Multiple Odontogenic Keratocysts: Report of a Case

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ABSTRACT

Although odontogenic keratocysts are common in clinical practice, the simultaneous occurrence of multiple cysts in both the maxilla and mandible of a patient is rare. We report a case of an otherwise healthy individual who developed 17 cysts over 15 years.

MeSH Key Words: mandibular diseases/pathology; maxillary diseases/pathology; odontogenic cysts/pathology

Usually, multiple odontogenic keratocysts (OKCs) occur as a component of nevoid basal cell carcinoma syndrome (NBCCS) with concomitant cutaneous, skeletal, ophthalmic and neurologic abnormalities. Gorlin and Goltz first described the spectrum of features associated with this syndrome in 1960; hence, it is also called Gorlin-Goltz syndrome.[1] We discuss the possibility that the current case is a partial expression of NBCCS and briefly review the current trends in treatment of recurrent OKCs associated with this syndrome.

Case Report

A 22-year-old patient presented with a complaint of pus discharge from the left maxillary posterior gums over the previous week. He did not complain of pain, facial swelling or foul odour and was apparently healthy, with vital signs within normal limits.

The patient had a history of multiple jaw surgeries for cysts, summarized in **Table 1**. Complete details of these surgeries were not available, as they were performed at a different hospital. On all those occasions, except one, the cysts were diagnosed as OKCs; in one case the diagnosis was dentigerous cyst.

Intraoral examination revealed a partly edentulous state; teeth 22, 23, 33, 34, 47 and 48 were missing and there was slight expansion of the buccal cortical plate in the left maxillary posterior region. With pressure, a white creamy exudate oozed out of the area distal to tooth 28, but there was no tenderness or bleeding.

A panoramic radiograph (**Fig. 1**) and intraoral periapical radiographs revealed multiple radiolucencies in all 4 quadrants and taurodontism in the left lower first and second molars. The radiolucencies are described in **Table 2**.

The patient's chest and skull radiographs were unremarkable. Dermatology consultation did not reveal any cutaneous abnormality.

Hematologic investigations were within normal limits. The patient was admitted to hospital, and enucleation of the cystic lesions was performed under general anesthesia. Three lesions (excluding the small lesion distal to tooth 46) were enucleated and sent for histopathologic examination. The small cystic lesion distal to tooth 46 was kept under observation.

The histopathologic report revealed that the cystic lining of all 3 lesions was parakeratinized stratified squamous epithelium of

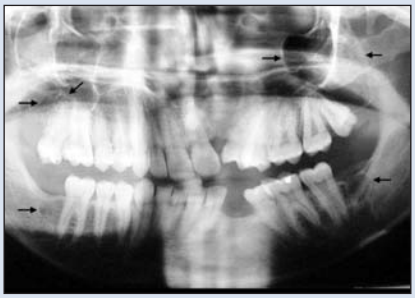

Figure 1: Orthopantomogram showing cystic lesions in all 4 quadrants.

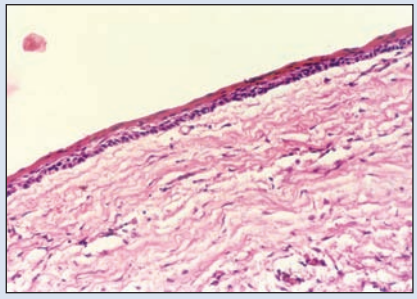

Figure 2: Section stained with hematoxin and eosin (400×) showing cystic lining with parakeratinized stratified squamous epithelium of uniform 6–8-cell thickness.

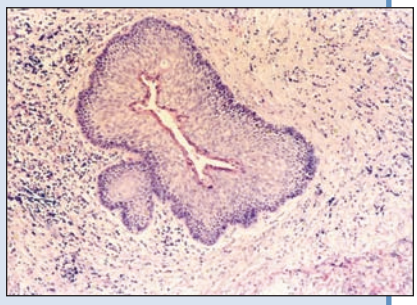

Figure 3: Section stained with hematoxin and eosin (200×) showing a satellite cyst.

uniform 6–8-cell thickness (**Fig. 2**). The lining epithelium consisted of well-defined columnar basal cells in a palisade arrangement and with polarized nuclei. The height of the epithelial cells and the number of nuclei they contained were reduced. Satellite cysts (**Fig. 3**) and epithelial remnants were observed in the connective tissue capsule.

Discussion

Multiple OKCs usually occur as a component of NBCCS or Gorlin-Goltz syndrome,[1] orofacial digital syndrome,[2] Noonan syndrome,[3] Ehler-Danlos syndrome,[4] Simpson-Golabi-Behmel syndrome[5] or other syndromes. Our patient was apparently healthy and had no features suggestive of these syndromes, 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.

NBCCS can also include concomitant skeletal features, such as bifid rib, frontal and parietal bossing and mandibular prognathism, and cutaneous abnormalities, such as multiple basal cell carcinomas and palmar and plantar keratosis. Hypertelorism, mental retardation, strabismus, calcification of the falx cerebri and medulloblastoma have also been reported.[2] In our patient, none of these features indicative of NBCCS was present.

Based on histopathologic studies, parakeratinization, intramural epithelial remnants and satellite cysts are more frequent among OKCs associated with NBCCS than in solitary keratocysts.[6,7] In our patient, the lining of the OKCs revealed the presence of parakeratinization and epithelial remnants in the connective tissue wall indicating NBCCS association.

Solitary keratocysts have greater epithelial height and more nuclei and basal nuclei compared with the multiple keratocysts of NBCCS.[6] In our case, the lining of the multiple OKCs had lower epithelial height and fewer nuclei than are common in the cystic lining of solitary keratocysts, suggesting NBCCS association. Immunohistochemical detection has shown that cytokeratins CK17 and CK19 are overexpressed in OKCs, suggesting that this may be a valuable additional parameter to distinguish between OKCs and other odontogenic cysts.[8] Cytokeratin expression was not investigated in our patient.

The biologic behaviour of OKCs associated with NBCCS is more aggressive and these cysts have higher recurrence rates (82%) compared with solitary keratocysts (61%).[6] The higher recurrence rates are attributed to epithelial remnants of the cystic lining or satellite cysts left behind following surgery.[9] A recurring OKC can be a new cyst that originates from epithelial residue or a microcyst left behind in the overlying mucosa. This is reinforced by the fact that OKCs can recur in bone grafts if the overlying mucosa is not completely excised.[9,10] It is believed that the aggressive behaviour and high rate of recurrence of OKCs associated with NBCCS is due to a higher rate of proliferation of the epithelial lining.[11] Our patient experienced a high rate of recurrence of cysts (**Table 1**). Thus, again, this case seemed to be a partial expression of NBCCS.

The term "multiple cysts" does not necessarily mean that the patient must have more than one cyst at a given time; rather it refers to the occurrence of cysts over the life time of the patient.[14] Our patient had a history of solitary and multiple cysts (**Table 1**).

The occurrence of multiple OKCs may be the first and only manifestation of NBCCS.[10] Multiple OKCs can occur a decade before other symptoms associated with NBCCS[10,11] and clinical manifestations of NBCCS may remain hidden in the earlier years of life.[12] 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. We emphasize 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.

The relatively early occurrence of multiple OKCs may be due to a genetic defect or mutation in the human

Table 1 Summary of patient's surgical history, showing age, site of cysts and treatment

Age of patient (years)	No. of cysts	Site	Classification of cyst	Treatment
7	1	Left maxilla in region of teeth 62 and 63	New	Observation
8	—	Same cyst in region of teeth 62 and 63	—	Enucleation of cyst in region of teeth 62 and 63 with extraction of tooth 62
9[a]	2	Left mandible in region of teeth 73 and 74	New	Enucleation and extraction of teeth 33 and 34 buds
10	2	Left mandible in region of tooth 35 Right maxilla in region of teeth 23 and 24	New New	Enucleation with extraction of teeth 22 and 23
13	1	Lower right mandible in region of teeth 47 and 48	New	Enucleation with extraction of teeth 47 and 48
15	1	Left mandible in region of teeth 32 and 33	Recurrent	Enucleation
17	3	Left maxilla in region of tooth 28 Left maxilla in region of tooth 23 Right maxilla in region of tooth 17	New Recurrent New	Enucleation Enucleation Enucleation
20	3	Left mandible in region of teeth 37 and 38 Left maxilla in region of teeth 22 and 23 Right maxilla in region of teeth 17 and 18	New Recurrent Recurrent	Enucleation Enucleation Enucleation
22	4	Right maxillary in apical region of tooth 17 Left maxilla, distal to tooth 28 Left mandible distal to tooth 37 Right mandible distal to tooth 46	Recurrent Recurrent Recurrent Recurrent	Enucleation Enucleation Enucleation Observation

[a]*Diagnosis of dentigerous cyst was considered.*

Table 2 Description of radiolucencies

Region	Radiographic appearance	Approximate size (cm)
Apical to tooth 17	Well-defined multilocular	2 × 1
Distal to tooth 28	Well-defined unilocular	4.5 × 3
Distal to tooth 37	Well-defined unilocular	1 × 1
Distal to tooth 46	Well-defined unilocular	0.5 × 0.5

"patched" gene.[13] The gene whose mutations cause NBCCS has been mapped to the long arm of chromosome 9q22.1-3-1[15] and has no apparent heterogeneity. Approximately 50% of cases of NBCCS are associated with allelic losses at this site.[15] The products of this gene may act as a tumour suppressor, as this gene controls growth and development of normal tissues.[15] Reports suggest genetic influences stimulating the formation of OKCs in NBCCS.[16] The occurrence of single or multiple OKCs in the absence of other features of the syndrome represents the least complete form of NBCCS[11,16] as observed in our patient. The absence of family history and other features of the syndrome can be due to variation in penetration and expression of different mutations within the same gene or the effects of modifier genes and environmental factors.[12]

In the treatment of recurrent OKCs associated with NBCCS, overlying surface epithelium should be excised along with the cystic lining to prevent recurrences from residual epithelial islands and microcysts.[1,9] In addition, use of Carnoy's solution following cyst enucleation (applied only over areas where the cyst is attached to the mucosa) and cryosurgery (because of the unique ability of liquid nitrogen to devitalize bone in situ while leaving the inorganic framework untouched) is advocated to kill epithelial remnants and dental lamina within the osseous

Table 3 Comparison of odontogenic keratocysts (OKCs) associated with nevoid basal cell carcinoma syndrome (NBCCS) and solitary OKCs

NBCCS-associated OKCs[a]	Solitary OKCs
Clinical characteristics	
Occur at an early age	Occur at middle or older age
Multiple cysts	Isolated cysts
Occur in both jaws with equal frequency	Occurs more often in the lower jaw
Higher recurrence rate (82%)	Lower recurrence rate (61%)
Histopathologic characteristics	
Smaller epithelial height	Greater epithelial height
Fewer total and basal nuclei	More total and basal nuclei
More frequent occurrence of odontogenic islands and daughter cysts	Less frequent occurrence of odontogenic islands

[a]*All these features of NBCCS-associated OKCs were observed in our patient.*

Table 4 Diagnostic criteria for nevoid basal cell carcinoma syndrome according to Evans and others[21] (2 major or 1 major and 2 minor criteria should be satisfied for positive diagnosis)

Major criteria
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
Minor criteria
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
Lymphomesenteric cysts
Congenital malformations, such as cleft lip or palate, polydactylism or eye anomaly (cataract, coloboma, microphthalmos)

margin and, thus, prevent recurrences.[17,18] Cryosurgery using liquid nitrogen is indicated not only to prevent recurrent OKC, but also in large complex mandibular lesions if there is a chance of involvement of vital structures with conventional treatment and, finally, in noncompliant patients.[18] OKCs are considered to be benign cystic neoplasms and require modified surgical procedures, such as curettage of bony walls, peripheral ostectomy with a bone bur or, occasionally, jaw resection.[19]

In our patient, 3 cysts were enucleated under general anesthesia and Carnoy's solution was applied to the osseous margins. The patient was followed regularly and after 18 months of treatment had no symptoms of recurrence of cysts, no increase in the size of the small cyst distal to tooth 46 and no occurrence of other features associated with NBCCS.

There is no specific laboratory test to diagnose NBCCS, although affected patients may have high levels of cyclic adenosine monophosphate and impaired phosphate diuresis on parathormone challenge.[20] The diagnosis is made clinically using the criteria suggested by Evans and others[21] (**Table 3**) and Kimons and others[22] (**Table 4**). However, there may be variations in the major diagnostic criteria for NBCCS in some populations due to genetic and geographic differences.[23] Our patient did not meet any of these diagnostic criteria for NBCCS. But in view of the clinical history and histopathologic correlations (**Table 2**), we suggest the possibility of this case being a

Table 5 Diagnostic criteria for nevoid basal cell carcinoma syndrome according to Kimons and others[22]

Major criteria
More than 2 basal cell carcinomas (BCCs) or 1 BCC in a patient < 20 years of age
Odontogenic keratocysts of the jaws (proven by histopathologic analysis)
3 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)
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)
Ovarian fibroma or medulloblastoma (not applicable if patient is male)

partial expression of NBCCS. As 35% to 50% of cases represent new mutations,[15] NBCCS patients have been found to carry 9 variants of mutations.[24] In our patient, the association of taurodontism with multiple OKCs might be considered a new feature or may be coincidental.

In conclusion, in any patient with multiple OKCs, the possibility of NBCCS must be considered. A complete clinical examination and histopathologic analysis must be performed to detect any features associated with this syndrome. As OKCs 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 counselling.[25]

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Acknowledgement: *We thank Dr. Krishnanand for his help in interpreting the histopathology slides.*

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The authors have no declared financial interests.

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