Case Report
Keratocystic odontogenic tumor simulating lateral periodontal cyst and nasopalatine duct cyst: report of cases and literature review

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Abstract: The odontogenic keratocyst, now officially known as the keratocystic odontogenic tumour (KCOT) is an intra-osseous tumor characterized by distinctive histopathologic findings. KCOTs comprise approximately 11% of all cysts in the maxillofacial region and due to unspecific clinical and radiographic features, it can be misdiagnosed which resulting in inadequate treatment. The differentiation between KCOTs and other jaw cysts is clinically important due to their aggressive, infiltrative behavior and high recurrence potential. This article reports two cases of KCOT that simulating lateral periodontal cyst and nasopalatine duct cyst and provides an overview on clinical and histopathologic features, treatment and the prognosis of these lesions.

Keywords: Keratocystic odontogenic tumor, lateral periodontal cyst, nasopalatine duct cyst, differential diagnosis

Introduction

The odontogenic keratocyst, which was first described by Philipsen in 1956, has drawn of great interest due to its unique histologic characteristics, aggressive biologic behavior, and high recurrence rate [1, 2].

In 2005, the World Health Organization (WHO) reclassified odontogenic keratocyst and defined these lesions as ‘a benign, uni- or multicystic intraosseous neoplasms of odontogenic origin, with a characteristic lining of parakeratinized, stratified squamous epithelium and a potential for aggressive, infiltrative behavior’ and recommending the term ‘keratocystic odontogenic tumor’ (KCOT) which would better reflect its neoplastic nature [3-5].

Histologically KCOTs are characterized by regular parakeratinized stratified squamous epithelium with an often corrugated surface, but without rete ridges. There is a well-defined, often palisaded, basal layer of columnar or cuboidal cells. Intense basophilic nuclei of the columnar basal cells oriented away from the basement membrane which is an important feature in distinguishing KCOT from jaw cysts with keratinization. Also the basal epithelial layer can show budding into the underlying connective tissue in the form of daughter cysts [6-8].

KCOTs show a slight predilection for males. They can occur over a wide age range with a peak incidence in the second and third decades. KCOTs may manifest with pain, swelling, infection and discharge, trismus and infrequently paresthesia or displacement of teeth. However in many cases they may be asymptomatic and detected incidentally routine imaging [7, 9, 10].

These lesions may occur in any part of the jaws but they are frequently located in the mandible, mainly in the posterior body, the angle region and the ascending ramus. Radiographically the lesion can appear either unilocular or multilocular radiolucency with well-defined sclerotic borders. KCOTs generally mimic other pathologic entities. For instance, a unilocular KCOT can be located periapically, simulating periapical cysts or it can surround the crown of an unerupted teeth which may be interpreted as a dentiger-
KCOTs simulating as jaw cysts

Figure 1. Healthy periodontal tissues was observed in intraoral examination. There was no intraoral swelling at premolar-molar area.

Figure 2. Well defined unilocular radiolucency (arrow) was observed in orthopantomograph.

Figure 3. The buccal cortical perforation was seen at intraoperative examination.

Figure 4. After enucleation. A: Curettaged bone cavity; B: Macroscopic appearance of the lesion.

ous cyst. If KCOT is localized between the roots of teeth, it may simulate lateral periodontal or lateral radicular cysts. When a KCOT develops in the maxillary midline that may be misdiag-

osed as a nasopalatine duct cyst. Additionally large unilocular KCOTs and cystic ameloblastoma are indistinguishable on X-ray [3, 6-8, 11]. The differentiation between KCOTs and other jaw cysts is clinically very important due to their ability to expand through bony walls and penetrate deeper structures and their high recurrence potential [5, 11]. Also, very rarely squamous cell carcinoma arising from KCOTs have been reported [12, 13].

The purpose of this paper to report two rare cases of KCOT simulating lateral periodontal cyst and nasopalatine duct cyst that created a diagnostic dilemma. In addition, we present a relevant review of literature and concisely discussing the distinctive aspects of KCOT, including its clinico- and histopathologic features, treatment and the prognosis of these lesions.

Case reports

Case 1

A 57-year-old male patient referred to Gazi University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery due to a radiolucent mandibular lesion which was discovered during routine radiographic examination. He
was apparently healthy, with vital signs within normal limits. He denied pain or any other symptoms. In intraoral examination, there was no swelling but tender on palpation in right mandibular premolar region (Figure 1). The orthopantomographic radiograph revealed oval, unilocular radioluency between the right mandibular first (44) and second premolar (45) (Figure 2). We performed a vitality test and both teeth were responsive to electrical pulp testing. Based on these clinical and radiographic findings, our provisional diagnosis was lateral periodontal cyst. On surgical intervention, a muco-periosteal flap was elevated, which showed a perforated buccal cortical plate (Figure 3). A cyst like lesion was present interdentally between 44 and 45. The cyst was enucleated and the area was thoroughly curetted (Figure 4).

The specimen submitted to Department of Oral Pathology and the histological examination of hematoxylin and eosin stained slides demonstrated a fibrous cyst wall with an uniform stratified squamous epithelium, six to eight cells in thickness. The epithelium was characteristic for a layer of columnar, hyperchromatic basal cells. The luminal surface was parakeratotic with a corrugated appearance (Figure 5). Thereby correlating these histopathological findings a diagnosis of KCOT was given. The patient healed uneventfully and was followed up for 24 months. There was no recurrence of the lesion and radiologic examination of the surgical site showed complete osseous healing (Figure 6).

Case 2

A 49-year-old man was referred to the Gazi University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery; he was complaining about spontaneous pain and swelling in anterior maxilla. His medical history was non-contributory. The patient’s dental history showed no previous buccal or facial pain, traumatic dental injury, or other abnormalities at the periodontal region. Clinical examination revealed a swelling in the anterior region of maxilla (Figure 7A). Central and lateral incisors are vital and no tooth mobility was detected.
The orthopantomographic radiograph revealed unilocular, well-circumscribed, heart-shaped radiolucent lesion located midline of anterior palatal region (Figure 7B). The lesion was not associated with any displacement of adjacent teeth or resorption of roots.

After the clinical examination, aspiration biopsy was made. As a result of biopsy, the initial diagnosis was confirmed as a cyst. Due to the proximity with the cyst cavity, the neighboring right maxillary central incisor underwent presurgical root canal therapy. Under the local anesthesia, sulcular incision was made between lateral incisors. Enucleation of the cyst, followed by resection of the right maxillary central incisor’s root (Figure 8A, 8B). Primary closure was performed after cyst cavity was currated completely (Figure 8C, 8D).

After surgery, the lesion was sent to Department of Oral Pathology to be examined microscopically. At the histopathologic examination a brownish cystic lesion measuring 2.3 × 1 × 0.7 cm was cut into small pieces, processed according to standardized histotechnical methods. Microscopically a parakeratinized stratified epithelium was observed lining the lesion and parts of the epithelium showed stratification. Additionally, the cystic wall was composed of fibrous connective tissue exhibiting a multifocal intense, chronic inflammatory infiltrate and also multiple satellite cells were seen (Figure 9).

Because of the detection of a parakeratinized epithelium lining and multiple satellite cysts in the connective tissue of the cyst wall, a final diagnosis of KCOT was concluded. After 1 year of follow-up, satisfactory bone formation was
observed and there was no recurrence of the lesion (Figure 10A-C).

Discussion

KCOT presents mostly at the posterior region of the mandible in young males as an intraosseous lesion [14]. Radiographically, KCOTs may appear unilocular or multilocular radiolucency with scalloped and well defined borders [8, 11]. Symptoms like pain, swelling, discharge and paresthesia may be present but also they can be symptom-free and recognised on the routine radiographic examination [5, 9, 10].

Radiographic and clinical characteristics of KCOTs are not pathognomonic and may cause a misdiagnosis especially when this lesion is seen between the roots, mimicking lateral periodontal cyst and lateral radicular cysts or located maxillary midline, presenting as nasopalatine duct cyst [3, 9, 15, 16]. Inflammatory symptoms can be seen occasionally in the patients with KCOT. Moreover, when KCOT occurs adjacent to a nonvital or endodontically treated tooth, due to the symptoms like pain, swelling and drainage, can be interpreted as a periapical lesion [6, 17]. Therefore KCOTs should be included in the differential diagnosis of cystic jaw lesions. The emphasis on diagnosis of the lesion is important for treatment choice. In general cystic lesions of oral cavity can completely be cured with simple enucleation, however a simple enucleation of KCOT can increase its recurrence risk due to their friable nature of capsule and aggressive behavior [18, 19].

KCOTs are generally thought to arise from either dental lamina or its remnants or extension of basal cells from the overlying epithelium [2, 11, 20]. The epithelial islands derived from dental lamina are mostly found in the gingiva and periodontal ligament which may clarify the lateral periodontal presentation of these lesions [2]. The stimulus which causes dental lamina or basal cells to form KCOT is determined by genetically. Also the studies, that investigated the development of KCOT, showed the evidence of allelic loss of heterozygosity in the p16, p53, PTCH, MCC, TSLC1, LTAS2 and FHIT genes [11, 20].

Several characteristics and molecular markers have identified in KCOT that support its aggressive growth pattern, neoplastic nature, and high recurrence potential, including the intraluminal hyperosmolality, active epithelial proliferation, collagenolytic activity in the cyst wall and synthesis of interleukin-1 and 6, tumour necrosis factor, increased levels of prostaglandins and increased expression of parathyroid hormone-related protein, and the greater frequency of proliferating cell nuclear antigen (PCNA) and Ki-67, p53, Bcl-2, Cytokeratin10, carcino-embryonic antigen, epithelial marker antigen and Gp38 positivity [11, 21].

The recurrence rates of KCOT has been reported to vary from 0% to 62.5%. Differences in reported recurrence rate may be related to the length of follow-up period, operative techniques employed, skill of the surgeon, size and location of the lesions, presence or absence of infection, associated teeth, involvement of mucosa, histopathological findings, age and gender of the patient, the number of cases investigated and inclusion of cases with nevoid basal cell carcinoma syndrome [1, 8, 11].
# KCOTs simulating as jaw cysts

## Table 1. Cases of KCOT that resemble Lateral Periodontal Cyst in the International Literature

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Age</th>
<th>Gender</th>
<th>Site</th>
<th>Symptomatology</th>
<th>Radioluency</th>
<th>Size</th>
<th>Vitality Test</th>
<th>Treatment</th>
<th>Recurrence</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neville et al, 1984 (16)</td>
<td>59</td>
<td>M</td>
<td>between the mandibular left canine and first premolar</td>
<td>buccal expansion</td>
<td>well-circumscribed radiolucency</td>
<td>2 × 1 cm</td>
<td>No Data (ND)</td>
<td>curettage</td>
<td>postoperative 2 years</td>
<td>ND</td>
</tr>
<tr>
<td>Nohl and Gulabival, 1996 (9)</td>
<td>38</td>
<td>M</td>
<td>between mandibular lateral incisor and canine (Bilaterally)</td>
<td>no complaints except poor esthetics of her bridge</td>
<td>unilocular, well circumscribed radiolucencies</td>
<td>5 mm</td>
<td>ND</td>
<td>curettage</td>
<td>No</td>
<td>5 month</td>
</tr>
<tr>
<td>Hiremath et al, 2011 (27)</td>
<td>45</td>
<td>F</td>
<td>between the mandibular left first and second premolars</td>
<td>swelling</td>
<td>round radiolucency with a radiopaque margin</td>
<td>1 cm</td>
<td>both teeth positive</td>
<td>curettage</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Bojan et al, 2015 (5)</td>
<td>20</td>
<td>M</td>
<td>between the right premolars</td>
<td>swelling</td>
<td>pear-shaped radiolucency</td>
<td>1 cm</td>
<td>both teeth positive</td>
<td>enucleation</td>
<td>ND</td>
<td>1 month</td>
</tr>
</tbody>
</table>
Woolgar et al [22] suggested 3 different mechanisms that may clarify the high recurrence rate in KCOT: incomplete removal of the cyst lining, growth of a new KCOT from small satellite cysts, or odontogenic epithelial rests left behind after surgical treatment and the development of a new KCOT in an adjacent region which is interpreted as a recurrence. Moreover some histological findings of KCOT; presence of 1 or more daughter cysts [1] and the budding of the basal layer of the epithelial lining [23] have found related with high recurrence.

Limited number of studies investigated the relationship between cell proliferative markers and recurrence in the KCOT. The study of Kuruyanagi et al [24] showed that recurrent KCOTs have higher expression of Ki-67 in the basal layer. Also in the research of Selvi et al [25] recurrent KCOTs demonstrated higher expression of Ki-67 and AgNOR count comparing to non-recurrent lesions. Although both studies advocated that the assessment of Ki-67 expression in KCOT during the histopathological diagnosis might be beneficial for the consideration of additional surgical procedures to avoid recurrence and useful as a prognostic marker [24, 25], Li et al [26] found no significant difference between recurrent KCOTs and nonrecurrent KCOTs with respect to the expression of Ki-67.

KCOTs simulating cystic jaw lesions were reported by several studies published in previous years [5, 6, 9, 15, 16, 27]. Our review identified 4 detailed cases of KCOT mimicking lateral periodontal cyst, which are presented in Table 1. Besides these cases in the study of Ali and Baughman [6] 15 KCOT cases in the maxillary canine region were provisionally diagnosed as lateral periodontal cyst. Also Neville et al [15] reported 18 anterior midline maxillary odontogenic keratocyst cases that seven of those were clinically diagnosed as nasopalatine duct cyst before histopathologic examination.

In the present study, we described two rare cases of KCOT. The first case was developed between mandibular premolar roots mimicking lateral periodontal cyst, the second case was located midline of anterior palatal region simulating nasopalatine duct cyst. Because the KCOT involves almost 11% of all cysts in the maxillofacial region [28], this lesion should be always considered in the differential diagnosis of the cystic jaw lesions. In case 1; patient was asymptomatic and the orthopantomographic radiograph exhibited an unilocular radiolucency between the right mandibular premolars; neither root displacement nor root resorption was observed. Owing to lateral periodontal cysts frequently located adjacent or lateral to the root of a vital tooth in the mandibular premolar region [29], our provisional diagnosis was lateral periodontal cyst. In case 2; patient complained of spontaneous pain and swelling in anterior maxilla. The orthopantomographic radiograph revealed unilocular, well-circumscribed, heart-shaped radiolucent lesion located midline of anterior palatal region which was compatible with nasopalatine duct cyst. Although in the second case an aspiration biopsy was done, in both cases our treatment plan based on the radiographic impression and due to the small size of the cysts preoperative incisional biopsy was not performed. The complication in radiographically differentiating between KCOT and any other cystic jaw lesions was affirmed in our study and another studies also in agreement with this knowledge [1, 30]. Lateral periodontal cyst and nasopalatine duct cyst can be certainly differentiated from KCOT histopathologically. Microscopically lateral periodontal cyst is lined by a thin nonkeratinizing squamous or cuboidal epithelium and usually cyst wall lacks inflammatory cell infiltrate [31]. Histologically nasopalatine duct cyst may show a combination of stratified squamous epithelium, pseudostratified columnar epithelium with or without cilia and goblet cells, simple columnar and simple cuboidal epithelium. Also the wall of cyst may contain some nerve bundles and blood vessels as well as the glandular structures [32, 33]. Likewise, the classic histopathologic features of the KCOT are distinctive, but may be altered by inflammation. The epithelium of KCOT is also distinctive for a well-defined, palisaded basal layer of hyperchromatic columnar of cuboidal cells. The luminal surface displays wavy parakeratotic epithelial cells and is frequently described as corrugated. Finally, the cystic cavity may contain keratinaceous material [34].

The conservative treatment for this pathology includes marsupialization, decompression, enucleation, and curettage. More aggressive approach is based on osteotomy, lesion resection, use of chemical agents like Carnoy’s solution, cryotherapy with liquid nitrogen or peripheral
osteotomy [35]. The type of treatment depends on innumerable factors including: (i) localization and size of the lesion; (ii) patient age; (iii) or whether the KCOT is recurrent or primary [36]. Pogrel et al [37] in an attempt to reduce the KCOT recurrence rate, established a protocol including bone osteotomy, 1-2 mm beyond the postenucleation cystic margin with methylene blue staining, aiming to remove any remnants of cystic epithelium. However, this technique is often considered invasive especially if involves large cystic extensions and anatomical structures, leading to paresthesia, and sinus complications. Clinicians should select the best treatment modality that associates with the lowest possible risk of recurrence and minimum morbidity [2, 10, 11]. In our cases, because of the diagnosis of KCOT was not suspected at the time of surgery along with the small size of the lesions, they were excised totally including curettage as conventional cyst treatment but without chemical adjuvant therapy or cryosurgery. The majority of recurrences develop during the first 5 years after treatment [10, 38-40], but yet few studies have reported recurrences that occur 9 or more years after the initial treatment [41-43]. Nevertheless our follow up periods in both cases were very short (first case 24 months, second case 12 months) both patients are still under routine control in our institution.

Because the timing of recurrence is indefinite in KCOT, irrespective of treatment modality, clinical and radiographic follow-up is compulsory for an indeterminate time after surgery [8, 11].

**Conclusion**

The knowledge acquired through these present cases, KCOTs can commonly mistaken for oral cystic lesions. The clinical and radiographic findings are not distinctive enough to make an accurate diagnosis of any lesion occurring in the jaws. By the reason of high recurrence rate and aggressive behavior of KCOT; all excised tissues should be submitted for histopathological examination to confirm the type of lesion and to differentiate other pathologic conditions which will ensure necessary treatment and further procedures. Also irrespective of the treatment choice, long term follow-up mandatory, because recurrence may occur after several years following initial intervention.

Recently genetic and molecular researches have enlightened our understanding of KCOT's nature and behavior. Even though prognostic factors related to recurrence of this benign neoplasm still remain ambiguous, in the future with more precise knowledge of KCOT will doubtless provide more effective treatment modalities.

**Disclosure of conflict of interest**

None.

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