Case Report

Incidental finding of orthokeratinized odontogenic cyst with unusual features

D B Nandini, T Premlata Devi[1], B S Deepak[1], Ngairangbam Sanjeeta

Departments of Oral Pathology and Microbiology, [1]Conservative Dentistry and Endodontics Dental College, Regional Institute of Medical Sciences, Imphal, Manipur, India

Abstract

Orthokeratinized odontogenic cyst (OOC) is a rare developmental odontogenic cyst occurring in the jaw with debated etiology. It was originally believed to be a variant of odontogenic keratocyst (OKC) but is now considered to be a distinct entity. The majority of the cases occur in the third and fourth decades of life. The common site is the mandibular posterior region with a male predilection. Swelling is the most common symptom which may be accompanied by pain, although in most cases, the lesion is asymptomatic. These lesions mostly present as unilocular radiolucency often associated with an impacted tooth. They may mimic dentigerous cyst and OKC in radiologic and histopathologic presentation, however, differ in biological behavior, pathogenesis and prognosis in comparison. Hence, making an accurate diagnosis is essential. This article describes an incidental finding of OOC in a 28-year-old female during radiographic investigation for orthodontic treatment. This case showed some rare features such as multilocular radiolucency, nonkeratinized epithelium in areas of inflammation, few cholesterol clefts with giant cells, presence of dentinoid-like material and dystrophic calcification in the capsule.

Keywords: Calcification, dentinoid, differential diagnosis, etiology, histopathology, inflammation, orthokeratinized odontogenic cyst, radiographic features

Address for correspondence: Dr. D B Nandini, Department of Oral Pathology and Microbiology, Dental College, Regional Institute of Medical Sciences, Imphal, Manipur, India.
E-mail: nannidb29@gmail.com

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INTRODUCTION

Orthokeratinized odontogenic cyst (OOC) is a rare type of odontogenic cyst, which shows an orthokeratinized stratified squamous epithelium. It was originally considered as a type of odontogenic keratocyst (OKC) but later identified as separate entity. There are subtle histological differences between OOC and OKC which confirms the diagnosis. OOC radiographically mimics dentigerous cyst which can confound the final diagnosis. We report a case of OOC which was incidentally detected with multilocular appearance in radiograph and unique histopathology.

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CASE REPORT

A 28-year-old female patient came for orthodontic correction of malposed teeth. Routine radiographic examination was advised to evaluate the status of dentition. The orthopantomogram (OPG) revealed a well-defined multilocular radiolucency with a sclerotic border in the

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right molar ramus region of the mandible distal to the impacted third molar [Figure 1]. There was no other associated symptom such as swelling or pain clinically. The extraoral examination revealed no facial asymmetry. Blood investigations were normal. Fine-needle aspiration cytology was not contributory. Based on the clinical and radiographic evaluation, a preliminary diagnosis of an odontogenic keratocyst (OKC) or a benign odontogenic tumor was made. An excisional biopsy was performed with the extraction of the impacted tooth and the specimen was sent for histopathological examination.

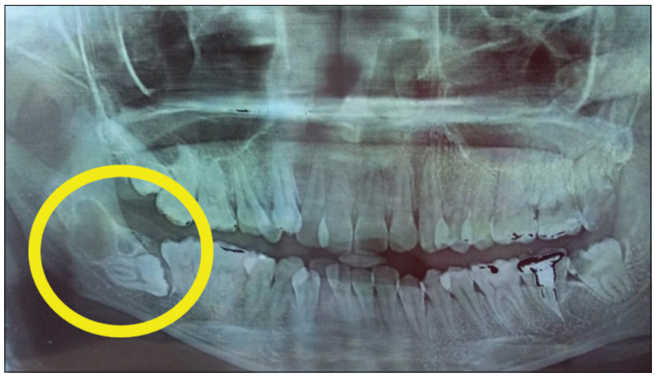

Figure 1: Orthopantomogram showing a well-defined multilocular radiolucency with sclerotic border in the right molar-ramus region of the mandible distal to the impacted third molar

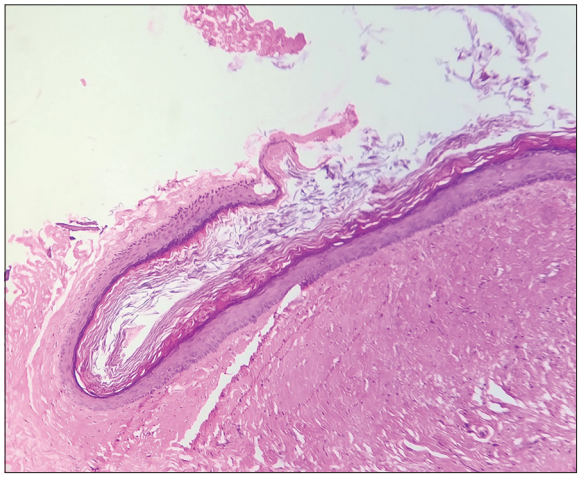

Figure 2: A cystic lesion with epithelial lining and fibrous connective tissue capsule (H & E, ×4)

Gross examination of the specimen revealed a cystic lesion measuring about 2 cm × 3 cm × 2 cm in size and grayish . The cystic lumen was smooth and contained white cheesy material. The histopathologic examination of the tissue section revealed a cystic lesion with epithelial lining and fibrous connective tissue capsule [Figure 2]. The epithelium revealed thin, uniform orthokeratinized stratified squamous epithelium with a prominent granular cell layer with a flat basement membrane [Figure 3a]. Orthokeratin flakes were seen on the surface epithelium and in the cystic lumen. The basal cells were low cuboidal to flattened without nuclear palisading, hyperchromatism and reversal of polarity [Figure 3b]. The epithelium was nonkeratinized in few areas of inflammation [Figure 3c]. The fibrous capsule showed dense collagen bundles, few chronic inflammatory cells, cholesterol clefts and giant cells [Figure 4a], hemosiderin pigments [Figure 4b], dystrophic calcification [Figure 4c] and dentinoid-like material focally [Figure 4d]. This led to the confirmation of the diagnosis of orthokeratinized odontogenic cyst (OOC).

DISCUSSION

The OOC is a rare developmental cyst of odontogenic origin. It was first described by Schultz in 1927 as a dermoid cyst.[1] In 1945, Philipsen considered it as an orthokeratinized variant of OKC.[2] In 1981, Wright defined it as a separate entity.[3] In 2005, the WHO redefined OKC as a neoplasm and termed it as keratocystic odontogenic tumor (KCOT) while OOC was considered a separate entity.[4,5] OOC differs in many aspects from the other developmental odontogenic cysts, especially dentigerous cyst and OKC.[6]

Pathogenesis

The pathogenesis of OOC is still uncertain. Many origins are suggested such as cell rests of dental lamina, oral epithelium influenced by dental papilla and reduced enamel

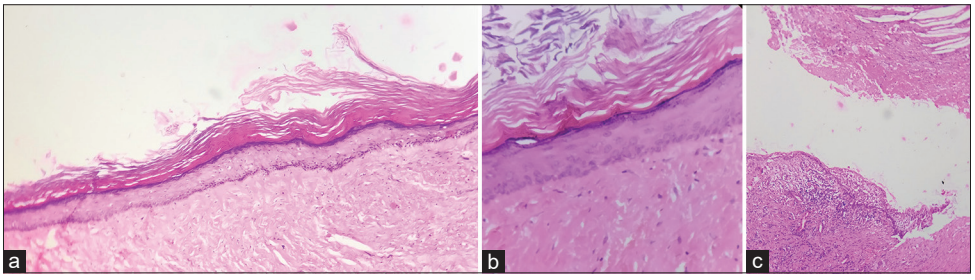

Figure 3: The epithelium revealed uniform orthokeratinized stratified squamous epithelium with a prominent granular cell layer (a: H & E, ×10). The surface showed sheaves of orthokeratin and keratin flakes were present in the cystic lumen. The basal cells were low cuboidal to flattened without nuclear palisading, hyperchromatism and reversal of polarity (b: H & E, ×20). Epithelium was nonkeratinized in few areas of inflammation (c: H & E, ×10)

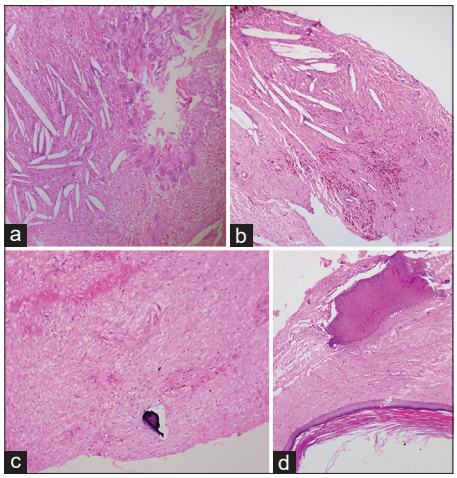

Figure 4: Fibrous capsule showed dense collagen bundles, few chronic inflammatory cells, cholesterol clefts and giant cells (a: H & E, ×10), hemosiderin pigments (b: H & E, ×10), dystrophic calcification (c: H & E, ×4) and dentinoid-like material focally (d: H & E, ×4)

epithelium.[7,8] The attachment of the cystic lining to the neck of the tooth prompted to contemplate the origin in reduced enamel epithelium. It was suggested that the reduced enamel epithelium surrounding the impacted tooth might keratinize under some stimulus owing to its pluripotent nature, thus forming a true dentigerous cyst with orthokeratinization.[9] They also raised the possibility that OOC could be a central epidermoid cyst.

Prevalence

The precise incidence of OOC is not clear and complicated as they were first considered an orthokeratinized variant of OKC. They have previously been accounted for 10% of OKCs.[6] There is conflicting documentation of occurrence ranging from 3% to 11%[10] by some authors and 5.2%–16.8% by others.[3] They make 1% of all odontogenic cysts. It represents 7%–17% of all the keratinizing jaw cysts.[6]

Clinical features

OOCs are common in the third and fourth decades. Males are more commonly affected (2–2.5:1).[5,6] Dong *et al.* found a higher incidence among females (ratio 2.59:1).[11] The mandible is affected twice more commonly than the maxilla.[10] The molar and ramus region is the more commonly involved site. About 46.5%–75% of OOCs are associated with an impacted tooth, especially the third molars, which appear radiographically similar to the dentigerous cyst.[12]

The majority of cases are asymptomatic and are often detected incidentally during radiographic investigation for other problems. Some may present as swelling with or without pain or mobility of teeth.[5,6,13,14] Rarely aggressive OOC reaching large size causing cortical expansion, malocclusion, facial asymmetry and paresthesia has been reported.[11,13] The size might vary from <1 cm–7 cm.[6]

OOCs are usually unilateral, however, few bilateral cases and cases with multiple cysts, cases occurring in siblings have also been reported.[14,15] At present, however, there is no convincing evidence to link multiple OOCs to nevoid basal cell carcinoma syndrome (NBCC) or Gardner syndrome.[10,14]

Some rare forms of OOC include peripheral OOC, OOC histologically associated with calcifying odontogenic cyst, ameloblastoma, complex odontoma, squamous cell carcinoma, verrucous carcinoma, cuniculatum carcinoma and combined OOC and OKC in a patient with Gardner syndrome, heterotopic cartilage, dentinoid and bilateral OOC.[15-24]

Radiographic features

Most cases appear as a well-circumscribed unilocular radiolucency and while multilocular radiolucencies[25] are rarely seen as in the present case. They may be associated with an unerupted tooth or the tooth root without causing resorption. Some may displace the neighboring teeth and the inferior dental canal too. The cortical bone expansion rate is larger than that of OKC.[25] Few reports of OOC mimicking periapical lesions have been reported.[26] A systematic review, however, revealed that 48% of OOC presented as incidental findings, with a slightly lower percentage presenting with swelling (41%).[27] The present case was also diagnosed incidentally during radiographic evaluation for orthodontic treatment. As many of the cases are incidental findings, careful assessment of all routine radiographs, especially OPGs, is essential to diagnose any unknown pathology. Nevertheless, OOC should be taken into account in the differential diagnosis of radiolucencies associated with an impacted tooth.

Histopathologic features

OOC shows a cystic cavity lined by orthokeratinized stratified squamous epithelium. The epithelial lining is usually thin and uniform, 4–9 cell layers thick with a prominent granular cell layer. The basal layer is made up of low cuboidal to flattened cells without nuclear palisading or hyperchromatism and reversal of polarity. The orthokeratin in the luminal surface shows an "onion skin appearance" with sheaves of orthokeratin.[10] The lining may be nonkeratinized in case of inflammation which was evident in the present case.[10] A mild verrucous appearance of the surface epithelium has also been reported.[14] The fibrous capsule is made up of collagenous

fibrous connective tissue, usually with no inflammation. If the cyst is infected secondarily, few chronic inflammatory cells such as lymphocytes, foamy histiocytes, occasional cholesterol clefts and hemosiderin deposits may be seen. Dystrophic calcifications are reported rarely. Hyalinization with abundant areas of eosinophilic globular structures resembling dentinoid is also reported.[23] These features have been reported in individual cases, however, the present case revealed most of these varied histologic features. Inflammation may obscure the histology and careful analysis of the noninflamed areas is required to arrive at an accurate diagnosis. The unusual histopathological findings such as lichenoid changes and basilar hyperplasia have been reported by some authors.[28]

Immunohistochemistry and special stains

Reduced expression of all these markers of Ki-67 and syndecan-1 proliferative index, p63 and bcl-2.[10,29] OOC does not show the activity of epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) unlike OKC.[29] OOC stains to cytokeratin 1, 2 and 10 and Loricin (LOR) suggesting a normal pattern of epithelial differentiation while OKC reacts to cytokeratin 4, 13, 17 and 19 showing immature keratinocytes and altered differentiation.[6] The positive expression of K2 and LOR in OOC indicated that the cells are in a completely differentiated stage and thus not aggressive in behavior. OOC significantly differs from OKC not only in its lining epithelium but also in its proliferating kinetics, clinical and biologic behavior, immunohistochemical profile and prognosis [Table 1].

Significant differences in polarization color were demonstrated in the subepithelial zones between OKC (greenish-yellow birefringence) and OOC (yellow or orange-red birefringence suggesting mature collagen) by a study conducted by Manthapuri *et al*.[30]

Differential diagnosis

Radiographic differential diagnosis of OOC should include dentigerous cyst (cyst attached to the neck of the impacted tooth, unilocular and root resorption is often seen), paradental cyst (not associated with impacted tooth), OKC [Table 1], ameloblastoma (more often multilocular which often shows resorption of roots) and radicular cyst (seen as periapical radiolucency and the associated tooth is nonvital). The histologic examination gives a final diagnosis. The histologic differential diagnosis of OOC should include epidermoid cyst (usually a soft tissue lesion and intraosseous occurrence is rare) and OKC [Table 1].

Treatment and recurrence

Conservative surgical removal with complete enucleation and curettage is the treatment of choice. The cyst rarely shows recurrence after treatment. 2.2% recurrence rate is reported by Crowley *et al*.,[31] while 4% recurrence is reported by González *et al*.[5] Chronic progression of recurrent OOC into squamous cell carcinoma is reported by Wu *et al*.[32]

Malignant potential

The malignant potential of the epithelial lining of OOC is

Table 1: Difference between orthokeratinized odontogenic cyst and odontogenic keratocyst

OOC	OKC
Less aggressive clinical behavior	Aggressive clinical behavior comparatively
Generally solitary, asymptomatic, often associated with impacted teeth	Can occur at multiple sites, often symptomatic, usually not associated with impacted tooth
Not associated with any syndromes	Associated with syndromes such as nevoid basal cell carcinoma syndrome
Radiographically appear as unilocular radiolucency in majority of cases. Very rarely multilocular	Often appear as multilocular radiolucency
Histologically	Histologically
Epithelium is thin and uniform orthokeratinized	Epithelium is thick, uniform, parakeratinized
Basal cells are flat to cuboidal without evidence of palisading, or reverse polarization and hyperchromatism	Basal cells are tall columnar showing palisading nuclei with reversal of polarity and hyperchromatism
Low mitotic index	High mitotic index
Fully differentiated mature keratinocytes	Lack mature keratinocytes
Epithelial cells have less proliferative and self-renewal potential	Epithelial cells have more proliferative and self-renewal potential
Pattern of normal cellular differentiation	Alterations in the differentiation process
Keratin profile in OOC identical to that of epidermis	Keratin profile similar to dental lamina
K1, K10 and LOR expression was strongly positive	K4, K13 and K17 expression was strongly positive
Stable stroma, the presence of dystrophic calcification, cartilage, dentinoid	Show diffuse and focal epithelial hyperplasia, epithelial budding, reactive cytological alterations, dystrophic calcification, daughter cysts, odontogenic epithelial remnants and ameloblastomatous epithelium
Daughter cysts and odontogenic epithelial remnants are absent	
Treatment: conservative surgical excision	Controversial treatment options: Decompression, enucleation and curettage followed by application of Carnoy's solution, surgical resection
Recurrence is rare	Recurrence is common
Convincing evidence for malignant transformation is lacking	Shows loss of heterozygosity in relation to PTCH gene and may progress to malignancy

OOC: Orthokeratinized odontogenic cyst, LOR: Loricrin, OKC: Odontogenic keratocyst

debatable. Convincing evidence is lacking. Some suggested triggering factors include chronic inflammation, genetic mutations in exon 6 of the TP53 gene, or oncogenic viral effects.[33] No role of human papillomavirus in OOCs was observed in a study conducted by Vera-Sierra *et al*.[33]

CONCLUSION

OOC is a rare developmental odontogenic cyst. Although the histopathologic features are well defined, knowledge about the etiopathogenesis and clinical behavior is still lacking and yet to be explored at a molecular level. OOCs are common in males and usually show unilocular radiolucency. The present case was seen in a female patient and showed some rare features such as multilocular radiolucency, nonkeratinized epithelium in areas of inflammation, presence of cholesterol clefts, giant cells, dentinoid-like material and dystrophic calcification in the capsule. OOCs should be considered in the differential diagnosis of both unilocular and multilocular radiolucencies, especially in the molar-ramus region of the mandible. It is of utmost importance to differentiate OOC from OKC since the latter differs in its clinical behavior, treatment and prognosis. Further research is needed to explore the biological behavior of these cysts.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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