Multiple odontogenic keratocysts: A case report

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Odontogenic cysts are common in clinical practice, but simultaneous occurrence of multiple cysts in both maxilla and mandible in one patient is rare. We report a case of an otherwise healthy individual who developed 17 cysts over 15 years. We discuss the possibility of this case being a partial expression of nevoid basal cell carcinoma syndrome, and briefly review the current trends in treatment of recurrent odontogenic keratocysts associated with nevoid basal cell carcinoma syndrome.

A 22-year-old patient reported with a complaint of pain discharge from the left maxillary posterior gums for one week. He had no pain, facial swelling or foul odor. He was apparently healthy with vital signs within normal limits.

Patient gave a history of multiple jaw surgeries for cysts in the past, a summary of which is depicted in Table 1. Complete details of previous surgeries were not available, as they were performed at a different hospital. On all the occasions, the cysts were diagnosed as odontogenic keratocyst except one occasion in which diagnosis of a dentigerous cyst was given.

Intra-oral examination revealed a partially edentulous state with missing teeth 22, 23, 35, 34, 47, 48, and a slight expansion of the buccal cortical plate in the left maxillary posterior region (Fig. 1). On exerting pressure, a white creamy exudate oozed out distal to 28, but there was no tenderness or bleeding.

Subsequently a panoramic radiograph (Fig. 2) and intra oral periapical radiographs were advised that revealed multiple radiolucencies in all four quadrants and taurodontism with respect to the left lower first and second molar.

i) A well-defined multilocular radiolucency of 2 x 1 cm in apical region of 47.
ii) A well-defined unilocular radiolucency of 4.5 x 3.0 cm distal to 28.
iii) A well-defined unilocular radiolucency of 1 x 1 cm size in edentulous region distal to 57.
iv) A small-unilocular radiolucency of 0.5 x 0.5 cm diameter with well-defined sclerotic border distal to 46.

The patient was referred for chest and skull x-rays, which were normal. Dermatological consultation did not reveal any cutaneous abnormality.

Hematological investigations were advised and were within normal limits. Patient was hospitalized and enucleation of cysts was performed under general anesthesia. Three cysts excluding the small cyst distal to 46 were excised, and sent for histopathological examination. The cyst in the right middle distal to 46 was very small and was kept under observation.

The histopathological report of all three cysts revealed that the cystic lining was para-keratinized, stratified squamous pithelium of a uniform 6-8 cell thickness. The lining epithelium was well-defined columnar basal cell with palisading arrangement and polarization of the nuclei (Fig 5). The pathologist compared the cystic lining of these cysts with an archived library of histopathology of a solitary keratocyst. The epithelial height and total number of nuclei were less in the cystic lining of our patient. In the cystic lining of our patient, satellite cysts and epithelial remnants were also observed in the connective tissue capsule.

Multiple odontogenic keratocysts (OKCs) usually occur as a component of syndromes like nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome, but our patient was apparently healthy with no features suggestive of any association to these syndromes.

Usually, multiple OKCs occur in association with NBCCS and are associated with features like bifid rib, frontal and parietal bossing, mandibular prognathism and cutaneous abnormalities like multiple basal cell carcinomas and palmar and plantar keratodermia. In addition, we can associate hypertelorism, mental retardation, strabismus, calcification of the falx cere-bri, medulloblastoma, etc. However, in our patient none of these characteristic features indicative of NBCCS were present.

Based on histopathological studies it is suggested that parakeratinization, intramural epithelial remnants and satellite cysts are a more frequent observation among OKCs associated with NBCCS than among the solitary keratocysts. The lining of the OKCs of our patient revealed the presence of parakeratinisation and epithelial remnants in the connective tissue wall indicating NBCCS association.

Solitary keratocysts have greater epithelial height, which is the total number of nuclei and basal nuclei as compared to multiple keratocysts of NRCCS. The lining of multiple OKCs in our case had lower epithelial height and a fewer number of nuclei compared to the cystic lining of solitary keratocysts, thus suggesting the NBCCS association. The biologic behavior of OKCs associated with NBCCS is more aggressive and these cysts have a higher recurrence rate: 82% compared to the solitary keratocysts recurrence rate of 61%. The higher recurrence rate is attributed to epithelial remnants of cystic lining or satellite cysts that can be left behind following the surgery.

Recurring OKCs can be a new cyst that originates from an epithelial remnant or microcyst left behind in the overlying mucosa. This is emphasized by the fact that recurrence of OKCs even occurs in the bone grafts if the overlying mucosa is not excised.

It is believed that aggressive behavior and high recurrence of OKCs associated with NBCCS is due to a higher proliferation rate of the epithelial lining. In our patient there was a high recurrence of cysts (Table 1). Thus, biological behavior is again suggestive of this case being a partial expression of NBCCS.

Table 1: Summary of past history with age, site and treatment.

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Number of Cysts</th>
<th>N</th>
<th>Recurrent (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 years</td>
<td>Same cyst in 62, 65 region</td>
<td>—</td>
<td>Observation</td>
</tr>
<tr>
<td>9 years</td>
<td>2</td>
<td>Left mandible in 25, 57 region</td>
<td>N</td>
</tr>
<tr>
<td>10 years</td>
<td>2</td>
<td>Left mandible in 55 region</td>
<td>N</td>
</tr>
<tr>
<td>15 years</td>
<td>Lower right mandible in 47, 48 region</td>
<td>N</td>
<td>Enucleation with extraction of 47, 48</td>
</tr>
<tr>
<td>15 years</td>
<td>3</td>
<td>Left mandible in 62, 53 region</td>
<td>R</td>
</tr>
<tr>
<td>17 years</td>
<td>2</td>
<td>Left maxilla in 25 region</td>
<td>R</td>
</tr>
<tr>
<td>20 years</td>
<td>2</td>
<td>Left mandible in 25, 35 region</td>
<td>R</td>
</tr>
<tr>
<td>22 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>24 years</td>
<td>Left maxillary region distal to 28</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>25 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>26 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>27 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>28 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
<tr>
<td>29 years</td>
<td>Right maxillary in apical region of 17</td>
<td>R</td>
<td>Enucleation</td>
</tr>
</tbody>
</table>

* Diagnosis of a dentigerous cyst was considered.

Table 1: Summary of past history with age, site and treatment.

Annexure 1: Diagnostic Criteria for Nevoid Basal Cell Carcinoma Syndrome

Major Criteria
1. More than two basal cell carcinoma (BCC), one BCC at younger than 30 years of age, or more than 10 basal cell nevi.
2. Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst.
3. Three or more palmar or plantar pits.
4. Ectopic calcification: laminar or early—at younger than 20 years of age—false calcification.
5. Positive family history of nevoid basal cell carcinoma syndrome.

Minor Criteria
1. Congenital skeletal anomaly: bifid rib, fused, spalved or missing rib, wedged or fused vertebrae.
2. Occipital-frontal circumference, more than 97 percentile, with frontal bossing.
3. Carolus or ovarian fibroma.
4. Medulloblastoma.
5. Lymphomatosous cysts.
6. Congenital malformations such as cleft lip or palate, polydactylism or eye anomaly cataract, coloboma, microphthalmos.

Clinical
MULTIPLE
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The occurrence of multiple OKCs can be the first and only manifestation of NBCCS. 
Occurrence of multiple OKCs can occur a decade earlier than other symptoms associated with NBCCS, and clinical manifestations of NBCCS remain hidden in earlier years of life. The relatively early occurrence of multiple OKCs can be due to a genetic defect or mutation in the human patched gene, which normally acts as a tumor suppressor gene. Therefore, a dentist may well be the first to detect this syndrome. A possibility of this young patient developing other features of NBCCS in the future cannot be excluded.

The term “multiple cysts” does not necessarily imply that the patient must have more than one cyst at a given time, rather it refers to the lifetime history of the patient. In our patient, there were multiple instances of occurrence of solitary and multiple cysts in the past (Table 1). We emphasize the complete examination of patients having recurrent OKCs in order to discover other features of the NBCCS syndrome, which is known for its variability of expression.

The gene whose mutations cause NBCCS has been mapped to the long arm of chromosome 9q22.3-q31 and has no apparent heterogeneity. Approximately 50 percent of NBCCS have allelic losses including the site 9q22.3-q31. It is suggested that the product of this gene acts as a tumor suppressor gene, and this gene controls the ability of expression.

There are reports suggestive of genetic influences stimulating the formation of OKCs in NBCCS. Occurrence of single or multiple OKCs in the absence of other features of the syndrome represents the least complete form of NBCCS as observed in our patient. The absence of a family history and other features of the syndrome can be due to variation in penetrance and expression of different mutations within the same gene, or the effect of a modifier gene and environmental factors.

In the treatment of recurrent OKCs associated with NBCCS it is advised that overlying surface epithelium be excised along with the cystic lining to avoid recurrences that originate from residual epithelial islands and microcysts. In addition, the use of Carnoy’s solution and cryosurgery is advocated to kill epithelial remnants and dental lamina within the osseous margin to prevent recurrences. Cryosurgery using liquid nitrogen is advantageous as it maintains the osseous architecture to facilitate new bone formation. OKCs are considered to be benign cystic neoplasms and require modified surgical procedures like curettage of bony walls, peripheral osteotomy with bone bur or an occasional jaw resection.

In our patient, three cysts excluding the small cyst distal to 46 were enucleated under general anesthesia and Carnoy’s solution was applied to the osseous margins. The patient is on regular follow-up until after 18 months of treatment there are no symptoms of recurrence of the cysts, no increase in the size of the cyst distal to 46, or any other associated features of 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 upon parathormone challenge. The diagnosis is made clinically using the major and minor criteria suggested by Evans et al. (Annexure 1). However, there may be variations in the major diagnostic criteria for NBCCS in some populations due to genetic and geographical differences.

Our patient does not fulfill any of these diagnostic criteria for NBCCS. But in view of the clinical history and histopathological correlations (Table 2), a possibility of this case being a partial expression of NBCCS is discussed. Since 55 to 50 percent of cases represent new mutations, association of taurodontism with multiple OKCs can be considered as a new feature or may be a coincidental finding in this patient. In conclusion, in any patient with multiple OKCs a possibility of NBCCS must be considered. A complete clinical examination and histopathological analysis must be performed to elicit any features associated with NBCCS.

Table 2: Comparison of NBCCS Associated OKCs & Solitary OKCs

<table>
<thead>
<tr>
<th>NBCCS Associated OKCs</th>
<th>Solitary OKCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occur at an early age.</td>
<td>Middle or older age</td>
</tr>
<tr>
<td>Multiple cysts.</td>
<td>Isolated cysts</td>
</tr>
<tr>
<td>Occur in both jaws with equal frequency.</td>
<td>Predilection for lower jaw</td>
</tr>
<tr>
<td>Higher recurrence rate of 82%.</td>
<td>Recurrence rate of 61%</td>
</tr>
</tbody>
</table>

Histopathological characteristics

| Lower epithelial height. | Higher epithelial height |
| Less total nuclei and basal nuclei. Higher total nuclei and basal nuclei |
| More frequent occurrence of odontogenic rests and daughter cysts. |

All these features of NBCCS associated OKCs were observed in our patient.

Annexure 2: Diagnostic Criteria for Nevoid basal cell carcinoma Syndrome by Kimons et al.

Major Criteria
1. More than two basal cell carcinomas (BCCs) or one BCC in patients younger than 20 years of age.
2. Odontogenic keratocysts of the jaws (proven by histopathological analysis)
3. Three or more palmar or plantar pits.
4. Bilateral calcification of the falx cerebri.
5. Rigid, fused or markedly splayed ribs.
6. A first-degree relative with NBCCS.

Minor Criteria
1. Macrocephaly.
2. Cerebro-oculo-mandibulopulmonary malformations (eg, cleft lip or palate, frontal bossing; coarse facies and moderate or severe hypertelorism).
3. Other skeletal abnormalities (eg, Sprengel deformity, marked pectus deformity and marked syndactyly of the digits).
4. Radiological abnormalities (eg, bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, flame shaped luencies of the hands and the feet).
5. Ovarian fibroma or mediastinal teratoma.

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