Follicular Keratocystic Odontogenic Tumor in Nevoid Basal Cell Carcinoma Syndrome – A Rare Case Report with Review of Literature

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Abstract: Nevoid Basal Cell Carcinoma Syndrome (NBCCS) also known as Gorlin-Goltz syndrome is an autosomal dominant disorder with complete penetrance but quite variable expressivity. It is characterized by multiple Basal Cell Carcinomas (BCCs), Keratocystic odontogenic tumors (KCOTs), palmar & plantar pits, skeletal abnormalities & medulloblastomas. BCCs & KCOTs are the most common incident manifestations of the syndrome. KCOT is 2nd most common feature associated with NBCCS. The occurrence of multiple KCOTs may be the first and only manifestation which can occur almost a decade before other symptoms & other clinical manifestations may remain hidden in earlier years of life. Thus, multiple KCOTs can herald the diagnosis of NBCCS & dentists may well be the first person to detect it.

Radiographically KCOTs can be follicular, envelopmental, replacemental, extraneous & collateral. Biologic behavior, prognosis, recurrence & therapeutic approaches vary in different studies. Among these, follicular variant of KCOTs greatly mimic dentigerous cyst radiographically & on gross pathology, often masking the diagnosis of a fatal syndrome when it is the only presented sign.

Herein, we report a case of 13 years old female with bilateral facial swelling & multiple follicular cysts on radiograph, with no other gross skeletal abnormalities.

Keywords: follicular, KCOT, NBCCS, odontogenic, radiographically

I. Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is a hereditary condition characterized by a wide range of developmental abnormalities and a predisposition to neoplasms. The condition was first described by Jarisch & White in 1894, probably also existed during dynastic Egyptian times. The syndrome was first delineated by Robert Gorlin & Robert Goltz in 1960, so called as Gorlin Goltz Syndrome. They established a classic triad of multiple BCCs, multiple odontogenic keratocysts of jaws and bifid ribs for the syndrome.¹ Other synonyms given for the syndrome are:

- Gorlin syndrome
- Gorlin-Goltz syndrome
- Nevoid basal cell carcinoma syndrome (NBCCS)
- Multiple nevoid basal-cell carcinoma syndrome (MNBCCS)
- Multiple basal-cell carcinoma syndrome
- Basal cell nevus syndrome (BCNS)
- Multiple basalioma syndrome
- Fifth phacomatosis
- Jaw cysts-basal cell tumors-skeletal anomalies syndrome
- Odontogenic keratocytosis-skeletal anomalies syndrome
- Multiple nevoid basal-cell epithelioma- jaw cysts-bifid rib syndrome
- Hereditary cutanemandibular polyoncosis
- Epitheliomatose multiple generalisee

The term nevus does not project the truly cancerous nature of the skin lesions—although only a small number of basal cell carcinomas become aggressive. Eponyms imply priority of description (and are often wrong, frequently chauvinistic, and say nothing about the disorder). The estimated prevalence varies from 1 in 50,000 to 1 in 50,000 with male to female ratio of 1:1.¹

NBCCS has an autosomal dominant inheritance with complete penetrance and variable expressivity. However, about 35% to 50% represent new mutations.¹² The characteristic features of NBCCS include BCCs, KCOTs, palmar & plantar pits, falk calcification & bifid ribs. These were considered the major criteria given first by Evans et al & modified later by Kimonis et al in 2004.¹³ However, in the first international colloquium ¹
on NBCCS criteria, there were alterations in major criteria changing rib anomalies to minor criterion & medulloblastoma as major criterion. More than 100 other anomalies have been associated with NBCCS.

KCOTs are the 2nd most common finding in NBCCS. Recurrent KCOTs are the main oral sign and present in 90% of patients. In majority of the literature, however, NBCCS is associated with orthokeratocyst, the older terminology for KCOT. In the present article the newer terminology KCOT will be used in order to avoid confusion. Radiographically KCOTs can be of different types follicular, envelopmental, collateral, replacemental & extraneous. On average KCOTs show very aggressive behavior with a high recurrence rate of 20% to 62%, and aggression and recurrence rate increasing with the syndrome.

Follicular type of KCOT mimics dentigerous cyst on gross pathology and radiographically. Very few cases of follicular KCOTs are reported so far. A case of follicular KCOT in association with NBCCS is presented here.

II. Case Report

13 years old female patient reported to our department of oral pathology and microbiology with the chief complaint of swelling in both the jaws since two months. On examination diffuse extraoral swelling was present bilaterally (Fig. 1). Intra oral examination revealed a diffuse bilateral swelling in upper labial vestibules extending from labial frenum to mesial of first molars (Fig.1). General examination revealed mild hypertelorism, depressed nasal bridge (Fig.1) & palmar and plantar pits (Fig.2). OPG showed multiple well defined corticated radiolucencies around the impacted 13, 23 and 33 encircling the crowns giving a follicular appearance (Fig.3). Chest radiograph and CT scan of the patient were unremarkable except for the jaw cysts in the CT scan. Aspiration yielded straw colored fluid from one cyst (Fig.4) showing keratin flecks and differentiation. Based on this model, mutations.

Germ line mutations in PATCH1 tumor suppressor gene mapped on chromosome 9q22.3 are found to be the main pathogenetic attribute in NBCCS. The PTCH gene product is part of a receptor for the protein called Sonic Hedgehog (Hh), which is involved in embryonic development. More recent investigations reveal the role of the Hh pathway in cell cycle regulation in adults. In the Drosophila model, the primary receptor for the Hh signaling pathway has two transmembrane protein components: Patched (Ptc) and Smoothened (Smo). In the absence of Hh protein, the Ptc protein inhibits the Smo. Under normal conditions, Hh, when present, binds Ptc releasing Smo to affect downstream events such as cell growth and differentiation. Based on this model, inactivation of Ptc or constitutive activity of Smo or Hh could lead to overactivity of Smo, resulting in neoplasm formation. Two mutagenic hits are required for the inactivation of this tumor suppressor gene. The first hit causes mutation in one allele. The second hit causes loss of heterozygosity & is seen in NBCCS, KCOTs & medulloblastomas. Only one hit is needed for various physical anomalies of the brain, ribs, vertebrae & limbs. The first hit that is present in a germ cell can be dominantly inherited. This accounts for the malformation & the variations seen in NBCCS patients. However, mutations in other genes such as Patched 2 (PTCH 2), Smoothened (SMO) and Sonic hedgehog (SHH) have reported in isolated cases of basal cell carcinoma and medulloblastoma.[2]

Due to variable expressivity all findings are not present in one patient. This disorder is known to run in families with an equal frequency in both sexes. Similar to the present case those who do not have any family members affected with NBCCS may comprise 60% of total NBCCS and 35-50% of these cases represent new mutations.
The diagnostic criteria for NBCCS was put forth by Evans and Colleagues and modified by Kimoni in 1997. Accordingly, diagnosis of Gorlins syndrome could be established when two major or one major with two minor criteria are present as described below.

**Major criteria:**
1) One BCC before age of 30 or more than 2 BCCs or more than 10 basal cell nevi.
2) Odontogenic keratocyst before 15 years of age or polyostotic bone cyst.
3) 3 or more palmar or plantar pits.
4) Falx cerebri calcification.
5) Rib anomaly.
6) First degree relative affected.
7) PTCH gene mutation.

**Minor criteria:**
1) Macrocephaly.
2) Congenital malformations - cleft lip, cleft palate, frontal bossing, hypertelorism.
3) Skeletal deformity – kyphosis, scoliosis.
4) Radiological abnormality – bridging of sella tursica, Hemivertebra.
5) Ovarian fibroma.
6) Medulloblastoma.

In the first international colloquium on NBCCS criteria, there were alterations in major criteria changing rib anomalies to minor criterion & medulloblastoma as major criterion.

Other diagnostic findings in adults with nevoid basal cell carcinoma reported by Gorlin et al 13 (1977) and their incidence of occurrences are as follows:

A. Skeletal Anomalies
1. Bifid ribs, splayed/fused ribs, absent/rudimentary ribs (60-75%)– may be bilateral and several ribs may be affected
2. Scoliosis– seen in 30 to 40% of the patients
3. Hemivertebrae
4. Flame-shaped lucencies of hand/feet
5. Polydactyly
6. Syndactyly
7. Shortened 4th metacarpal.

B. Craniofacial Anomalies
1. Frontal bossing (25%): Increased size of calvaria (occipitofrontal circumference 60 cm or > in adults)
2. Brachycephaly
3. Macrocephaly (40%)
4. Coarse face (50%)
5. Calcification of the falxes (37-79%)
6. Tentorium cerebelli calcification
7. Bridged sella turcica
8. Heavy fused eyebrows
9. Broadened nasal root
10. Low positioning of occiput.

C. Ophthalmic Findings
- Hypertelorism (40%)
- Glaucoma
- Exotropia choroidal and/or optic nerve coloboma
- Congenital amaurosis
- Congenital blindness and opaque cornea
- Ptosis, internal strabismus (15%) convergent/divergent, Chalazion
- Congenital or precocious cataract.

D. Neurological Anomalies
1. Agenesis/disgenesis of corpus callosum
2. Congenital hydrocephalus
3. Mental retardation
4. Medulloblastoma (3-5%) developing in the first 2 years of life. About 20% of them cause death during infancy
5. Meningioma (1% or <)

E. Oropharyngeal Anomalies
Oral abnormalities are of fundamental importance mainly in childhood and adolescence and are important signs for diagnosis. They are:
1. Cleft lip/palate (4%)
2. High arched palate or prominent ridges (40%).

F. Sexual Anomalies
1. Uterine and ovarian fibromas (15%), supernumerary nipple
2. Ovarian fibrosarcoma, hypogonadism and cryptorchidism.
3. Calcified Ovarian Cysts
4. Female distribution of the pubis hair, scarce beard in men and gynecomastia.

As NBCCS has a vast diversity of presentation Lu Muzio et al given the diagnostic protocol for NBCCS as shown in table 1:

- KCOT is the 2nd most common feature associated with NBCCS. The occurrence of multiple KCOTs may be the first and only manifestation which can occur almost a decade before other symptoms & other clinical manifestations may remain hidden in the earlier years of life. Thus, multiple KCOTs can herald the diagnosis of NBCCS & dentists may well be the first person to detect this syndrome.

- KCOT, now termed as Keratocystic Odontogenic Tumor, is defined by WHO as a benign intra-osseous neoplasm of odontogenic origin, with characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behaviour.

- KCOTs associated with NBCCS are found to be more aggressive & with more recurrence potential than sporadic KCOTs.

- Saranya et al summarized the differences between KCOTs associated with NBCCS & sporadic KCOTs are as shown in table 2:

- According to Katase et al, heparanase & endo-D-glucuronidase enzyme is specifically responsible for cleaving heparan sulfate. Its level is found to be increased in tumors & promotes invasion, angiogenesis & metastasis. Intense expression of this gene & protein is seen in KCOT associated with NBCCS as compared to sporadic KCOT.

- Different immunotype of KCOT associated with NBCCS than sporadic KCOT is documented by Kolar et al. The former is found to exhibit higher expression of bcl-2, p27 & C-erb B-2 than the later. Higher expression of p53 & cyclin D1 in former are reported by Lu Muzio et al.

- Radiographically odontogenic keratocyst can be of different varieties - follicular, envelopmental, replacemental, extraneous and collateral.

- The follicular type of odontogenic keratocyst may be defined as a cyst with typical histology of an OKC which surrounds the crown of an unerupted tooth and is attached to the neck of the tooth. On radiography it mimics a dentigerous cyst.

- The concept of follicular KCOT has been introduced by Browne & developed by Altini & Cohen. They postulated that follicular keratocysts are extrafollicular in origin and might arise following eruption of a tooth into a pre-existing keratocyst cavity in the same way as a tooth erupted into the oral cavity.

- Follicular KCOTs are relatively uncommon. They account for 25 to 40% of all the KCOTs. The KCOT associated with an impacted tooth appears to arise at a younger age and grow more rapidly than a cyst unrelated to an impacted tooth. An impacted tooth and its dental follicle may affect the occurrence and proliferation of an adjacent KCOT.

- Kim DK et al in 2003, revealed that the staining pattern and intensity for Ki-67 was same for both the follicular and extrafollicular variant of KCOT & suggested that the aggressiveness of the follicular OKC is similar to the extrafollicular one and should be attended with the same therapeutic approach in order to prevent recurrence.

- In the present case clinical & radiographic presentation of the swelling depicted it to be dentigerous cyst. General examination of the patient revealed hypertelorism and palmar & plantar pits. But gross findings & histopathologic features confirmed both left & right side lesions as KCOTs of follicular variety. Thus clinical, radiographic & histopathologic findings on the basis of fulfilment of two major criterias i.e. KCOTs, palmar &
plantar pits and one minor criteria i.e. hypertelorism led to the final diagnosis of Follicular KCOTs associated with NBCCS.

As KCOTs associated with NBCCS are more aggressive & having more recurrence rate apart from surgical enucleation, adjunctive therapies like chemical cauterization are useful to prevent recurrence by fixing the daughter cyst or remnants of epithelial lining that are not removed during the enucleation procedure. Carnoy’s solution is a phenolic compound with tissue fixative properties. Voorsmit et al. have demonstrated that Carnoy’s solution penetrates the bone to the depth 1.54 mm following a 5 minutes application without any damage to the inferior alveolar nerve. Hence application of Carnoy’s solution is considered to be beneficial for preventing its recurrence.[3]

Still Further research is necessary in order to establish relationship between markers of proliferation and aggressiveness with regard to the radiographic varieties in OKC.

Till date no case of follicular KCOT has been reported in association with NBCCS. This makes our case a rare occurrence.

IV. Figures And Tables

**Fig. 1:** Clinical examination showing Hypertelorism, Intraoral swelling on left & right sides

**Fig. 2** Palmar & Plantar Pits

**Fig. 3** OPG showing unilocular radiolucencies surrounding crowns of impacted 13 & 23
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Fig. 4 Aspirate showing straw colored fluid

Fig. 5 Gross specimen of left side

Fig. 6 Gross specimen of right side

Fig. 7 H & E stained section 10X
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![Fig.8 H & E stained section 40X](image)

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<th>Table 1: Diagnostic Protocol for NBCCS</th>
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V. Conclusion

By presenting this case of follicular KCOT in NBCCS it can be stated that the final diagnosis of any odontogenic cyst requires a proper clinical, radiological and histopathological coordination because each type has a different clinical behaviour and prognosis. Also as multiple KCOTs may be the only presenting sign of NBCCS, dentists may be the first person to diagnose this syndrome.

Further research should be conducted for such reported cases with proper follow-up of patients to note the prognosis of follicular type of KCOT.

References


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