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Case Report

Nevoid Basal Cell Carcinoma Syndrome: A Case Report and Review of Korean Cases

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Abstract

Nevoid basal cell carcinoma syndrome (NBCCS) is a rare autosomal genetic disease caused by a PTCH mutation. The disease is characterized by multiple basal cell carcinomas of the skin, multiple keratocystic odontogenic tumors (KCOTs) in the jaw, palmar and/or plantar pits, bifid ribs, ectopic calcification of the falx cerebri, and skeletal abnormalities. Early diagnosis is difficult in many cases because there may be a number of systemic symptoms. The purpose of this study is to report the case of a 12-year-old girl who was hospitalized with multiple KCOTs that occurred in the upper and lower jaws. Through characteristic clinical symptoms and radiologic findings, she was finally diagnosed as having NBCCS. This study also aims to organize the symptoms often observed in Korea using previously published case reports to provide useful information for the early diagnosis of NBCCS.

Key words: Basal cell nevus syndrome, Nevoid basal cell carcinoma syndrome, Nevoid basal cell carcinoma syndrome, Odontogenic cyst

Introduction

In 1960, Gorlin and Goltz[1] defined nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin-Goltz syndrome, as a disease characterized by multiple basal cell carcinomas (BCCs), multiple keratocystic odontogenic tumors (KCOTs) in the jaw, and skeletal anomalies. NBCCS is an autosomal genetic disease showing high penetrance and variable expressivity. It is currently accepted that NBCCS is caused by a mutation of the tumor suppressor gene PTCH, but there are claims that it may be caused by new mutations because about 60% occur without a family history[2,3].

This multisystem disease is often difficult to diagnose early because it may show numerous systemic clinical symptoms that can occur inconsistently[4]. However, early diagnosis is important because it can predict possible disease and provide patients with the opportunity to receive conservative treatment and prevent exacerbations through frequent examination. In Korea, 48 cases of NBCCS were reported from 1981 to 2013 by the *Journal of Korean Association of Maxillofacial Plastic and Reconstructive Surgeons*, the *Journal of Korean Association of Oral and Maxillofacial Surgeons*, the *Korean Journal of Oral and Maxillofacial Radiology*, the *Korean Journal of Otorhinolaryngology*, the

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Korean Journal of Dermatology, and the *Annals of Dermatology*, among others (Table 1)[4-18]. We experienced a NBCCS case in a 12-year-old female patient admitted with multiple recurring KCOTs. In this study, we examine the symptoms expressed in Korean NBCCS patients by analyzing the above 49 Korean cases.

Case Report

A 12-year-old female patient had a unicystic KCOT surgery of the mandibular anterior region at Chonbuk National University Dental Hospital, two years prior. She then visited the hospital for regular exams. There were no clinical findings such as extraoral swelling, redness, or heat generation. Teeth #17, 27, 37, and 47 were unerupted and primary molars #75, 85 remained in the oral examination. A panoramic view showed that the previous surgical site had healed well, but that five different sizes of radiolucent lesions with clear boundaries were observed around #17, 35, 37, 45, and 47 impacted teeth (Fig. 1). The lesion surrounding the crown, while displacing #17 upward and laterally in the cone beam computed tomography (CT) and the CT of the facial bone, filled the right maxillary sinus. In addition, radiolucent lesions surrounding the crowns of #35, 37, 45, and 47 resulted in cortical thinning and expansion. The initial impression of these lesions were dentigerous cysts or KCOTs. Under general anesthesia, extraction of #17, 75, and 85 and surgical enucleation were carried out, and Carnoy solution was applied to prevent recurrence. Upon biopsy, they were all diagnosed as KCOTs.

NBCCS was suspected, so the patient's clinical findings, family history, medical history, and radiographic examinations were reviewed. Six to seven cutaneous nevi on the face and many pits on the palms and plantar were observed. There was no family history of NBCCS or KCOTs. Bifid ribs in the left and right were discovered through

Table 1. Journals reporting nevoid basal cell carcinoma syndrome cases in Korea

Departments	Reported cases (n)
Oral and maxillofacial surgery	35
Dermatology	9
Otorhinolaryngology	2
Pathology	1
Oral and maxillofacial radiology	1
Pediatric Neurosurgery	1

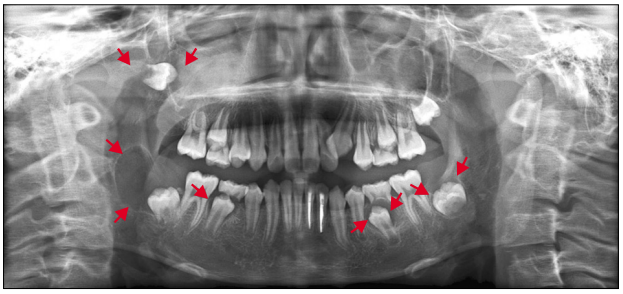

Fig. 1. Preoperative panoramic view.

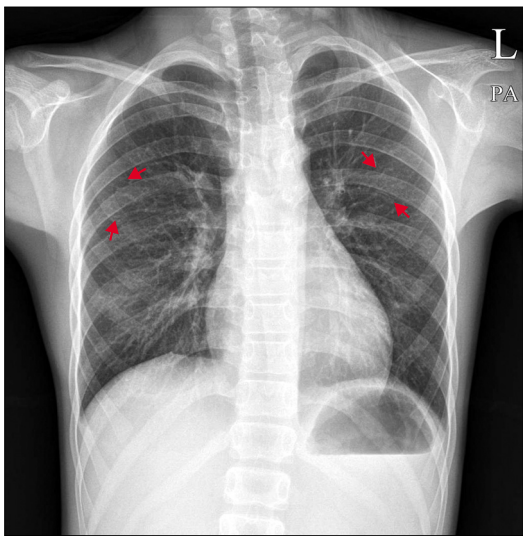

Fig. 2. Chest x-ray view showing bifid ribs in the posterior aspect of both 3rd rib.

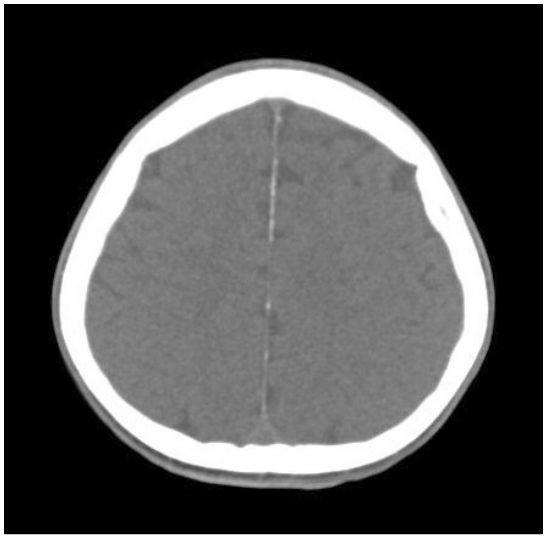

Fig. 3. Facial computed tomography view showing calcification of falx cerebri.

chest x-rays (Fig. 2), and calcification of the falx cerebri was found through a CT of the facial bones and an x-ray of the skull (Fig. 3). Four symptoms including multiple KCOTs, palmar and/or plantar pits, bifid ribs, and ectopic calcification of the falx cerebri fit the major diagnostic criteria of NBCCS organized by Kimonis *et al.*[19] in 1997. NBCCS was diagnosed based on these findings.

While observing progress after surgery, small radiolucent lesions surrounding impacted tooth #27 were observed, and surgical enucleation was conducted under local anesthesia. Upon biopsy, this lesion was diagnosed as KCOT as well. Regular check-ups were carried out for the patient through collaborative treatment with dermatology and neurosurgery. We observed the patient for 13 months, and teeth #35, 45, and 47 erupted to the occlusal surface (Fig. 4). We recommended that the patient and her family undergo genetic testing, but they refused to do so.

Discussion

Reports of NBCCS prevalence vary from 1/57,000 to 1/256,000, but 1/60,000 is generally accepted[20,21]. The prevalence in Korea is estimated to be very low[5]. NBCCS occurs at a similar rate in men and women and varies by race. Clinical symptoms of NBCCS usually appear before the age of 30 and early diagnosis is difficult in many cases because the symptoms may appear systemically and variously widely.

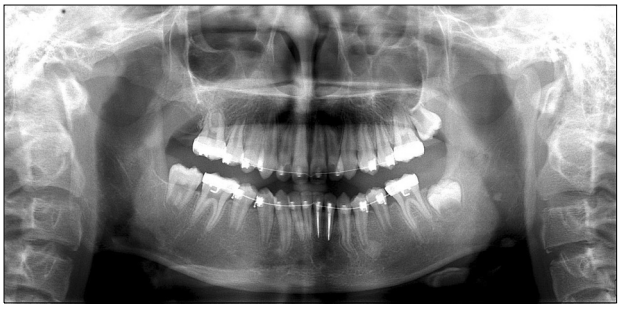

Fig. 4. Postoperative 13 months panoramic view.

Evans *et al.*[22] and Kimonis *et al.*[19] organized the criteria for NBCCS. Evans *et al.*[22] presented two or more BCCs, KCOTs in the jaw, three or more palmar and/or plantar pits, bi-lamellar calcification of the falx cerebri, and family history as major criteria. Kimonis *et al.*[19] also included rib anomalies of bifid in the major criteria. They said that other symptoms were classified as minor criteria and that if two major or one major and two minor criteria are observed, one can diagnose NBCCS.

In Korea, the first case of NBCCS was reported in 1981[23]. In 2004, Ahn *et al.*[5] analyzed 33 NBCCS cases reported in Korea from 1981 to 2002. This study also analyzed NBCCS cases published in Korea through Korea's journals of oral and maxillofacial surgery, oral and maxillofacial radiology, otorhinolaryngology, pathology, and dermatology from 1981 to 2013 (Table 1). Forty-nine cases were reported excluding duplicate cases and cases not suitable for Kimonis diagnostic criteria, and including our one case (Table 2~4). NBCCS patients in Korea occur almost equally in men and women (25:24) who first presented between the ages of 6 and 68. The mean age was 21.6, and 17 people were included in a total of six households (34.7%).

BCCs of the skin are the most common symptom of NBCCS and occur about 80% in European ethnicities and about 38.0% in African Americans[19,24]. However, they

Table 2. Relative frequencies of associated complications compared with other countries

	Evans *et al.*[22]	Shanley *et al.*[26]	Kimonis *et al.*[19]	Lo Muzio *et al.*[27]	Pruvost-Balland *et al.*[28]	Ahn *et al.*[5]	Shimada *et al.*[25]	This study
Year	1993	1994	1997	1999	2006	2004	2013	2014
Nationality	UK	Australia	USA	Italy	France	Korea	Japan	Korea
Diagnostic criteria	-	-	-	Evans	Shanley	Evans	Kimonis	Kimonis
No. of cases	84	118	105	37	22	33	25	
Mean age (yr)	-	35	34.5	31.4	44.9	21.2	23.8	21.6
BCC (%)	47	76	80	30	100	15	28	22
KCOT (%)	66	75	74	92	62	91	100	86
Palmar or plantar pits (%)	71	80	87	35	45	67	76	63
Rib anomaly (%)	-	45	42	32	-	36	44	39
Calcification of the falx cerebri (%)	-	92	65	70	66	21	28	37

BCC, basal cell carcinomas; KCOT, keratocystic odontogenic tumor.

occurred in 11 cases (22.5%) out of 49 in Korea, and a lower rate was also reported in Japan, at 28.0% (Table 2)[25]. Ahn *et al.*[5] suggested that such a difference may be attributed to genetic and geographic differences. According to the results of this study, 35 out of 49 NBCCS cases were reported in oral and maxillofacial surgery, nine cases in dermatology, and five cases in other areas. NBCCS accompanied by BCCs accounted for 11 cases and eight of these cases were reported in dermatology (Table 1). The most NBCCS cases were published in oral and maxillofacial surgery and the main symptoms in Korea were KCOTs. Therefore, clinical findings of BCCs may have been missed. Because low BCC incidence was also reported in Italy, the low frequency of BCCs in Korea and Japan is difficult to consider an Asian feature, as epidemiological investigations in other Asian countries are needed for further study. Nevi on the skin begin to turn into intrusive and aggressive moles after puberty, so periodic examination and careful observation are required. In addition, individuals should not be exposed to ionizing radiation or ultraviolet light, both of which are risk factors for BCCs.

Palmar and/or plantar pits have been reported at a high rate (64%~87%) in many countries[5,19,22,25,26] and observed at a rate of 63.3% (31 cases) in Korea, consistent with other studies except for Italy (35%) and France (45%) (Table 2)[27,28]. The pits are usually 1~3 mm in depth and 2~3 mm in diameter, and they usually develop in the second decade. Their number can increase up to 500 or more with age[29]. A pit itself is not malignant, but continuous observation is required because a pit may result in BCCs occurring in the hands and feet.

Multiple KCOTs of jaws appear at the highest rate (66%~100%) in NBCCS patients. Multiple KCOTs can provide a chance for diagnosis in many cases because they occur earlier than other symptoms of NBCCS and are often accompanied by symptoms such as swelling and pain. In

Table 3. Frequency of findings in 49 Korean patients with nevoid basal cell carcinoma syndrome

Reporting frequency	Value
≥50%	
Keratocystic odontogenic tumor	42 (85.71)
Palmar and plantar pits	31 (63.27)
Hypertelorism	25 (51.02)
30%~50%	
Frontal, parietal, and temporal bossing	19 (38.78)
Rib anomaly	19 (38.78)
Calcification of the falx cerebri	18 (36.73)
Family history	17 (34.69)
Multiple nevi	16 (32.65)
10%~30%	
Basal cell carcinomas	11 (22.45)
Scoliosis	8 (16.33)
Mental retardation	8 (16.33)
Mandibular prognathism	5 (10.20)
Visual disturbance and blindness	5 (10.20)
<10%	
Scoliosis	8 (16.33)
Cleft lip and/or palate	4 (8.16)
Congenital hydrocephalus	4 (8.16)
Ovarian cyst, tumor	4 (8.16)
Dental agenesis	2 (4.08)
Medulloblastoma	2 (4.08)
Hypogonadism, megaloureter	2 (4.08)

Values are presented as number (%).

Table 4. Nevoid basal cell carcinoma syndrome cases reported between the years 1981 to 2013 in Korea

	Ahn *et al.*[5]	Tak *et al.*[18]	Lee *et al.*[6]	Lee *et al.*[7]	Roh *et al.*[8]	Park *et al.*[9]	Park *et al.*[10]	Heo *et al.*[11]	Kim *et al.*[12]	Park *et al.*[13]	Rye *et al.*[14]	Gang *et al.*[15]	Lee *et al.*[16]	Go *et al.*[17]	This study	Total
Year	1981~2003	2002	2004	2005	2006	2007	2008	2008	2008	2008	2008	2009	2010	2011	2014	1981~2013
No. of cases	33	1	1	1	1	1	1	1	1	2	2	1	1	1	1	49
Mean age (yr)	21.2	66	19	31	14	13	32	10	17	15	9.5	9	20	60	12	21.6
Sex ratio (M:F)	1:1.1	0:1	1:0	0:1	0:1	1:0	1:0	0:1	1:0	1:1	1:1	1:0	1:0	1:0	0:1	1.04:1
Basal cell carcinomas (n)	5	1	-	1	1	-	-	-	-	-	-	-	-	1	-	11
Keratocystic odontogenic tumor (n)	30	1	1	-	-	1	1	1	-	2	1	1	1	1	1	42
Palmar or plantar pits (n)	22	1	1	1	1	-	-	-	-	-	1	1	1	1	1	31
Rib anormaly (n)	12	-	-	1	1	-	1	-	-	1	1	1	-	-	1	19
Calcification of the falx cerebri (n)	7	-	1	1	1	1	1	1	1	1	-	1	-	1	1	18
Department	OMFS	DT	OMFR	ENT	DT	ENT	OMFS	PD	OMFR	OMFS	DT	OMFS	OMFS	DT	OMFS	OMFS

M, male; F, female; OMFS, oral and maxillofacial surgery; DT, dermatology; OMFR, oral and maxillofacial radiology; ENT, otolaryngology; PD, pediatric dentistry.

Korea, KCOTs were present in 42 cases out of 49 NBCCS cases (85.7%). Surgical enucleation, enucleation after marsupialization, or bone resection was conducted for treatment, and Carnoy solution was used to prevent recurrence. Choi *et al.*[30] reported that when treating KCOT patients, Carnoy solution was applied for 3~5 minutes after surgical enucleation and most patients obtained good results without recurrence. KCOT that occurs with NBCCS occurs at an early age compared to general KCOT and shows a 60% higher recurrence rate. In addition, it may occur both in the upper and lower jaws and usually appears in multiples[31,32]. Therefore, when faced with a case of multiple or recurrent KCOTs in the jaw, oral and maxillofacial surgeons should conduct further investigations to exclude NBCCS[33]. Long-term surveillance for KCOTs is required because of the high recurrence rate.

While reporting the high rate (65%~92%) in Australia, the USA, and Italy, ectopic calcification of the falx cerebri is uncommon, seen 18 cases (36.7%) in Korea. Rib anomalies, including bifid ribs, were observed in 19 cases (38.8%), similar proportion to other countries (Table 3)[19,26,27].

Additional symptoms may include abnormalities of the dental and skeletal system such as cleft lip/palate, mandible prognathism, scoliosis and frontal bossing, and abnormalities of the ocular system including visual problems and hypertelorism, nervous system abnormalities such as mild mental retardation, medulloblastoma and congenital hydrocephalus, and abnormalities of the genitourinary system including cysts or tumor of the ovaries[19].

The low frequency of BCCs and ectopic calcification of the falx cerebri were two major differences of this study compared with studies in other countries. Hypertelorism (25 cases, 51.0%) and frontal bossing (19 cases, 38.8%) occurred frequently in Korea. These symptoms can be useful for diagnosing patients with early-stage NBCCS in Korea. In addition, since 34.7% of cases have a family history, genetic tests may be useful for patients and their families for more accurate diagnoses and disease prevention.

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