up panorama radiography at post-operative one, three, six, and 14 months (Fig. 7). In the present case, there was no evidence of recurrence of jaw cysts after 14 months.

Discussion

NBCCS is also referred to by several other names, including basal cell nevus syndrome (BCNS), basal cell carcinoma nevus syndrome, Gorlin syndrome, and Gorlin-Goltz syndrome[1,14]. In the scientific papers published in English, there are many synonyms for the syndrome, which often stem from its symptoms (Table 1)[15].

The assumed prevalence of the syndrome is 1:60,000; however, in several studies its values range from approximately 1:57,000 (in England) to 1:164,000 (in Australia)

Table 1. Synonyms of nevroid basal cell carcinoma syndrome (NBCCS)

Designations of the NBCCS used in the scientific papers	
Basal cell nevus carcinoma syndrome	Multiple basal-cell carcinoma syndrome
Epithelioma naevique multiple	Multiple basal-cell naevi syndrome
Fifth phakomatosis	Multiple hereditary cutaneomandibular polyoncosis
Gorlin syndrome	Multiple naevoid basal-cell carcinoma syndrome
Gorlin-Goltz syndrome	Naevous epitheliomatodes multiplex
Hereditary cutaneo-mandibular polyoncosis	Nevoid basal cell carcinoma epithelima-jaw cysts
Hermans-Grosfeld-Spaas-Valk syndrome	Ward syndrome II

Table 2. Clinical features of nevroid basal cell carcinoma syndrome

≥50% frequency	15~49% frequency	<15% frequency (but not random)
Multiple basal carcinoma	Calcified ovarian fibromas	Medulloblastoma
Keratocystic odontogenic cyst	Short fourth metacarpals	Meningioma
Epidermal cyst of skin	Kyphoscoliosis or other vertebral anomalies	Lymphomesenteric cyst
Palmar/plantar pits	Petous excavatum or carnatum	Cardiac fibroma
Calcified falx cerebri	Stabismus (exotropia)	Fetal rhabdomyoma
Enlarged head circumference		Marfanoid build
Rib anomalies		Cleft lip and/or palate
Mild ocular hypertelorism		Hypogonadism in males
Spina bifida occulta of cervical or thoracic vertebrae		Mental retardation

to 1:256,000 (in Italy) to 1:13,900,000 (in Korea). The syndrome occurs with an equal frequency in men and women and in almost all ethnic groups, except for the Caucasian race, which is most often affected by it[1,5,6].

The syndrome is characterized by multiple basal cell carcinoma, numerous KOTs in the jaws, ectopic calcification of the falx cerebri, and palmar and/or pits[5-9].

These traits are considered major clinical diagnostic criteria. The most notable and characteristic skin abnormality is nevroid basal cell carcinoma. Basal cell carcinoma is reported in approximately 76% of NBCCS cases, primarily affecting the face and back, followed by the chest[5]. In addition, 75% of patients affected by NBCCS often show multiple KOTs[7]. The dental clinician may be the first to encounter and identify this syndrome when multiple cyst like radiolucencies are discovered on radiographs of the jaws[8,10-12].

More than 100 minor criteria have been described for NBCCS; however, cardiac or ovarian fibroma, bifid ribs, macrocephaly, kyphoscoliosis, cleft palate, and medulloblastoma are the most frequent[5]. In addition, frontal and temporal bossing, mild ocular hypertelorism, mild mandibular prognathism, polydactyly, and vertebral fusion can be included[1,5]. The Ellsworth-Howard test is used for differentiation of NBCCS from other disease status[8]. Gorlin listed the clinical features of the BCNS according

to frequency (Table 2)[15].

Diagnosis of NBCCS may be difficult due to the numerous clinical features and different ages of onset for various traits of this syndrome. This syndrome begins to appear early in life, usually after five years of age, and before 30 years of age[9]. Average age for diagnosis is 13 years, while the average age for detection of basal cell carcinoma is 20 years[2,5].

NBCCS is a hereditary complex of abnormalities transmitted as an autosomal dominant trait with a high degree of penetrance and a variable expressivity characterized by several developmental defects and predisposition to cancer[16]. Although its occurrence among family members is an important diagnosing criteria, between 20% and 40% of cases have been reported to result from a *de novo* mutation of the PTCH1 (9q22.3) gene[17,18]. According to the current state of knowledge, mutations of other genes such as Patched2 (PTCH2), Smoothened (SMO), and Sonic Hedgehog (SHH), also observed in relation to basal cell carcinoma and medulloblastoma[19,20], may exert a certain influence on the occurrence of the syndrome.

The authors report on a 16-year-old boy with NBCCS who showed multiple symptoms related to this syndrome. He presented with many conditions associated with NBCCS, including multiple KOTs, bifid rib, cleft lip, frontal bossing, a mild ocular hypertelorism, and mandibular

prognathism. The presence of minor and major criteria allowed the diagnosis of NBCCS. Characteristic cutaneous manifestation (nevoid basal cell carcinoma) was not observed in this patient. The histopathologic features indicated that the mass was consistent with KOT.

A patient presenting with NBCCS requires multidisciplinary medical care. In addition, he should understand the nature of the disorder. Medical specialists are important in diagnosis and treatment of NBCCS because this syndrome presents with various conditions and traits. It is important to note that dentists may be the first to encounter and identify this syndrome when multiple cystic lesions are discovered on radiographs of the jaws.

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