



## REVIEW

### Journal Section

# Calcifying odontogenic cyst : An enigma

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## 1 | INTRODUCTION

Calcifying odontogenic cyst (COC) is an unusual benign odontogenic lesion and it is defined as a simple cyst lined with ameloblastoma-like epithelium containing calcifications and primarily ghost cells.<sup>1-3</sup> It was initially mentioned by Rywkind et al.<sup>4</sup> in 1932 and Gorlin et al. in 1962 described it as a specific entity which may represent the oral analog of dermal calcifying epithelioma of Malherbe.<sup>5,6</sup> It was classified with SNOMED code 9301/0, in the World Health Organization (WHO) publication Histological typing of Odontogenic tumors.<sup>7</sup> There have been many terminologies for COC [Fig. 1]. However,

#### Abstract

The calcifying odontogenic cyst (COC), discovered in 1962, is a rare developmental odontogenic cyst clinically present as slow-growing swelling mainly in the anterior portion of the jaws, generally present in the second and sixth decades of life. It accounts for 0.3%–0.8% of odontogenic cysts. COC showed variations in clinical and radiographic features that are not pathognomic, whereas histomorphology forms exist in 3 patterns: benign cystic, solid (neoplastic), and aggressive (malignant) forms. The radiograph shows well-defined radiolucency with irregular masses, while the histopathologic features include a cystic lining with characteristic “Ghost” cells and immunohistochemical reactions positive for various enamel proteins.

#### KEYWORDS

Calcifying odontogenic cyst; cyst; calcification; neoplastic; malignant

WHO recently gave a classification in 2022 for odontogenic and maxillofacial bone tumors which suggested a slight change in diagnostic criteria for COC, which suggests that existence of ghost cells that may undergo calcification is an adequate feature for making diagnosis whereas the presence of the ameloblastic epithelial lining is not mandatory for diagnosis. Moreover, the existence of odontoma with COC is no longer considered a separate subcategory of COC.<sup>8</sup> COC accounts for approximately 0.3% of all lesions and 1 to 7% of odontogenic cysts and tumors.<sup>9</sup> Over the years different classifications were proposed for CEOC, as specified in the Fig. 2.<sup>5,6,10-12</sup>

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## 2 | PATHOGENESIS

Studies have suggested that formation of COC is a uncystic process which is initiated from reduced enamel epithelium or remnants of odontogenic epithelium. The lining epithelium may induce formation of dentinoid or odontome in the cyst wall.<sup>10</sup> According to Gorlin et al. and Abrams and Howell theory, during development of COC, formation of ghost cell is initiated by enlargement of mural cells, followed by epithelial cells of cystic lining into abnormal keratinized cells while basal cells transform at last.<sup>13</sup>

| Terminology                                  | Authors                        |
|--|--------------------------------|
| Calcifying odontogenic cyst/ Gorlin cyst     | Gorlin 1962                    |
| Keratinizing ameloblastoma                   | Bhaskar 1965                   |
| Calcifying ghost cell odontogenic tumor      | Fejerskov & Krogh 1972         |
| Cystic calcifying odontogenic tumor          | Freedman & his associates 1975 |
| Dentogenic ghost cell tumor                  | Practurus et al 1981           |
| Epithelial odontogenic ghost cell tumor      | Ellis and Shmooker 1986        |
| Odontogenic ghost cell ameloblastoma         | Shear 1994                     |
| Odontocalcifying odontogenic tumor           | Wirthsberg 1994                |
| Odontogenic ghost cell tumor                 | Colmenero                      |
| Keratinizing and calcifying odontogenic cyst | Gold 1963                      |

FIGURE 1 Various terminologies of COC

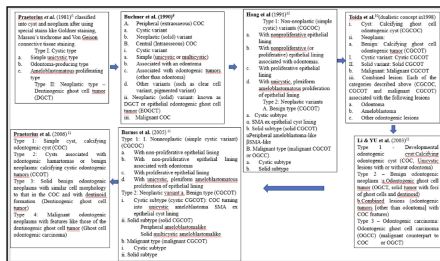


FIGURE 2 Several Classification of COC

COC is characterized by presence of enlarged, ballooned, elongated ellipsoid epithelial cells or ghost cells found in epithelial lining. The eosinophilic ghost cells show different stages of degeneration, especially in nucleus, after which remnants of chromatin disappears leaving only a faint outline or remnants. The ghost cells are representation of abnormal keratinization resulting in dystrophic calcification or coagulative necrosis of odontogenic epithelium. Under fluorescent microscope, they

show a yellow fluorescence with rhodamine B.<sup>10</sup>

## 3 | CLINICAL FEATURES

COC is an uncommon entity; classified as a developmental cyst occurring intraosseously (near canine area) as well as extraosseously (gingiva or alveolar mucosa). It constitutes 0.3% to 0.8% of odontogenic cysts occurring in oral cavity.<sup>1,3,5,14,15</sup> Age of occurrence includes patient from one year to 80 years. Generally highest peak of incidence is present in second decade of life. The COC may show occurrence in sixth decade as well (bi-modal age distribution). There is no predominant gender and race predilection.<sup>2,7,16</sup> According to various studies maxilla is the more commonly affected site, especially canine-premolar area, as compared to mandible. Anterior part of jaws is more affected as compared to posterior region. Asians showed more predilection for the maxilla, while whites have more predilection for mandible (62%).<sup>2,7</sup> COC presents as a slow growing painless solitary swelling, lesion may show bone expansion, teeth displacement, resorption of root and occasionally show cortical bone perforation. Extrasosseous lesion may appear red to pink, circumscribed elevated masses.<sup>2,5,7,16</sup>

## 4 | RADIOGRAPHIC FEATURES

In radiograph, the lesion of COC appears as unilocular to multilocular; radiolucent area with well demarcated margins. In some cases, irregular and poorly defined margins are also seen. The radiolucent area may consist of irregular calcified bodies with varying opacity. An important radiographic feature of COC is presence of resorption of root and teeth displacement. The lesion may be accompanied by local bone expansion, perforation of cortical plate, saucer shaped radiolucencies or resorption etc.<sup>10</sup>

## 5 | HISTOPATHOLOGY

In 1962, Gorlin et al. discussed the development of ghost cells along with COC.<sup>13</sup> The histopathologic features of COC are very well specified in WHO definition 1992, as “A cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble stellate reticulum, and masses of ‘ghost’ epithelial cell that may be in the epithelial lining or in the fi-

brous capsule. The 'ghost' epithelial cells may become calcified.<sup>10</sup> Ghost cells, if they reach connective tissue, then they are considered as foreign bodies. Along with ghost cell, Osteodentine-like (Dentinoid) eosinophilic material is another feature which is present at the interface between epithelium and cyst wall.<sup>17</sup> Dysplastic dentine may be laid down adjacent to the basal layer of the epithelium, and in some instances the cyst is associated with an area of more extensive dental hard tissue formation resembling that of a complex or compound odontoma".<sup>10</sup> Melanin deposits in the epithelial lining are occasionally present.<sup>16</sup> Researchers have mentioned various histopathological variants of COC, including mainly cystic and neoplastic type. The cystic type has four variants [Fig. 3].<sup>18</sup> Similarly, The neoplastic type have in four variants[Fig. 4].<sup>18</sup> In 2017 classification, COC relationship was established with other odontogenic tumors, the cystic form of tumor came back to the developmental cyst scheme and the solid form was confined as a mixed odontogenic neoplasm.<sup>19</sup>

The ghost cells in COCs shows specific immunolocalization of the enamel-related proteins, which is not present in the ghost cells of the dermal calcifying epitheliomas (Malherbe).<sup>10</sup> Enamelysin was also detected in ghost cells in COCs. Positive immunoreaction for phosphothreonine also found in ghost cells which are generally detected in hard alpha-keratins.<sup>10</sup> Ghost cells also show strong localization of amelogenin. CK-19 protein was expressed in the all cells containing epithelial lining except ghost cells. Whereas, Bcl-2 protein was minimum expressed in the epithelial linings as well as in ghost cell while cells containing epithelial lining showed only sporadic Ki-67-positive reactions in nuclei.<sup>10</sup>

## 7 | DIFFERENTIAL DIAGNOSIS

Differential diagnosis of COC radiographically includes benign radiolucent lesions such as ameloblastoma, adenomatoid odontogenic tumor, dentigerous cyst, odontogenic keratocysts, peripapical cyst, ameloblastic fibro-odontoma and calcifying epithelial odontogenic tumor.<sup>1,11</sup> Clinically, it includes common non-neoplastic gingival lesions and other extra-osseous odontogenic tumors.<sup>20</sup>

## 8 | TREATMENT

Simple enucleation and curettage are the treatment of choice for central cystic lesions of COC and En-bloc resection is recommended for neoplastic COC. Long term follow up is recommended as recurrence after 8 years has been reported and recurrence carries higher risk of malignant transformation.<sup>11,21</sup>

## 9 | CONCLUSION

The true COC is a rare developmental odontogenic cyst that clinically and radiographically resemble other common jaw lesions and represents about less than 1% of all odontogenic lesions. Histopathological interpretation is the only key to diagnosis for COC as clinical and radiographic features are nonspecific. Enucleation is the line of treatment with long term follow up as recurrence after long duration is possible.

## Acknowledgements

Nil

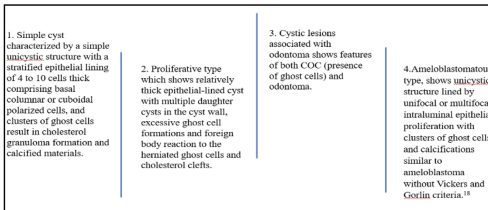


FIGURE 3 Variants of Cystic COC

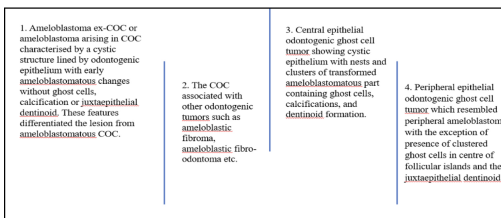


FIGURE 4 Variants of neoplastic COC

## 6 | IMMUNOHISTOCHEMISTRY

Studies have shown various type of immunohistochemical reaction using antibodies against enamelin, amelogenin, enamelysin (MMP-20), sheathlin (prism sheath protein) and monoclonal antibody 203-IC7 etc.

## Conflict of interest

The authors have no conflicts of interest to declare.

## Supporting Information

Additional supporting information may be found at the journal's website.

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