

# Multiple, Multifocal Odontogenic Keratocysts in Non-Syndrome Patient: A Case-report

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## Summary

Occurrence of multiple odontogenic keratocyst involving the jaws is rare. When multiple, it is usually associated with a syndrome. Occurrence of multiple odontogenic keratocyst without syndromic association is extremely rare. Gorlin–Goltz syndrome which is also known as Nevoid Basal Cell Carcinoma Syndrome is a rare autosomal dominant disorder. Multiple Odontogenic Keratocysts (OKCs) are principle features of nevoid basal cell carcinoma syndrome (NBCCS; Gorlin-Goltz syndrome). However, a case of multiple odontogenic keratocysts unassociated with any syndrome is reported here so as to add to the growing number of such cases in the literature. The possibility of this case being a partial expression of the Gorlin-Goltz syndrome is discussed.

*Key Words: Multiple Odontogenic Keratocyst, Nevoid Basal Cell Carcinoma Syndrome, PTCH gene*

## Introduction

Odontogenic keratocyst is the traditional term used to describe a benign but locally aggressive odontogenic cystic lesion with distinctive clinical and histopathologic features. World Health Organization proposed the term "Keratocystic Odontogenic Tumor" (KCOT) to reflect the neoplastic nature of this lesion. Keratocystic odontogenic tumor (KCOT) is a benign unicystic or multicystic intraosseous neoplasm of odontogenic origin [1]. The presence of OKC in children or adolescents before the age of 19 is seen in 75% of cases and can be the first sign of NBCCS [2].

Gorlin and Goltz first described the spectrum of features associated with this syndrome in 1960; hence, it is also called Gorlin-Goltz syndrome [3]. On basis of analysis of clinical features of 312 acceptable cases of odontogenic keratocysts, R. B. Brannon found that 5.8% were from patients with multiple keratocysts but with no other features of the syndrome [4]. This article reports a case of multiple OKCs in a non-syndrome patient and highlight the general practitioners the importance of diagnosing the disease and enforcing a strict long-term follow-up whenever such a case is identified.

## Case Report

A 20 year-old male patient reported to ACPM Dental College Dhule, with a chief complaint of swelling in lower left side of the face since 2 months (*Figure 1*). The swelling was small initially which gradually increased to the present dimension which was progressive. Patient also complained of pain in the upper posterior region bilaterally.

Intra-orally, there was a marked bone expansion of the buccal cortical plate in mandibular left region with obliteration of the vestibule (*Figure 2*). In associated soft tissues there was no ulceration or fistula formation. On palpation, the swelling was bony hard in consistency but no tenderness. No swelling or tenderness in relation to maxillary posterior region on both sides.

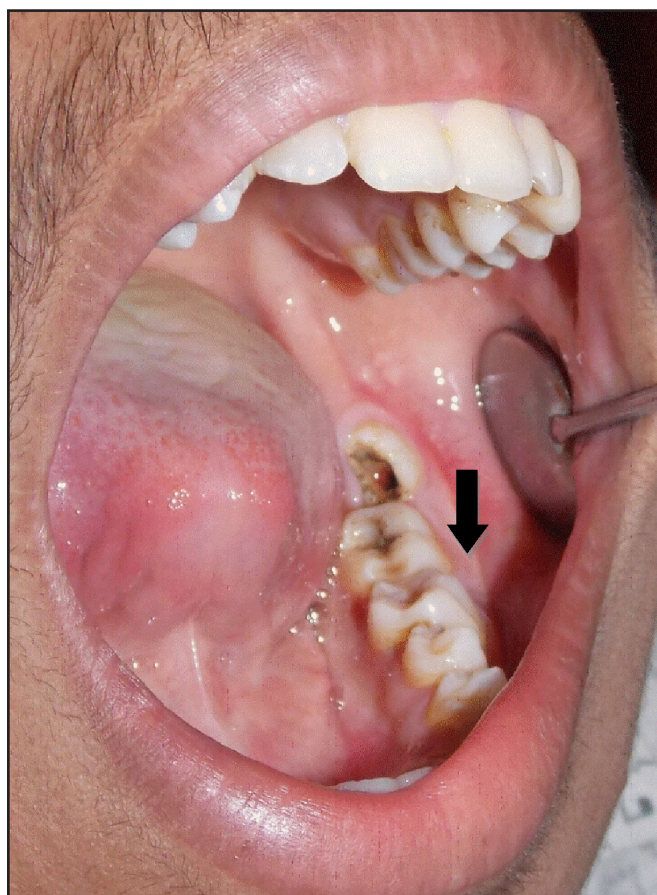
A panoramic radiograph revealed presence of four radiolucencies involving the maxilla and mandible on both



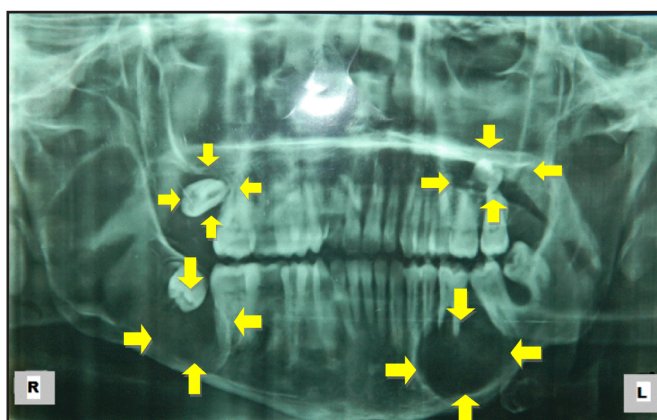
*Figure 1. Facial asymmetry with swelling seen in left mandibular region.*

sides. On the left side of mandible there was well corticated unicystic radiolucency extending from first premolar to second molar and on right side the radiolucency was extending from second molar till half the ramus of mandible involving impacted third molar tooth bud (*Figure 3*). CT scan revealed right maxillary cortical bone expansion extending from second molar till the distal aspect of tuberosity measuring around 2x2 cms involving third molar and on left side, the radiolucency

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**Figure 2.** Expansion of the cortical plate with obliteration of buccal vestibule shown by arrow mark.



**Figure 3.** Radiolucencies involving the maxilla and mandible on both sides outlined by arrow marks.

was measuring around 3x3 cms causing erosion of floor of maxillary sinus (*Figure 4*). Provisional diagnosis of OKC was made in relation to left mandibular region and dentigerous cyst with respect to rest. The patient's chest and skull radiographs were unremarkable. Dermatology consultation did not reveal any cutaneous abnormality. Hematologic investigations were within normal limits. Enucleation of all the cystic lesions was performed under general anesthesia and tissue samples were sent for histopathologic examination. The histopathology report revealed all four cysts showed 6-8 cell layered parakeratinised corrugated epithelium, absence of rete ridges with hyper chromatic basal cells arranged in a characteristic tomb stone or palisading pattern (*Figure 5*). The connective tissue capsule showed variable amount of inflammation

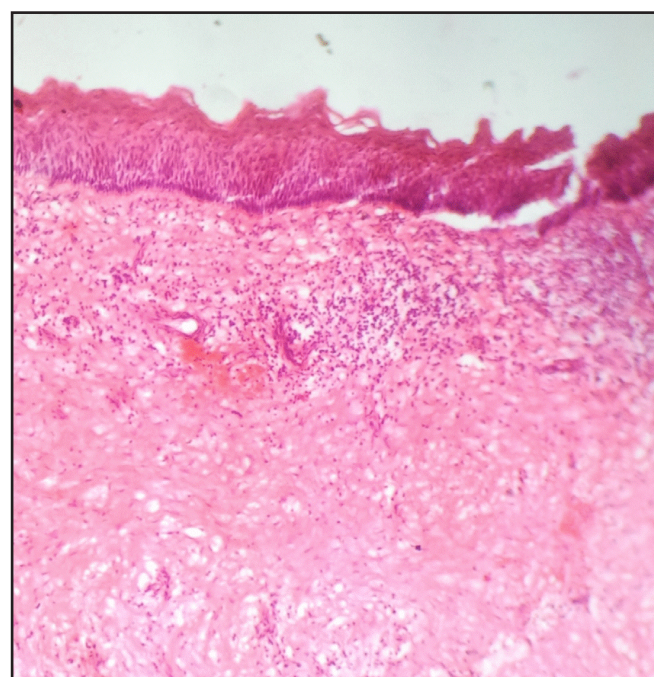
as well as few odontogenic epithelial islands (*Figure 6*). Histopathological diagnosis of parakeratinised Odontogenic Keratocyst was established in all the four lesions. With the histopathology report and correlating with the clinical and radiographic findings, a final diagnosis of Odontogenic Keratocyst for all four cystic lesions was established.

### Discussion

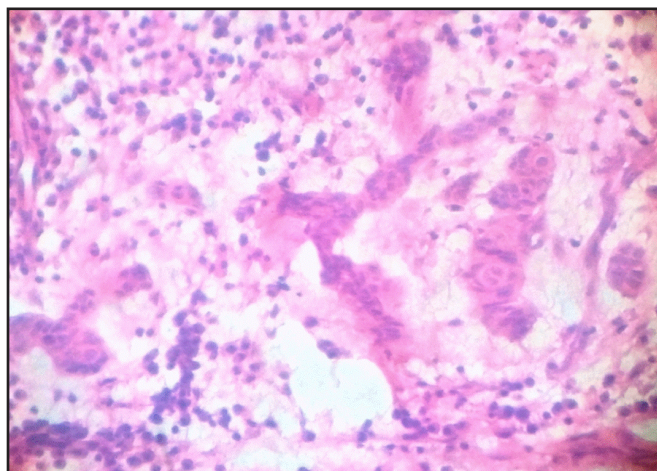
NBCCS is characterized by multiple OKCs, nevoid basal cell carcinomas of the skin, bifid ribs, calcification of the falx cerebri, and other features. However, except for odontogenic



**Figure 4.** CT scan showing Radiolucencies bilaterally involving impacted third molars. This was not clearly evident on OPG.



**Figure 5.** Hematoxylin and eosin stained tissue section (10X) showing 6-8 cell layered parakeratinised corrugated epithelium, absence of rete ridges with hyper chromatic basal cells arranged in a characteristic tomb stone or palisading pattern.



**Figure 6.** Hematoxylin and eosin stained tissue section (40X) showing odontogenic epithelial islands in connective tissue stroma.

keratocysts other features were not present in our case [5]. Multiple OKCs can also occur as a component of orofacial digital syndrome, Ehler-Danlos syndrome, Noonan syndrome, Simpson-Golabi-Behmel syndrome, or other syndrome [6-9]. There is no specific laboratory test to diagnose NBCCS, although the diagnosis is made clinically using the criteria suggested by Evans et al. [10] (Table 1) and Kimons et al. [11] (Table 2). However, there may be variations in the major diagnostic criteria for NBCCS in some populations due to genetic and geographic differences [12]. Our patient was apparently healthy and did not meet any of these diagnostic criteria for NBCCS, such as basal cell carcinoma, skeletal or orofacial defects, stunted growth, bleeding diathesis, hyperextensible skin and hypermobile joints or other congenital anomalies associated with overgrowth.

Odontogenic Keratocysts occur in a wide age range, with a peak incidence in the second and third decades of life. The mandible: maxilla ratio was 2:1, with the mandibular third molar area and ramus being the most common sites [4]. Patients with multiple OKCs with or without NBCCS, are generally younger than those with single OKCs [13]. These features coincide with the case presented in our study. Most frequent clinical manifestations of odontogenic keratocyst were reported to be swelling, pain or both. In the present case patient reported with swelling in mandibular left region. The odontogenic keratocyst on conventional radiographs has a varied appearance viz. a well-defined radiolucent lesion; a radiolucent lesion associated with a tooth (not distinguishable from a dentigerous cyst), or an expansive multilocular or unilocular lesion (similar to the ameloblastoma) and therefore should always be considered in the differential diagnosis of the cystic lesions in the jaws. Our case complied with these findings, with the detected radiolucencies being unilocular in relation with maxillary posterior region bilaterally and left mandibular region and multilocular with right side of mandibular region, being associated with an unerupted third molar.

The general dentists are the persons who come across these cases first and should be in a position to identify the condition. Recognition of this cyst is important for three reasons; the odontogenic keratocyst often tends to act more

**Table 1.** Diagnostic criteria for nevoid basal cell carcinoma syndrome according to Evans et al. [10] (2 major or 1 major and 2 minor criteria should be satisfied for positive diagnosis).

Major Criteria	Minor Criteria
More than 2 basal cell carcinomas (BCCs), 1 BCC before 30 years of age; or more than 10 basal cell nevi	Congenital skeletal anomaly (e.g., bifid rib, fused, splayed or missing rib, wedged or fused vertebrae)
Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst	Occipital–frontal circumference higher than the 97th percentile, with frontal bossing
3 or more palmar or plantar pits	Cardiac or ovarian fibroma
Ectopic calcification; lamellar or early (< 20 years of age) falx calcification	Medulloblastoma and Lymphomesenteric cysts
Family history of nevoid basal cell carcinoma syndrome	Congenital malformations, such as cleft lip or palate, polydactylysm or eye anomaly (cataract, coloboma, microphthalmos)

**Table 2:** Diagnostic criteria for nevoid basal cell carcinoma syndrome according to Kimons et al. [11].

Major criteria	Minor criteria
More than 2 Basal Cell Carcinomas (BCCs) or 1 BCC in a patient <20 years of age	Macrocephaly
Odontogenic keratocysts of the jaws (proven by histopathologic analysis)	Congenital malformations (e.g., cleft lip or palate, frontal bossing, coarse facies and moderate or severe hypertelorism)
3 or more palmar or plantar pits	Other skeletal abnormalities (e.g., Sprengel deformity, marked pectus deformity and marked syndactyly of the digits)
Bilamellar calcification of the falx cerebri	Radiologic abnormalities (e.g., bridging of the sella turcica, vertebral anomalies, modelling defects of the hands and feet, flame-shaped lucencies of the hands and the feet)
Bifid, fused or markedly splayed ribs	Ovarian fibroma or medulloblastoma (not applicable if patient is male)
A first-degree relative with NBCCS	

aggressively than other odontogenic cysts; the odontogenic keratocyst has higher recurrence rate than other odontogenic cysts and the odontogenic keratocyst is specific type of cyst that sometimes may be associated with the nevoid basal cell carcinoma syndrome. The important clinical signs and symptoms which the dentist should know for OKC are that it can occur at any age but most commonly found between 10 to 40 years, male to female ratio is 2:1, mainly found in mandibular molar, angle, and ramus area. Patients may present with swelling, pain and discharge or may be asymptomatic. Distinctive clinical features include a potential for local destruction, tooth mobility and a tendency for multiplicity, especially when the lesion is associated with Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Gorlin-Goltz

syndrome. If the diagnosis of multiple OKC is confirmed after the histopathologic examination then the patient should also be ruled out for nevoid basal cell carcinoma syndrome. Diagnostic criteria for identification of nevoid basal cell carcinoma syndrome have been mainly divided as major and minor criteria by Evans and others. The major criteria are more than 2 Basal Cell Carcinomas (BCCs), 1 BCC before 30 years of age; or more than 10 basal cell nevi, any odontogenic keratocyst (proven on histology) or polyostotic bone cyst, 3 or more palmar or plantar pits, ectopic calcification; lamellar or early (<20 years of age) falx calcification, family history of nevoid basal cell carcinoma syndrome and minor criteria are congenital skeletal anomaly (e.g., bifid rib, fused, splayed or missing rib, wedged or fused vertebrae), occipital–frontal circumference higher than the 97th percentile, with frontal bossing, cardiac or ovarian fibroma medulloblastoma and lymphomesenteric cyst, congenital malformations, such as cleft lip or palate, polydactylism or eye anomaly (cataract, coloboma, microphthalmos). According to Evans and others 2 major or 1 major and 2 minor criteria should be satisfied for positive diagnosis.

The occurrence of multiple OKCs may be the first and only manifestation of NBCCS. Multiple OKCs can occur a decade before other symptoms associated with NBCCS [14,15]. Thus, a dentist may well be the first to detect this syndrome. The possibility of our young patient developing other features of NBCCS in the future cannot be excluded. It emphasizes the need for thorough examination of patients with recurrent OKCs to detect other features of the NBCCS syndrome, which is known for its variability of expression. It is being suggested that PTCH (“patched”) gene plays important role in pathogenesis of OKCs. PTCH is a tumor-suppressor gene, involved in both NBCCS and sporadic KCOTs, occurs on chromosome locus 9q22.3-q31 [16]. Under normal circumstances, the PTCH forms a receptor complex with the proto oncogene SMO (“smoothened”) for the SHH

(“sonic hedgehog”) ligand. Binding of PTCH to SMO inhibits growth-signal transduction, but the binding of SHH to PTC reverses this inhibition [17]. However, in the event of loss of normal functioning of PTCH, the proliferation-stimulating effects of SMO predominate.

The main stay in the treatment of OKC is enucleation and surgical excision, but recent research has hinted at possible novel techniques for the treatment of KCOT. In 2000, Taipale et al. through scientific research, proved that cyclopamine, a plant-derived, steroidal alkaloid/ teratogen, can block cellular proliferative responses to the SHH growth-signal transduction via the activated SHH pathway caused by oncogenic mutation of proto oncogene Smoothed and tumor suppressor Patched (PTCH) [18]. Thus, a “mechanism-based” therapeutic strategy emerged for the treatment of human tumors associated with both types of oncogenic mutation [19]. Furthermore, in 2003, Williams et al. discovered another compound CUR622414, an Hh small-molecule inhibitor, for the SHH pathway [20]. Its binding to the Smoothed oncogene, consequently inhibits SHH pathway activity resulting from oncogenic mutations in Patched1. This agent is known to suppress proliferation and induce apoptosis of basaloid cell nests in the BCC, whereas having no effect on normal skin cells. Hence, Hh inhibitors would serve as a valid therapeutic tool for NBCCS-associated OKCs [21].

## Conclusion

Multiple OKC is considered as one of the important feature of NBCCS. So, in patients with multiple OKC, NBSCCS should also be ruled out. A complete clinical examination and histopathologic analysis must be performed to detect any features associated with this syndrome. As OKCs are important and may be the first and only manifestation of NBCCS, the dentist may be the first to detect it and refer the patient to a clinical geneticist for counseling.

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