Tetrad presentation of non-syndromic odontogenic keratocyst: An uphill diagnostic and therapeutic challenge

Abstract

Odontogenic keratocyst (OKC), in the last decade sceptically referred to as keratocystic odontogenic tumor (KCOT), is known for its subclinical extensive growth potential and significant rate of recurrences. Odontogenic keratocyst, being the third most common cystic lesion (10–20%) of the maxillofacial region, is often recognized as a sporadic lesion and is well-documented in the literature. Multiple presentation of these cysts over a lifetime is relatively uncommon and is usually seen in conjunction with nevoid basal cell carcinoma syndrome (NBCC), orofacial digital syndrome, Noonan syndrome, Ehlers–Danlos syndrome, Simpson–Golabi–Behmel syndrome, or other syndromes. The ‘two-hit’ hypothesis postulated by Knudson best explains this anomaly, wherein multiple OKCs associated with the syndromes arise as a consequence of the allelic loss in the patched (\(PTCH\)) gene, mapped to the long arm of chromosome 9q22.3-q31. A partial expression of the gene may result in multiple OKCs (5%) without any related syndromes. Though concurrent occurrence of non-syndromic multiple OKCs is a rare phenomenon, a handful of cases have been documented over the past few years. Adding to this, we report a case of multiple OKCs occurring synchronously and bilaterally in all 4 quadrants in non-syndromic, otherwise healthy persons, which could indicate a shift in trend.

Key words: multiple, odontogenic cysts, keratocyst, non-syndromic

Słowa kluczowe: mnogie, zębopochodne torbiel rogowaciejące, rogowaczyjący guz nowotworowy, bezobjawowy
Introduction

Odontogenic keratocyst (OKC) is a distinctive form of developmental odontogenic cyst that deserves special consideration owing to its specific histopathological features and clinical behavior. Odontogenic keratoctysts arise from the dental lamina, its remnants or odontogenic basal cell hamartia. Multiple OKCs usually occur at younger age as a component of nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin–Goltz syndrome, orofacial digital syndrome, Noonan syndrome, Ehler–Danlos syndrome, Simpson–Golabi–Behmel syndrome, or other syndromes. The patched (PTCH) gene, a tumor suppressor gene located on chromosome 9q22.3-q31, is involved in both sporadic OKCs and OKCs associated with NBCCS. A partial expression of the PTCH gene may result in the occurrence of only multiple recurring OKCs, without any associated systemic findings. The term ‘multiple’ refers to the lifetime history of the patient and not to many cysts present at any one time. Any patient with more than 1 OKC other than a recurrence is generally said to show some other features of the syndrome, albeit only minor anomalies, which may be revealed only during full examination. Contrary to the above statement, we report a case of multiple OKC occurring at one time in all 4 quadrants, without any syndromic features found during systemic examination.

Case report

A 28-year-old female patient was referred from a private clinic to our institution (Department of Oral Pathology and Microbiology, the A.B. Shetty Memorial Institute of Dental Sciences, NITTE (Deemed to be University), Deralakatte, India) to evaluate an incidental finding of cyst in the orthopantomogram (OPG). Three months before the patient reported to our institution, the extraction of the bilateral lower third molars, followed by the drainage of the abscess was carried out, and medical termination of pregnancy was advised due to the spread of infection from the periapical abscess and adverse effects of antibiotics. During extraoral examination, diffuse bilateral swelling of the face was noticed (Fig. 1). Hyperelorism was evident. During intraoral examination, there was no cortical expansion noticed. The orthopantomogram revealed ill-defined radiolucency present bilaterally in the posterior region of the maxilla and the mandible, impacted teeth 18 and 28, and loss of cortication in the anterior ramus of the mandible (Fig. 2).

The presence of syndrome in this patient was ruled out after detailed clinical examination, blood tests, and chest and skull radiograph procedure. In order to enucleate the cyst, the patient was subjected to surgery, supplemented with an intraoral application of Carnoy’s solution. There was performed extensive curettage bilaterally, along with the extraction of the embedded teeth on either side. Primary closure was done. The patient had an uneventful post-operative course and was discharged the next day. All the excised cystic lining from the 4 quadrants was sent for histopathological evaluation.

The histopathological report revealed that the cystic lining of all 4 lesions was parakeratinized stratified squamous epithelium of uniform 6–8-cell thickness (Fig. 3). The lining epithelium consisted of well-defined columnar basal cells in a palisaded arrangement with polarized nuclei and surface corrugation. The underlying connective tissue capsule showed loose bundles of collagen fibers, inflammatory cells – predominantly lymphocytes, and numerous blood vessels, lined by endothelial cells. Satellite cysts (Fig. 4,5) and epithelial remnants were observed in the connective tissue capsule. In a few areas of the satellite cysts, budding of the basal layer into the connective tissue
wall was also noticed. Thus, the final diagnosis was OKC. The patient had been followed up for the subsequent 6 months at the time of this report.

Discussion

Odontogenic keratocyst, in the last decade sceptically referred to as keratocystic odontogenic tumor (KCOT), is deemed an odontogenic cyst of developmental origin. Odontogenic keratocyst was first identified and described in 1876, and further characterized by Phillipsen in 1956. The emphasis on keratinization was considered deceptive, masking other histological characteristics that were actually responsible for the biological behavior of the cysts. In 1963, Hansen pointed out that the designation ‘keratocyst’ was used invariably to describe any keratin-forming jaw cyst and highlighted the need for specific histological criteria. Studies by Browne (1971) and Forssell and Sainio (1979) showed that the characteristic epithelial lining of OKC was unique, different from the metastatic keratinizations in other jaw cysts, affirming its recognition as a discrete entity.

Odontogenic keratocysts occur over a wide age range from the 1st to the 9th decade, commonly involving the mandible. Sporadic and non-syndromic OKCs are reported to have bimodal age incidence with the 1st peak in the 2nd–3rd decade (15–45 years), and the 2nd peak in the 5th decade or later (55–65 years), with the maxilla commonly involved. In females, the 2nd peak of incidence is often 1 decade earlier as compared to males, but this can vary among races. However, OKCs associated with syndrome show only 1 peak of incidence at the age of 10–30 years. Ours is a case of non-syndromic OKC in a patient of 28 years, probably exhibiting the 1st peak of incidence, thereby mandating long-term follow-up and patient education on the possibility of the 2nd peak of incidence.

A slightly higher prevalence of OKC is reported in males than in females, with a ratio of 1.42. But the male to female ratio in the case of multiple OKCs associated with syndrome is 1:1, indicating its relatively higher incidence in females as compared to sporadic OKCs. This is in contrast to this case report of a female presenting with multiple OKCs without any features in line with syndrome, portraying the rarity of this case and imposing a diagnostic challenge. Odontogenic keratocysts showed a higher incidence rate in Caucasian males than in black males in 2005. This was expected to be reversed in the course of time, taking into consideration the selection bias in the previous studies, but a systematic review by MacDonald-Jankowski from 2010 still showed a relatively lower incidence in South African blacks; they were more prone to ameloblastoma than to OKC.

Multiple OKCs mean the occurrence of these cysts over a lifetime, and only 5% of such cases have been reported in non-syndromic individuals. Hardly a handful of cases showing synchronous presentation of multiple OKCs at one time have been reported in the literature (Table 1). Ours may be the next case following.
Radiographically, OKCs may occur as unilocular or multilocular radiolucency. Sometimes the unilocular radiolucency appears to have a scalloped border, suggesting unequal growth activity, and is often misinterpreted as multilocular radiolucency. Voorsmit described such types as ‘multilobular’. Varied presentations of OKCs in the radiograph are interpreted based on their anatomical locations as follicular keratocyst (envelopmental/replacemental type), extraneous and collateral types. In our case, the cysts in the mandible appeared as multilocular radiolucency and the cysts in the maxilla were of follicular keratocysts associated with impacted teeth 18 and 28.

Nevoid basal cell carcinoma syndrome is associated with a mutation in the *PTCH* gene at 9q22.3-q31. The patched (*PTCH*) gene is a tumor suppressor gene which encodes a transmembrane receptor for the sonic hedgehog pathway in humans, controlling cell patterning and growth of various organs, including tooth development. Knudson’s ‘two-hit’ or ‘multiple-hit’ hypothesis best explains this mutation, wherein basal cell carcinomas and keratocysts associated with NBCCS emerge as the result of the first hit of the allelic loss of *PTCH* within the precursor cell. Sporadic OKC is an outturn of 2 somatic hits in which the mutations of *PTCH* within locally susceptible cells ultimately result in the allelic loss. The absence of all the manifestations of NBCCS, which may be due to the variability of the *PTCH* gene expression, highlights the need to periodically monitor patients with multiple OKCs.

Biological behavior of OKCs associated with NBCCS is more aggressive and these cysts have higher recurrence rates (63%) compared with solitary keratocysts (37%). Recurrent OKC may develop in 3 different ways: by incomplete removal of the original cyst lining; by retention of daughter cysts, from microcysts or epithelial islands in the wall of the original cyst; or as new OKCs from epithelial offshoots of the basal layer of the oral epithelium. The latter case supports the hypothesis of Shear and Altini (1976), which addresses the possibility of initiating the process of cyst formation by the overlying epithelium under the influence of residual ectomesenchymal inductive activity. The presence of a higher number of satellite cysts, odontogenic epithelial remnants and a higher number of mitotic figures in the epithelium lining of the parent cyst cavity of OKCs associated with NBCCS indicates an inherent genetic potential for proliferation of odontogenic epithelium in syndromic patients. In our case, OKCs presented a bizarre picture of satellite cysts and odontogenic epithelial remnants in almost all of the multiple cysts, making the diagnosis difficult and necessitating periodic follow-ups to elicit recurrences and also delayed presentation of syndromic features, if any.

Treatment of OKC is generally classified as either aggressive or conservative. The goal is to choose the right modality, carrying the lowest risk of recurrence and least morbidity, and, at the same time, restoring the morphology and function of the affected area. Therapeutic interventions of OKC include marsupialization and enucleation, combined with adjuvant cryotherapy with Carnoy’s solution, and marginal or radical resection. Voorsmit et al. advocated excision of the overlying mucosa and popularized the use of Carnoy’s solution as a chemical fixative. Carnoy’s solution contains ferric chloride (dehydrating agent), absolute alcohol (fixative hardening the tissue by shrinkage), chloroform (increasing the speed of fixation), and glacial acetic acid (making the tissue swell and preventing over-hardening), which cauterize and fix the tissue to a predictable time-dependent depth. At the same time, the neurovascular bundle is protected by a coat of vaseline. Its average depth of penetration is 1.54 mm after 5 min of application.

With tetrad OKC presentation being reported only in the present decade, documentation of such cases throws a light on the changing trend in OKC presentation. Thus, it is important to report such cases, taking into account their oddity and perplexing clinical presentation, which pose a diagnostic and therapeutic challenge. Thorough clinical evaluation assisted with appropriate investigations ruled out the presence of syndrome in our case. However, genomic studies were not carried out to determine the presence of syndrome, if any.

### Conclusions

The possibility of multiple OKCs should be considered in any patient with OKC. Therefore, careful histopathological and radiological examination of any other existing lesion should be done. Any patient reporting with multiple OKCs should be evaluated thoroughly for the possibility of NBCCS, as OKC may be the first and only manifestation of this syndrome. Furthermore, due to the fact that OKC associated with this syndrome has a higher rate of recurrence than the isolated cases, a very strict follow-up has to be conducted, along with serial screening for the development of malignancies and other complications beside OKCs, for a long period of time. Most important

### Table 1. Literature review of multiple non-syndromic odontogenic keratocysts (OKCs) in all 4 quadrants

<table>
<thead>
<tr>
<th>Study</th>
<th>Age [years]</th>
<th>Gender</th>
<th>Satellite cysts and/or odontogenic remnants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartake et al. 2011</td>
<td>20</td>
<td>F</td>
<td>satellite cysts</td>
</tr>
<tr>
<td>Kargahi and Kalantari 2013</td>
<td>11</td>
<td>M</td>
<td>–</td>
</tr>
<tr>
<td>Kudekar et al. 2013</td>
<td>23</td>
<td>M</td>
<td>satellite cysts and odontogenic remnants</td>
</tr>
<tr>
<td>Maheshwari et al. 2015</td>
<td>20</td>
<td>M</td>
<td>–</td>
</tr>
<tr>
<td>Reddy et al. 2016</td>
<td>14</td>
<td>F</td>
<td>satellite cysts</td>
</tr>
</tbody>
</table>

F – female; M – male.
of all, care should be taken for complete excision and thorough enucleation. The increase in the reported cases of non-syndromic multiple OKCs from 2011 to 2018, in conjunction with the present case report, reflect a change in trend, where multiple OKCs may not necessarily be associated with NBCCS.

References
