Case Report

Odontogenic keratocyst with granular cell changes: A distinctive finding

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Abstract

Odontogenic keratocyst (OKC) originates from the dental lamina and is more commonly seen in the posterior mandible than in the maxilla. OKC is the most aggressive cyst of the oral cavity and is known for its rapid growth and its tendency to invade bone of the adjacent tissues. The recurrence rate of OKC is very high due to various reasons debated upon. Cases of OKC have shown the presence of calcifications, dentinoid formation and ossification. Here, we report the first case of OKC in a 27-year-old male showing granular cell changes.

Keywords: Granular cells and granules, keratocystic odontogenic tumor, lysosomes, odontogenic keratocyst

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INTRODUCTION

Philipsen, in 1956, first used the term odontogenic keratocyst (OKC). It is known to be one of the most aggressive odontogenic cysts. It has the tendency to invade the adjacent tissues including bone and is known for its rapid growth.[1] It is a unique pathological entity characterized by destructive behavior and propensity for recurrence. Since its introduction in 1956, the word OKC has been under a lot of debates. The World Health Organization (WHO) reclassified this entity in 2005 as keratocystic odontogenic tumor (KCOT).[2]

The WHO consensus group concluded again in 2018 that "OKC" remains the most appropriate name for this lesion.[3]

It was defined by the WHO as "a benign uni- or multicystic intraosseous tumor of odontogenic origin with a characteristic lining of parakeratinized stratified squamous epithelium and potentially aggressive, infiltrative behavior."[2] OKC originates from the remnants of dental lamina.[1,4] It is consistently found in nevoid basal cell carcinoma syndrome or Gorlin and Goltz syndrome.[5] Unusual cases of parakeratinized cysts in the skin, facial soft tissues, muscles of mastication and also temporomandibular joint which are similar to intraosseous OKC histopathologically, have been reported.[6] Although a search of the English literature showed that this is the first reported case of OKC with granular cell changes.[6]

CASE REPORT

A 27-year-old male patient complained of a swelling in the anterior mandibular region. The swelling was firm in consistency. The overlying mucosa was normal. The patient gave a history of intermittent pain for the past 6 months. There was no history of trauma or any kind of discharge.

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There was no evidence of submental or submandibular lymphadenopathy.

Radiograph revealed a large unilocular radiolucency with ill-defined borders extending from the left canine to the right canine region and root resorption of the incisors within the anterior mandibular area.

The differential diagnosis thought of was either of central giant cell granulomas, odontogenic tumors or mesenchymal tumors. Further investigations were mandatory.

Histopathology

On microscopic examination, the tissue section showed a cystic lesion lined by parakeratinized stratified squamous epithelium of 6–10 cell layers in thickness exhibiting surface corrugations. The basal cells were predominantly columnar in shape, with hyperchromatic nuclei exhibiting palisading [Figures 1 and 2]. At few areas, basal cell hyperplasia was evident. Epithelial infoldings were also seen. The interface between the epithelium and the connective tissue wall was flat and showed the epithelium stripped away from the connective tissue [Figures 1 and 2] which is known to be due to lack of rete ridges.

The underlying connective tissue wall showed numerous satellite cysts [Figure 3] with marked transformation of the centrally placed cells within the cystic spaces. Few of the satellite cysts revealed cells which were polyhedral, with distinct cellular outlines, granular eosinophilic cytoplasm and hyperchromatic nucleus. These cells are suggestive of a granular cell change [Figure 4]. Degeneration of the granular cells was also visible. Abundant keratin formation

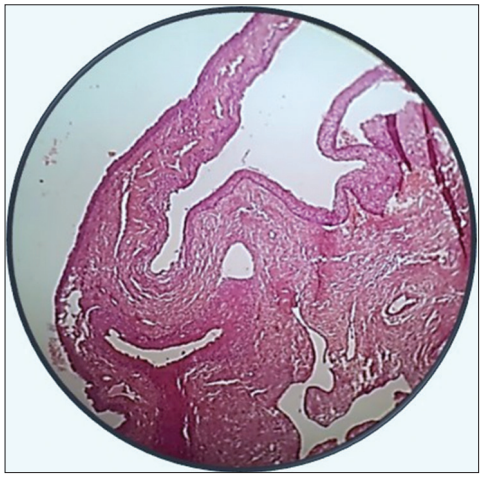

Figure 1: Low-power view of the odontogenic epithelium with corrugations and cystic cavity

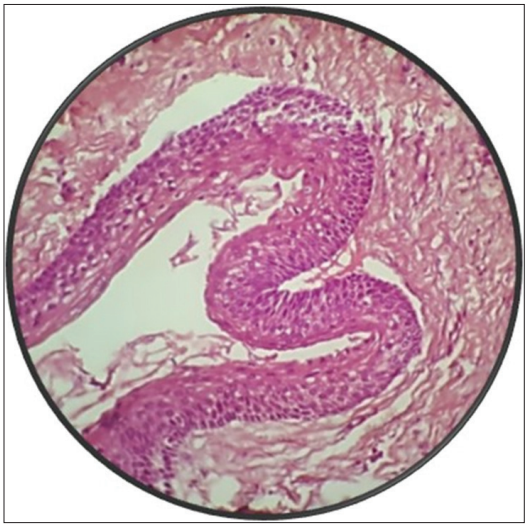

Figure 2: High-power view showing 4–6 cell layers of the epithelium with palisaded basal layer of cells and separation of the connective tissue from the epithelium

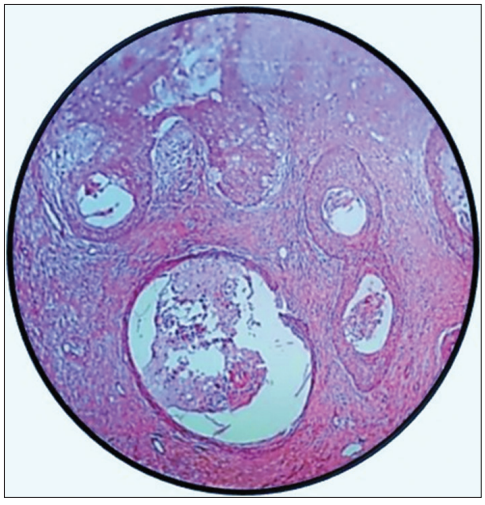

Figure 3: Odontogenic keratocyst showing satellite cysts

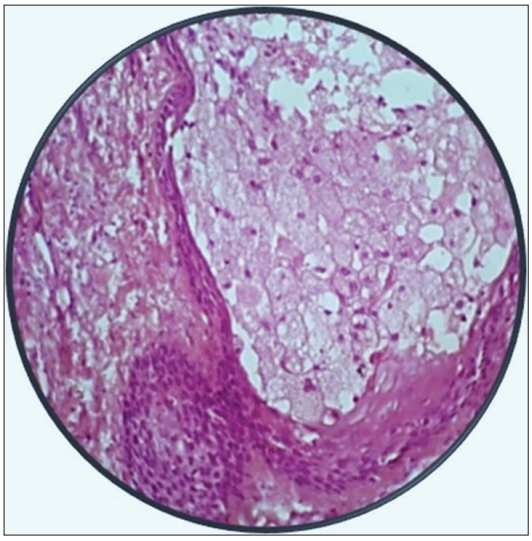

Figure 4: High power view showing polyhedral cells with distinct outline, cytoplasm packed with eosinophilic granules and hyperchromatic nucleus suggestive of granular cell change

was noted. Few inflammatory cells, predominantly neutrophils, few eosinophils, lymphocytes and plasma cells along with mast cells, were evident in various areas. Calcification was also seen at a few places [Figure 5].

Cystic lining and satellite cysts along with granular cells of the lesional tissue were observed in the same field [Figure 6].

The intervening stroma was fibrous with collagen arranged in the form of fibers and bundles associated with fibroblasts and fibrocytes, endothelial-lined blood capillaries and mast cells. Areas of hemorrhage and degeneration were evident.

On the basis of histopathological examination, the diagnosis of OKC with granular cell changes was made.

Immunohistochemical analysis was carried out for this lesion. Cytokeratin positivity was seen in the odontogenic epithelium and granular cells [Figure 7]. This confirmed the epithelial origin of the granular cells. Granular cells also showed positivity for CD68 [Figure 8]. Stromal cells were positive for vimentin [Figure 9].

Granules within the lesional tissue were positive for periodic acid–Schiff stain at few places [Figure 10].

DISCUSSION

OKC originates from the dental lamina remnants before odontogenesis is complete and may also originate from the basal cells of the overlying epithelium. It arises within the mandible or maxilla.[7]

Their pathognomonic microscopic features, potentially aggressive clinical behavior and high recurrence rate make OKC unique among odontogenic cysts.[8]

In 1956, Philipsen, working with Jens J Pindborg, described it as the "OKC." The term "keratocyst" was used to

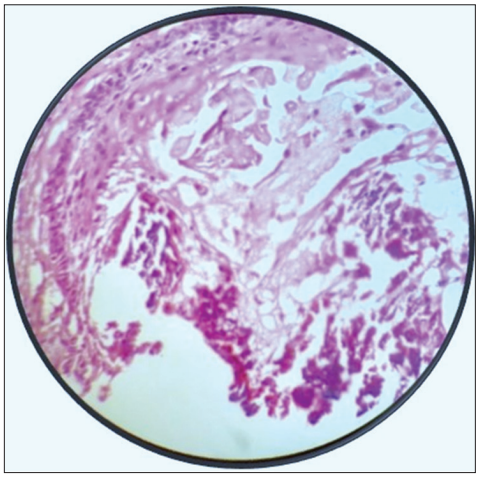

Figure 5: Calcifications seen beneath the odontogenic epithelium

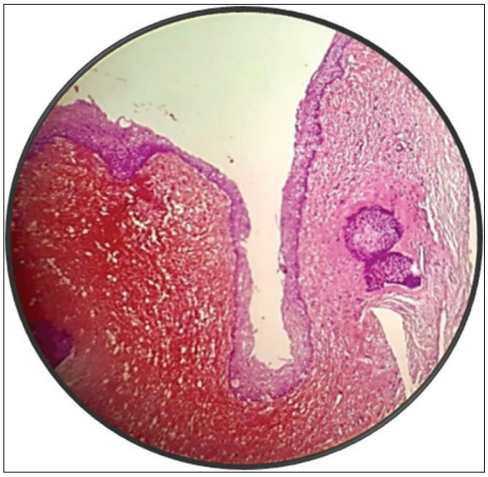

Figure 6: Cystic lining, satellite cysts showing cells with granular cytoplasm in the lesional tissue

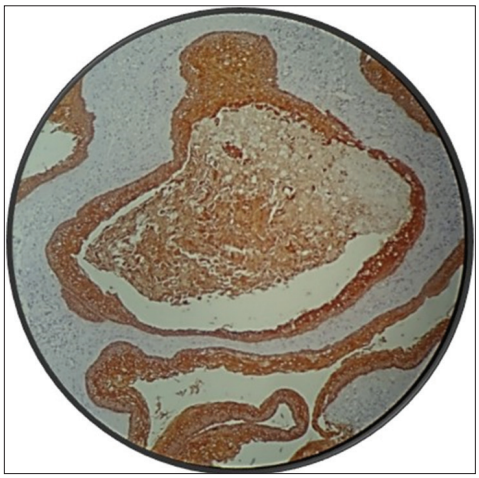

Figure 7: Cytokeratin positivity in odontogenic epithelium and cells with granular changes

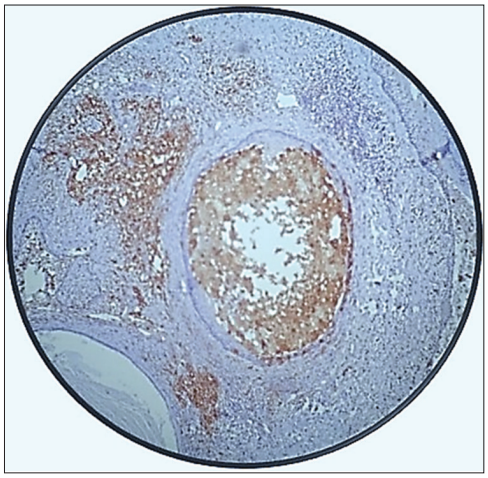

Figure 8: CD 68 positivity seen in cells with granular cytoplasm

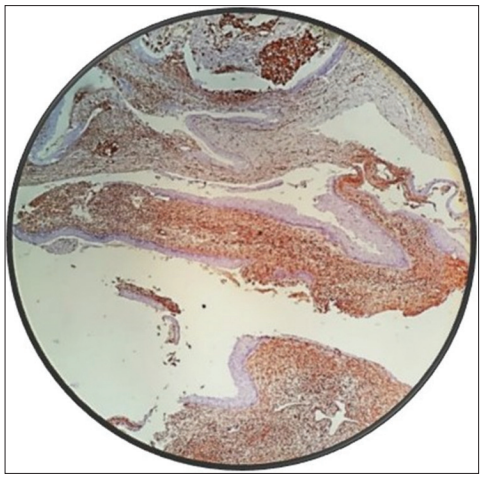

Figure 9: Vimentin positivity in the stromal cells

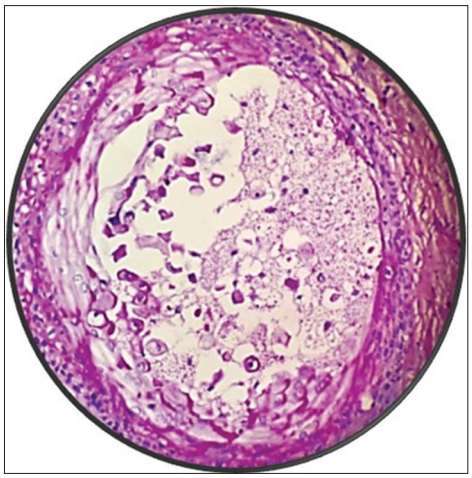

Figure 10: Granules showing Per-iodic acid Schiff's stain (PAS) positivity

represent any jaw cyst in which keratin was formed in a large amount. Pindborg and Hansen in 1962 suggested the histological criteria for the diagnosis of OKC.[9]

The WHO reclassified this lesion as KCOT in 2005 and defined it as "A benign unicystic or multicystic, intraosseous tumour of odontogenic origin with a characteristic lining of parakeratinised stratified squamous epithelium and potential for aggressive infiltrative behaviour."[9]

Again in 2018, The WHO consensus group concluded that "OKC" remains the most appropriate name for this lesion and deleted KCOT from the classification of cysts.[3]

It is commonly found in the mandibular ramus area and angle of the mandible and makes approximately 11% of all cysts in the maxillofacial region.[9]

OKC has a high recurrence rate of 16%–30% and is well known for its rapid expansion and its tendency to invade the neighboring tissues including bone.[10]

OKC does not show characteristic clinical and radiographic features which may lead to misdiagnosis, especially when the cyst is in association with a nonvital tooth.[11]

It has the tendency to expand in an anteroposterior direction within the medullary cavity of the bone and does not cause obvious buccolingual expansion.[11]

Radiographically, it presents as a well-defined radiolucency with thin, corticated margins. Majority of the lesions are unilocular, but larger lesions may be multilocular. Around 20%–40% of OKCs are seen in association with an unerupted tooth and can be similar to a dentigerous cyst in appearance. Root resorption is relatively uncommon.[12] Due to its keratin content, the cystic lumen may be cloudy.[2] Some have stated that the radiographic findings of the lesion are not diagnostic but are highly suggestive of OKC.[1]

The histopathological findings of OKC are typical and characteristic. It includes stratified squamous parakeratinized epithelium which is corrugated, uniform and 4–8 cell layers in thickness. There is a tendency of the epithelium to detach from the underlying connective tissue, as the epithelium and the fibrous tissue junction are devoid of rete ridges. The fibrous capsule is thin and lacks inflammatory infiltrate.[7]

In 1992, the WHO classified OKC histologically into three variants: (a) parakeratinized, (b) orthokeratinized and (c) combination of the two. The parakeratinised variant of OKC was many a times associated with nevoid basal cell carcinoma.[13] The other contents of the syndrome are basal cell carcinomas and skeletal, dental and ocular anomalies.

Basal cells are cuboidal in shape showing palisaded arrangement with polarized and hyperchromatic nuclei of uniform size. The capsule is friable and thin. Expression of Ki-67 or p53 as growth markers is observed in the suprabasilar epithelium.[3]

Most of the cases studied microscopically showed at least focal areas of classic OKC, but different histological aspects were also seen which include diffuse and focal epithelial lining hyperplasia (48.6%), epithelial budding (12.4%), reactive cytological alterations (11.3%), dystrophic calcification (7.9%), daughter cysts (7.8%), odontogenic epithelial remnants (4.5%), focal areas of orthokeratinization (2.8%) and ameloblastomatous epithelium (1.7%). This made the diagnosis of OKC challenging in some cases, so understanding of these

unusual histological features associated with OKC and careful analysis is essential for correct diagnosis.[14]

Hard tissue formation in the wall of this cyst is an uncommon finding. It is generally seen in the form of dystrophic calcifications, dentinoid or cartilaginous tissue.[15]

Molecular pathogenesis of OKC shows that the gene involved in both sporadic OKC and the associated syndrome is present on chromosome 9q22.3-q31.36–40. Patched (PTCH) is a tumor suppressor gene. PTCH binding to smoothened (SMO) inhibits growth-signal transduction. If normal functioning of PTCH is lost, the proliferation-stimulating effects of SMO are permitted to predominate.[8]

Different theories are put forth for the expansion of OKC, which include active epithelial proliferation, intraluminal hyperosmolality, collagenolytic activity of the cyst wall and synthesis of interleukin-1 and interleukin-6 by the keratinocytes.[9]

Variants of OKC showing dentinoid formation, calcifications and peripheral types are reported.

- Ng and Siar in 2003 reported a case of OKC with dentinoid formation[16]
- Naveen *et al*. in 2011 reported a maxillary KCOT with calcifications[15]
- Vij *et al*. in 2011 reported a peripheral variant of OKC[17]
- Shetty and Srilatha in 2013 reported a KCOT with mural calcification[18]
- Soumya *et al*. in 2015 reported a large extragnathic KCOT[6]
- Gotmare *et al*. in 2016 reported a case of KCOT showing ossification and calcification[19]
- Palakshappa *et al*. in 2016 reported extensive mural calcifications in the wall of KCOT[20]
- Bajpai *et al*. in 2017 reported a rare case of orthokeratinized odontogenic cyst with dentinoid formation.[21]

Probable reasons for granular changes to occur in granular cell lesions are noted here as follows: (1) aging or degenerating process and (2) with age, unnecessary or aged components in the cytoplasm of some tumor cells become more numerous, but the capacity to digest these materials decreases with age, and hence, the cytoplasm of tumor cells is packed with lysosomal granules.[22,23]

In the present case, this theory may not play any role as the individual is young. Possibility of granularity being seen here could be due to a long-standing lesion, without obvious clinical symptoms.

Granular cells immunohistochemically show positivity for CD68, lysozyme and cytokeratins. They are negative for vimentin, desmin, S-100, neuron-specific enolase and CD15, indicating that cytoplasmic lysosomal aggregates are of epithelial origin and not of mesenchymal, myogenic or neurogenic origin.[24]

Different granular cells are seen in physiological states such as enamel organ of developing teeth, ameloblasts during amelogenesis, odontogenic epithelial oxyphils in the parathyroid, oncocytes in the salivary glands and Hurthle or Askanazy cells in the thyroid.[25]

The granular cells seen in pathologic states are granular cells in granular cell ameloblastoma, granular cell myoblastoma, granular cell odontogenic fibroma, congenital epulis of newborn, congenital gingival granular cell tumor, granular cell leiomyoma (very rare), granular cell basal cell carcinoma and calcifying epithelial odontogenic tumor. The granularity in these lesions is due to aggregated mitochondria, lysosomes and polyribosomes.[25]

Electron microscopy of granular cells has been suggested that the cytoplasmic granules measure about 0.6 μ (0.4–1.4 μ) in diameter. They are surrounded by a limiting membrane. Most of these granules have high electron density and are osmiophilic, exhibiting various patterns (pleomorphic) and are identified as lysosomes. The various patterns described in granular cells are homogenous, myelin figures, fingerprint pattern and few cells packed with minute vesicles.[25]

In the case reported here, the granular cells seen are highly suggestive of lysosomal aggregation.

Lysosomes are organelles that contain digestive (acid hydrolyzes) enzymes and thus digest excess or worn-out organelles, food particles and engulfed viruses or bacteria, resulting in quality control and self-adaptation. They have emerged as sophisticated signaling centers that govern cell growth, division and differentiation. Faulty execution of lysosomal growth and catabolic programs may lead to such granular change.[26]

CONCLUSION

This is the first case of OKC with granular cell changes in the anterior mandibular area in a 27-year-old male individual. The anterior mandibular area has a lower incidence of occurrence of OKC than the posterior

region. It has also been suggested that the granular cells are just a transitional phase in the occurrence of ameloblastoma starting with normal stellate reticulum-like cells, leading to the production of granules and finally to degeneration and therefore the formation of cystic areas. Hence, a thought to ponder is that do the granular cell changes predispose OKC to (a) transformation into ameloblastoma and/or (b) an aggressive granular cell ameloblastoma.

The unwanted components are digested by lysosomes, which represent increased cellular action of tumor ameloblasts.

In this case, lysosomes do not represent a degenerative change but may attribute as a long-standing pathology which showed delayed signs and symptoms.

Therefore, oral and maxillofacial surgeons should take precaution that a thorough removal of the cyst and if required, surgical intervention should be mandatory. Such lesions should be considered as benign with an aggressive behavior and should be treated accordingly. A regular follow-up every 6 months is also necessary as recurrence of up to 8 years after the initial treatment is a possibility.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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