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Title: Non syndromic multiple keratocystic odontogenic tumors – an arduous challenge for Oral and Maxillo facial specialists

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Short Running Title: Non syndromic multiple keratocystic odontogenic tumors

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ABSTRACT

Introduction
Keratocystic odontogenic tumor is a common developmental odontogenic cyst affecting the maxillofacial region. Multiple OKCs are usually seen in association with nevoid basal cell carcinoma syndrome but approximately only 5% of patients with keratocystic odontogenic tumor have multiple cysts without concomitant syndromic presentation. Very few cases have been reported till date.

Case Report
This report emphasizes a unique case of a young 14 year old female suffering since an early age and the role of multidisciplinary approach in the diagnosis and management of a case of multiple keratocystic odontogenic tumors in a non-syndromic patient.

Conclusion
The non-syndromic KCOTs are linked to the expression of a characteristic gene. They are associated with severe morbidity in the younger age group due to their multiple involvement of the jaws but their recurrence rate is less compared to that of syndromic type. The diagnosis and management of these tumors mandates multidisciplinary approach which can instill confidence and improve quality of life of the patients.

Keywords: Keratocystic odontogenic tumour, benign neoplasm, Gorlin –Goltz syndrome, Tumor suppressor gene.
TITLE: Non syndromic multiple keratocystic odontogenic tumors – An arduous challenge for Oral and Maxillo facial specialists

INTRODUCTION

Keratocystic odontogenic tumor (KCOT/KOT) is a developmental cyst derived from the enamel organ or dental lamina. The definition “Odontogenic keratocyst” was first proposed by Philipsen in 1956 [1]. KCOTs are the most common form of cystic lesions affecting the maxillofacial region, with an incidence rate of about 12-14% of all odontogenic cysts, more frequent in males (M/F 2:1) [2]. Multiple KCOT are associated with syndromes such as Nevoid basal cell carcinoma syndrome (NBCCS)/Gorlin Goltz syndrome/ Bifid rib syndrome) usually in younger patients [3,4]. Occurrence of multiple KCOT is rare and to date only few cases have been reported in the literature. We report a rare case of multiple KOTs in a non syndromic patient associated with impacted/partially erupted teeth.

CASE REPORT

A 14 yrs old female patient reported with a chief complaint of swelling in the right side of face (Figure1A) since 4 months with a history of slowly progressing swelling. Her past history revealed that she was a diagnosed and surgically operated case of Dentigerous cyst in relation to left deciduous maxillary teeth (C, D) at her 6 yrs of age. At age of 10 yrs, she was suspected for re-infection of the cyst with intra oral sinus opening and was advised an orthopantomogram (OPG) which revealed multiple radiolucencies involving maxilla and mandible (Figure 2A). Her personal history revealed mixed diet with no deleterious habits and family history was not contributory and there was no history of consanguineous marriage of her parents. On Extra oral examination, her face was asymmetrical due to diffuse swelling measuring 4x4 cm approximately in the right middle third of face with involvement of right ala of nose and upper lip associated with obliteration of naso labial fold (Figure 1A) and it was non tender, firm to hard in consistency with no local rise of temperature on palpation. Temporomandibular joint examination revealed tenderness on palpation on right side while opening with adequate mouth opening of 35mm. Intraoral examination revealed missing 13, 25, 37 and an oval shaped
swelling measuring 4x2 cm approximately in relation to right maxillary teeth (Figure 1B). It was soft in consistency, fluctuant, compressible, and tender. A panoramic radiograph was taken which revealed well defined unilocular multiple radiolucencies bilaterally in maxilla and mandible (Figure 2B) and the radiolucencies are described in (Table 1).

The patient was further evaluated to rule out any syndrome due to the presence of multiple cystic lesions. The patient’s chest (Figure 3) and skull radiographs were unremarkable. Dermatological examination did not reveal any cutaneous abnormalities like palmar and plantar defects. Hematologic investigations were within normal limits. CT scan of Maxillo facial region with axial (Figure 4A) and coronal (Figure 4B, 4C) sections revealed multiple hypodense lesions in the maxilla and mandible.

Aspiration of the cystic lesions showed white cheesy keratin like material. Incisional biopsy was done in relation to right and left maxilla and mandible and was subjected to histopathological examination which was suggestive of multiple KOTs. Under general anesthesia, four lesions were enucleated (Figure 5A,5B) followed by chemical cauterization (Carnoy’s solution) and tissue specimens were sent for histopathologic examination (Figure 6) which revealed “Parakeratinized Odontogenic Keratocyst” from all 4 Quadrants which were of uniform epithelial lining 6-8 cells thick lacking rete ridges. The lumen was filled with keratin, cholesterol clefts and hyaline bodies and the connective tissue wall shows 3-4 micro cysts, cholesterol clefts and inflammatory cells at few areas.

Follow up was done on 1st, 2nd and 3rd month postoperatively. The post-operative period was uneventful without any complications. Patient is asymptomatic since then without any complaints.

**DISCUSSION**

KOT is a common developmental odontogenic cyst and its biologic behavior is similar to a benign neoplasm [5]. It occurs at any age with peak incidence during the second and third decades, with a slight male predominance [6]. In 25-40% cases, involvement of unerupted tooth has been reported [5]. Brahnon in his analysis of clinical features of 312 cases of OKC found that, 5.8% of patients with multiple OKC
had no other features of syndrome [7]. The KOT is locally destructive and recurrence rate is very high where published recurrence rates for keratocystic odontogenic tumors range from 5% to about 70%. The recurrence rate of KOT associated with NBCC is about 82% whereas for solitary KOT it is ranging between 2.5% to 62.5% [6].

PTCH (patched), a tumor suppressor gene involved in both syndrome associated and sporadic KOTs, occurs on chromosome 9q22.3 – q31. Syndromes associated with Multiple KOTs are Gorlin-Goltz syndrome/NBCCS, Oro facial digital syndrome, Noonans syndrome, Ehler danlos syndrome [5]. There is no specific laboratory test to diagnose NBCCS, although the diagnosis is made clinically using the criteria suggested by Evans et al [6]. Evans et al. first published major and minor criteria for diagnosis of Gorlin-Goltz syndrome, later modified by Kimonis et al. and according to them the positive diagnosis of Gorlin-Goltz syndrome is when two major or one major and two minor criteria are satisfied [6,7].

The major criteria are:
- Multiple Basal cell carcinomas (BCCs) or one occurring under the age of 20 years
- Histologically proven KOTs of the jaws
- Palmar or plantar pits (three or more)
- Bilamellar calcification of the falx cerebri
- Bifid, fused or markedly splayed ribs
- First degree relative with NBCCS

The minor criteria are:
- Macrocephaly (adjusted for height)
- Congenital malformation: Cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism
- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
• Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modelling defects of the hands and feet or flame shaped hands or feet
• Ovarian fibroma
• Medulloblastoma

However, there may be variations in the major diagnostic criteria for NBCCS in some populations due to genetic and geographic differences [8]. Our patient was apparently healthy and did not meet any of these diagnostic criteria for NBCCS, such as pits on the palms of the hands or soles of the feet, multiple basal cell skin cancers, skeletal (bone) changes, calcium deposits in the brain and developmental disability.

Histopathological examination in our case revealed parakeratinized stratified squamous epithelium with absence of rete pegs and palisaded basal cell layer, giving an appearance of tombstone or picket fence. The connective tissue revealed multiple daughter cysts and cystic lumen revealed keratin, giving a picture of KOT.

Treatments are normally classified as conservative or aggressive. Conservative treatment modalities include simple enucleation, with or without curettage, or marsupialization [8]. Aggressive treatment modalities includes peripheral ostectomy, chemical curettage with carnoy’s solution, cryotherapy, or electrocautery and resection [9]. The goal is to choose the treatment modality that carries the lowest risk of recurrence and the least morbidity. Voorsmit et al [9] (1981) have observed a reduction in recurrence rate if enucleation followed by application of carnoy’s solution (2.5%) when compared with enucleation alone (13.5%). Therefore, enucleation followed by application of carnoy’s solution can result in a reasonably low recurrence rate with less morbidity when compared to other treatment modalities. Kuroyanagi et al suggested the presence of Ki-67 expression in OKC, which might be helpful for considering the alternative surgical procedure to avoid recurrence and might be used as a prognostic indicator. In recent studies, the hypothesis that suppression of sonic hedgehog (SHH) signaling pathway might be effective for the treatment of OKC [10].
CONCLUSION

“These lesions take a giant leap in its stride”. It is the responsibility of the Oral and maxillofacial specialists to do a comprehensive clinical examination and necessary investigations to not only diagnose but also rule out any associated syndromes and provide apt treatment. Since partial expression of the gene can result in non-syndromic multiple KOTs, the patient must be referred to a clinical geneticist for counseling. Long-term follow up after treatment must be performed to detect any other features associated with NBCCS, a tendency for multiplicity and recurrence. Hence, apart from surgery even gene therapy can play a significant role in such patients.

AUTHOR’S CONTRIBUTIONS

Reddy GV
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

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Group 1 - Analysis and interpretation of data
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Group 3 - Final approval of the version to be published

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Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Anusha Rembers
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
REFERENCES


Table 1: Showing region, extent and appearance of large multiple radiolucent lesions in maxilla and mandible of Orthopantamograph.

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>Region</th>
<th>Radiographic appearance</th>
<th>Approximate Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mesial of 11 to Distal of 15</td>
<td>well defined large unilocular radiolucency with corticated border in relation to vertically impacted impacted 13</td>
<td>4x5 cm</td>
</tr>
<tr>
<td>2</td>
<td>Mesial of 25 to distal 27</td>
<td>Non homogenous density of bone in relation to root apices of 23, 24, 26, Missing 25 and partially erupted 27 (Surgical scar)</td>
<td>1.5x2 cm</td>
</tr>
<tr>
<td>3</td>
<td>Mesial of 36 to ramus region of mandible</td>
<td>Well defined unilocular radiolucency with impacted 37</td>
<td>5x3 cm</td>
</tr>
<tr>
<td>4</td>
<td>Distal of 47 to ramus region of mandible</td>
<td>Well defined unilocular radiolucency with 47</td>
<td>5x4 cm</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1: A 14 Year old female girl presenting with asymmetrical face: (A) - Clinical photograph of extra oral frontal view showing swelling on right of the face. (B) - Clinical Intra-oral photograph showing an oval shaped swelling measuring approximately 4x2 cm in size.

Figure 2: OPG at different ages: (A) - Orthopantamograph showing large multiple radiolucent lesions in maxilla and mandible at the age of 10 years (B) - Orthopantamogram showing large multiple radiolucent lesions in maxilla and mandible.

Figure 3: Chest PA view reveals normal anatomic findings

Figure 4: CT scans showing lesions in four quadrants (A) - Axial section of CT scan showing well defined osteolytic lesion, predominantly hypodense measuring approximately 1X2 cm involving alveolar process of left maxilla in relation to 27. (B) - Coronal section of CT scan showing well defined osteolytic lesion, predominantly hypodense measuring approximately 4x4 cm involving alveolar and palatine process of right maxilla with impacted 13 displaced superiorly (C) - Coronal section of CT scan showing Well defined osteolytic lesion, predominantly hypodense measuring approximately 2x2 cm involving left sided body and ramus of mandible in relation to impacted 37.

Figure 5: Excision of lesions (A) - Photograph showing bony cavity after cyst enucleation in the right ramus region (B) - Photograph showing bony cavity after cyst enucleation in the right anterior maxilla.

Figure 6: Excisional biopsy specimens of four quadrants showed sections stained with hematoxylin and eosin (400x) showing cystic lining with para keratinized stratified squamous epithelium of uniform 6–8-cell thickness.
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