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Case report **Pathology**

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VARIATIONS IN THE BIOLOGICAL BEHAVIOR OF CALCIFYING ODONTOGENIC CYST TO CALCIFYING CYSTIC ODONTOGENIC TUMOR: A CASE REPORT

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ABSTRACT

Calcifying cystic odontogenic tumor (CCOT) is a rare odontogenic lesion comprising about 2% of all odontogenic pathological changes in the jaw. Clinically presents as painless swelling of jaw, while histopathology demonstrates characteristic "Ghost" epithelial cells with a propensity to calcify. Due to its varied clinical presentation, including cystic and neoplastic forms and recurrence rates posses a great challenge to decide its course of treatment. Here, we report, a classic case of CCOT, showing an aggressive clinical course and different histopathologic presentations along with a brief review of literature.

KEY WORDS: Calcifying cystic odontogenic tumor, Calcifying odontogenic cyst, Ghost cell

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INTRODUCTION

The Calcifying Odontogenic Cyst (COC) is a rare developmental lesion arising from odontogenic epithelium with varied spectrum of clinical presentations including benign cystic and aggressive neoplastic. It was first described by Gorlin et al in 1962 and a year later by Gold in 1963, since then there have been controversies about its exact clinical existence.[1] In 2005, World Health Organization, reclassified this lesion under odontogenic tumor as "calcifying cystic odontogenic tumor"(CCOT)and defined as "a benign cystic neoplasm of odontogenic origin characterized by an ameloblastoma, like epithelium with ghost cells, that may calcify".[2] CCOT presents intraosseously and extraosseously. Intraosseous CCOT are usually painless, slow growing swelling whereas sessile and pedunculated growth with smooth surfaced mass are the features of extraosseous lesions. The lesion shows bimodal age of occurrence (2nd and 7th decades of life) with equal sex distribution. Radiographically, unilocular or multilocular radiolucency with different grades of radio-opacities are observed. Microscopically, it reveals 4-10 layer of odontogenic epithelium with basal ameloblasts like cells and loose stellate reticulum like cells along with ghost cells which shows calcification.[5] Multinucleated giant cells are observed surrounding the ghost cells in connective tissue stroma. Masses of dentinoid like material may be present in close proximity to the epithelial islands.[3] The dualistic nature and terminologies of CCOT has made controversies among various authors in classifying and reclassifying the lesions. We aimed to present a rare case of CCOT in posterior maxilla of 78 year old patient with varied clinical, radiographic and histological features. We also highlight the use of term "CCOT" than "COC", to describe this unique tumor of controversial nature.

CASE REPORT

A female patient aged 78 years, reported to out-patient Department with a chief complain of slow enlarging swelling in right side of the face since one year. Extra oral examination revealed asymmetry with diffuse swelling. Intraorally, the patient was partially edentulous and the swelling was well defined, smooth textured, hard, non-tendered and non-ulcerated, involving the right maxillary alveolar ridge causing obliteration of buccal vestibule. Orthopantomogram (OPG) revealed the presence of a radiolucent destructive lesion causing resorption of right maxillary residual ridge and involvement of maxillary antrum with areas of radio opacities. (Fig 1) Based on the clinical and radiological features the provisional diagnosis of ameloblastoma, odontogenic keratocyst, salivary gland tumors and squamous cell carcinoma was made. Fine Needle Aspiration Cytology was performed where 1ml of straw colored fluid was aspirated which confirmed the lesion's cystic benign nature. Assuming the cystic benign nature of the lesion, the incisional biopsy was performed and the tissue sections were stained with Hematoxylin and Eosin (H/E) for microscopic evaluation. H/E staining revealed cystic space lined by odontogenic epithelium, of 4-6 layers of columnar cells showing ameloblast like features, overlying by loosely arranged stellate reticulum like cells. The ghost cells were observed in the epithelium and in the connective tissue showing the foreign body type of giant cell reaction and areas of calcification. The presence of ghost cell was confirmed by Van Gieson special stain which revealed it light orangish to dark pinkish in color.(Fig 2 a &b) The histopathological features confirm the diagnosis of COC. Excisional biopsy was planned after explaining the procedure and by obtaining informed consent of the patient. The excisional biopsy specimen was sectioned, stained and microscopically examined. The ghost cells observed on excisional biopsy showed individual cell calcification and also the sheet of calcification of ghost cells occupying the entire thickness of epithelium resembling keratin.(Fig 3) Hence, the diagnosis of COC was confirmed

as “CCOT”. No recurrence is observed at 6 months of follow- up period.

Figure 1
Orthopantomogram showing mixed radiopaque and radiolucent lesion in the right maxilla filling the maxillary antrum.

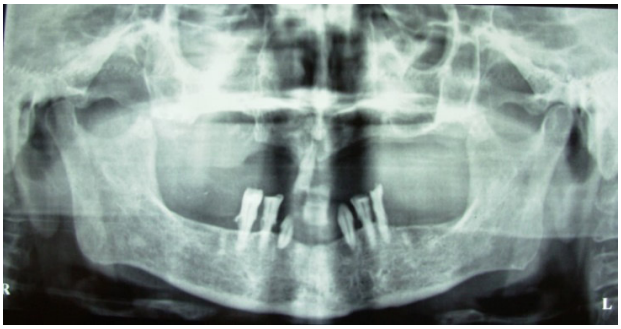


Figure 2 (a)
Histopathology showing odontogenic epithelium with ameloblast like cells and ghost cells in the epithelium and in the connective tissue with foreign body reaction. (40X)

Figure 2 (b)
Van Geison stain showing positivity of orangish color ghost cells.

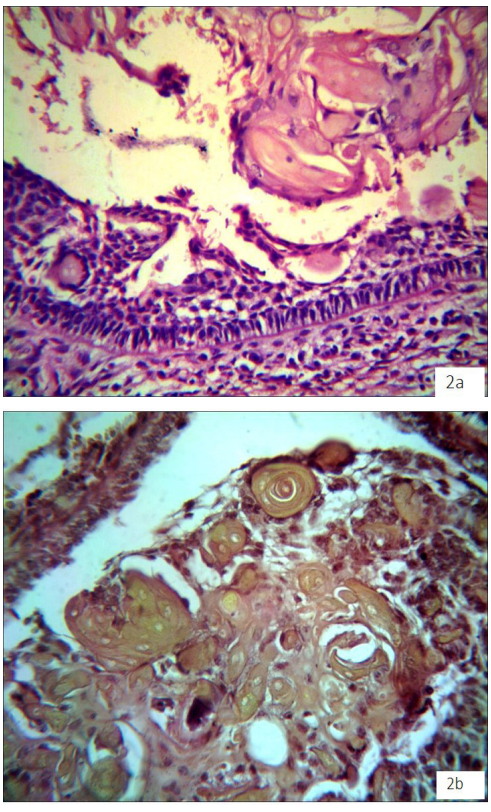
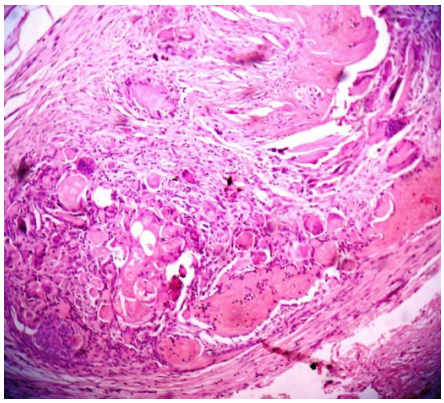


Figure 3
Histopathology showing sheets of ghost cells undergoing calcification. (10X)



DISCUSSION

CCOT constitutes 1 to 2% of all odontogenic tumors in which 88.5% are cystic and 11.5% are solid tumors. The average age for the presentation of this lesion is 50 years (range 17 to 72 years) with same frequency in upper and lower jaw. Radiographically, a well-circumscribed unilocular or multilocular radiolucent lesion associated with calcified material ranging from tiny flecks to large radiopaque calcified masses are observed.[3,4]The article presented a large swelling in the maxilla of 78 year old female showing destructive radiolucency with tiny flecks of radio-opacities radiographically. The defining microscopic feature is the presence of variable numbers of altered epithelial cells without nuclei which appear as swollen, pale, eosinophilic cells, singly or in sheets with a clear cellular outline without nucleus. These are termed as “ghost cells”. Ghost cells may undergo calcification and form sheet-like areas resembling calcified keratin. These features are characteristically seen in calcifying cystic odontogenic tumors (CCOT), cranio-pharyngiomas and pilomatricomas.[5]The present case showed these features on excisional biopsy which made us to diagnosis it as “CCOT”. The origin of ghost cells can be from any layer of epithelium i.e., basal, intermediate or superficial. They have a tendency to breach the epithelial lining and reach connective tissue where they initiate a foreign body reaction and calcium salt deposition.[1]The questionable nature of ghost cell formation has led confusions in understanding the mechanism behind its formation. Lan et al (2003) suggested that the ghost cells are formed due to some transitional changes in the epithelium, which represent the process of apoptosis of the poorly differentiated odontogenic cells.[6] Kim et al supported it immunohistochemically by using apoptosis related proteins like Bcl-2 and Bcl-X_L. Ghost cells can also result due to abnormal differentiation of the keratinocytes or present as a fragment of disintegrated epithelial cells.[7] Murakami et al suggested it to be a dystrophic calcification and supported it immunohistochemically by using cbfa-1 marker, which showed positivity to the osteoblasts and not to the ghost cells.[8]Gunhan et al and Yoshida et al suggested that the ghost cells represents the product of abortive enamel matrix in odontogenic epithelium. Immuhistochemical staining of enamelysin showed positivity in ghost cells and amelogenin protein positivity in the cytoplasm of ghost cells.[9,10] Ultrastructure study of ghost cells by Regezi et al have showed large bundles of keratin filaments and gradual packing of tonofilaments into homogeneous mass. This suggested that ghost cells are the product of aberrant keratinization of the lining epithelium.[11] Owing to the diverse clinicohistologic features and the neoplastic potential of the CCOT, there have

been disagreement on the terminology whether to classify it as a cyst or a neoplasm. CCOT often tends to occur in association with other odontogenic tumors showing similar histological areas, such as odontoma, ameloblastoma, ameloblastic fibroma, ameloblastic fibro-odontoma, odonto-ameloblastoma, calcifying epithelial odontogenic tumor and adenomatoid odontogenic tumor. Gold in 1963 reported first CCOT with compound odontoma. There is higher frequency of association of odontoma with CCOT (20 – 24%) which debated the etiology as hamartomatous growth and lack its classification as a separate entity.[1]Hirshberg (1994) analyzed 52 cases and proposed that CCOT with odontoma, should be regarded as separate entity and suggested the term 'Odontocalcifying odontogenic cyst'.[12] However, this association creates challenges in diagnosing on conventional imaging due to the presence and overlapping of other anatomical structures in the jaw region. CCOT is regarded as tumor by WHO (2005) due to its neoplastic nature. The evidence in support includes:

a. The histological features of CCOT is similar to other odontogenic tumors specially the epithelial lining which resembles ameloblastoma.
b. CCOT does not always present as cystic lesion. Praetorius et al and McGowan Browne reported 13% and 17% CCOT as solid lesions respectively. Fejerskow and Krogh considered CCOT as a tumor or hamartoma with marked tendency for cystic degeneration.
c. The biologic behavior of CCOT presents root resorption (13 – 50% cases), erosion of bony cortices and bone destruction.[13]

Ahn SG et al (2008) revealed that CCOT shows disregulation of wnt/- catenin signaling which activates the transcription factor T-cell factor / lymphoid enhancer factor and other wnt/- target genes which favor cell cycle proliferation. The activation of wnt/-catenin and TCF – mediated transcription is known to play a role in oncogenesis and this may also influence the development of CCOT as well. Hence this reflected in the change of name to 'CCOT' by the WHO.[14] Another characteristic feature microscopically, is the presence of dentinoid or osteoid material. Abrams and Howell suggested it to be inflammatory response whereas Nagao et al stated it to be an inductive phenomenon. Till date, it remains non conclusive, whether the dentinoid or the osteoid material represents the true inductive effect or the metaplastic effect of the connective tissue.[15] The present study did not observe any dentinoid or osteoid like material. Based on the origin of the lesion, histopathological features and the architectural pattern, we prefer the term 'CCOT' rather than 'COC' because the advertent use of the term 'COC' mask the real biological behavior with high proliferation index. The author emphasize that the use of terminologies should focus on the biological behavior of the lesion so that the lesion will be treated appropriately with reduce chances of recurrence. In the present study considering the size and the aggressiveness of the lesion, en-block resection was performed. The patient is under follow-up since six months and will be further evaluated by prosthodontist.

CONCLUSION

The confusion regarding the terminologies and classification of calcifying odontogenic cyst should remain as academic exercise and more emphasis should be laid on the biological behavior of the lesion.

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