

MULTICYSTIC VARIANT OF CALCIFYING CYSTIC ODONTOGENIC TUMOR ASSOCIATED WITH ODONTOME – REPORT OF A CASE AND REVIEW

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ABSTRACT

Calcifying cystic odontogenic tumor is an uncommon odontogenic neoplasm which is included in the heterogenous group of lesions under a broader description of Ghost cell odontogenic tumors. All these lesions have the presence of ghost cells as a common feature. Calcifying cystic odontogenic tumor is a unique lesion with variable biologic behaviour and found to occur with other odontogenic tumours. We present a case of Calcifying cystic odontogenic tumor occurring in a 15 year old boy involving an unerupted permanent canine and premolar. The tumor was multicystic in nature and was associated with a complex odontome. This article also includes an update on nomenclature and classification of ghost cell odontogenic lesions.

KEYWORDS: Calcifying Cystic Odontogenic Tumor, Calcifying Odontogenic Cyst, Odontome, Ghost cells, Dentinoid.

INTRODUCTION

Calcifying odontogenic cyst (COC) was first categorized as a distinct entity by Gorlin *et al.* in 1962.¹ Since then it has been recognized to include various subtypes that show diversity in clinical and histopathological features as well as in biological behaviour. COC usually occurs intraosseously, but it may also occur extraosseously. COCs are primarily cystic in nature and appear to be non-neoplastic, but can appear as solid lesions; at least some of which are neoplastic in nature. There is also an extremely rare malignant variant. Radiologically, the lesion can be a well-defined, uni- or multi-locular radiolucency that may or may not contain varying amounts of radiopaque material; some lesions are associated with unerupted teeth. Histologically, these lesions share the similar feature of presence of ameloblastomatous epithelium with ghost cells with or without dentinoid formation. COC is frequently found in association with, or exhibits areas histologically similar to, various odontogenic tumours, including complex or

compound odontoma, ameloblastoma, odontoameloblastoma, ameloblastic fibroma, ameloblastic fibro-odontoma and the adenomatoid odontogenic tumour.²

There has been an extended debate about the biologic behaviour of these lesions and many nomenclatures and classifications have been published towards this effect. In the World Health Organization (WHO) histologic classification of odontogenic tumors (2005)³, COC were categorised into three types, one cystic type, the Calcifying cystic odontogenic tumour (CCOT) and the two solid types, the Dentinogenic ghost cell tumor (DGCT) and Ghost cell odontogenic carcinoma (GCOC). The GCOC's are cases that had been reported previously as odontogenic ghost cell carcinoma and malignant epithelial odontogenic ghost cell tumours. This case report describes a case of multicystic variant of CCOT associated with complex odontome.

Case Report

A 15 year old boy visited our maxillofacial surgical unit with the chief complaint of swelling in the right midfacial region since 6 months. There were no other accompanying symptoms. The patient was otherwise healthy with no significant medical and family history.

On extraoral examination, the swelling in the midface extended about 5 cm from the midline to 3 cm anterior to the right ear (**Fig.1**). The surface appeared normal with diffuse borders. On palpation, there was no local rise in temperature and the swelling was non-tender.

Intraoral examination revealed a swelling in the buccal vestibule extending from tooth 11 (FDI) to buccal sulcus of 16 and measuring about 5 cm with diffuse borders. On palpation the swelling was firm and non-tender. Hard tissue examination revealed retained 53 with clinically missing 13 and 14.

Based on the clinical findings of expansile swelling associated with clinically missing teeth a working diagnosis of ameloblastoma was considered.

The patient was subjected to radiographic evaluation wherein, OPG (Ortho Pantamograph) revealed a large unilocular radiolucent lesion of the right maxilla measuring about 4 cm, extending from the roots of 11 to 16 with well defined corticated borders. The lesion was associated with impacted 13 and 14. Multiple radio-opaque areas were noted with the largest of them measuring about 1cm (**Fig.2**).

On aspiration of the swelling, about 1 ml of straw colored fluid was obtained. Based on the above findings a differential diagnosis of Adenomatoid odontogenic tumor, Calcifying odontogenic cyst and Ameloblastic fibro-odontoma was arrived upon.

Enucleation of the lesion was performed under general anaesthesia and the lesional tissue sent for histopathologic examination. Post-enucleation radiovisiography of the specimen revealed multiple flecks of radio-opaque areas about 2 mm in size with a large radio-opaque mass about 1 cm in size within the specimen (**Fig. 3**).

On gross examination, the lesion was nodular, oval in shape and encapsulated (**Fig.4**). It measured about 3 X 2.5 X 2 cm in size and was firm in consistency. Cut surfaces revealed a solid lesion with a single macrocyst of size 7 mm. The solid areas were grayish-white in color and showed a deposit of white to yellowish hard material of about 1 cm in size.

Histopathological examination showed the macrocystic area lined by epithelium of varying thickness composed of basal ameloblast like cells and superficial stellate reticulum like cells (**Fig.5**). The epithelium exhibited ghost cell keratinization and associated spherical calcifications. Ghost cells were also seen in the stroma just beneath the luminal epithelium associated with abundant dentinoid material (**Fig.6**). The stroma revealed multiple microcystic areas with similar lining epithelium and enclosing ghost cells (**Fig.7**). Many areas in these cysts showed dystrophic calcification of ghost cells. The focus correlating the large radio-opacity was composed of dentine, cementum and pulp like soft tissue arranged haphazardly (**Fig.8**). Based on the above features a diagnosis of CCOT, multicystic variant associated with complex odontome was arrived upon.

The immediate post operative healing was uneventful and the patient is on regular follow-up since the last 6 months and has not showed any signs of recurrence.

Discussion

Ghost cell odontogenic tumors⁴ comprise a diverse group of lesions which are characterized by ghost cell keratinisation and vary in their biologic behaviour. The cystic form was recognized first and it is only subsequently the full range of spectrum of these lesions is being understood. Initially it was noted by Rywkind in 1932, who termed it as a variant of the cholesteatoma. Thoma and Goldman reported three cases in 1940, and considered the lesions to be odontogenic tumors of ectodermal and mesodermal origin⁵, while Maitland in 1947 regarded it as a type of ameloblastoma.⁶ It was Gorlin, Pindborg, Prætorius-Clausen and Vickers who initially described the lesion and called it Calcifying Odontogenic cyst.¹ They regarded it as the oral analogue of the cutaneous calcifying epithelioma of Malherbe. Gold referred to it as 'Keratinizing and Calcifying Odontogenic cyst'.⁷



Fig 1: Intraoral swelling on the right maxilla obliterating the vestibule.



Fig 2: Unilocular radiolucency in upper right canine-premolar region with multiple radio opaque areas along with an impacted canine and first premolar.

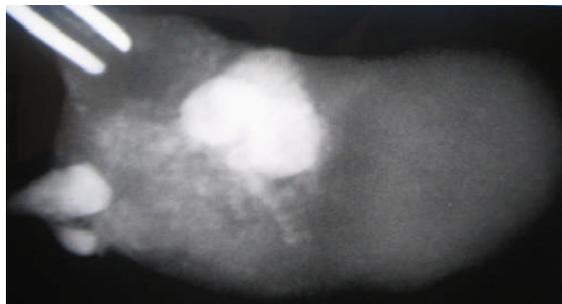


Fig 3: Post enucleation radiovisiography revealing multiple flecks of radio opaque areas with a large radio opaque mass within the specimen.



Fig 4: The enucleated lesion.

Since then numerous case reports have been published and various presentation of the lesion have been recognized- solid, neoplastic, extraosseous and malignant.

Cyst v/s Neoplasm:

Few authors have regarded COC as a tumour with a tendency for marked cystic formation. Towards this effect, Fejerskov and Krogh (1972) used the term 'Calcifying Ghost Cell Odontogenic Tumor'⁸ and Freedman et al (1975) referred to it as Cystic calcifying odontogenic tumour (CCOT).⁹ The WHO classification of 1992 is also based on this 'Monistic concept' that all COCs are neoplastic in nature, even though most of the lesions are cystic in architecture and appear to be non-neoplastic.¹⁰

In contrast to this, the 'Dualistic' concept recognizes two entities of the lesion: a cyst and a

neoplasm. Praetorius *et al* in 1981 proposed a classification of COC (**Table 1**) in which they divided COC into the two entities and the neoplastic variant was referred to as 'Dentinogenic Ghost Cell Tumour' based on the conspicuous presence of dentinoid and varying amounts of ghost cells.¹¹ In 1983, Shear noted the similarity to ameloblastoma and referred to it as 'Dentinoameloblastoma'.¹² Scott and Wood were of the opinion that the name dentinogenic ghost cell ameloblastoma was acceptable for aggressive lesions in which ameloblastomatous tumour was present, and proposed the name odontogenic ghost cell ameloblastoma for the rare cases in which both dentine and enamel were present.¹³ Ellis & Shmookler emphasized the presence of ghost cell keratinization and proposed the term 'Epithelial Odontogenic Ghost Cell Tumour' (EOGCT).¹⁴ Colmenero *et al.* in 1990 termed it as 'Odontogenic Ghost Cell Tumour' (OGCT).¹⁵ Buchner (**Table 2**)¹⁶

Table.1. Classification of so-called COC proposed by Praetorius *et al.*

<p>Type 1. Cystic type</p> <ul style="list-style-type: none"> A. Simple unicystic type B. Odontoma producing type C. Ameloblastomatous proliferating type <p>Type 2. Neoplastic type: Dentinogenic ghost cell tumour (DGCT)</p>
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Table.2. Classification of so-called COC proposed by Buchner

<p>A. Peripheral (extrasosseous) COC</p> <ul style="list-style-type: none"> 1. Cystic variant 2. Neoplastic (solid) variant <p>B. Central (intraosseous) COC</p> <ul style="list-style-type: none"> 1. Cystic variant <ul style="list-style-type: none"> a. Simple (unicystic or multicystic) b. Associated with an odontoma c. Associated with odontogenic tumours (other than odontoma) d. Other variants (such as clear cell variant, pigmented variant) 2. Neoplastic (solid) variant: known as DGCT or EOGCT 3. Malignant COC
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Table.3. Classification of so-called COC proposed by Hong *et al*

<p>Type 1. Cystic</p> <ul style="list-style-type: none"> A. Nonproliferative B. Proliferative C. Ameloblastomatous D. Associated with odontoma <p>Type 2. Neoplastic</p> <ul style="list-style-type: none"> A. Ameloblastoma ex COC B. Peripheral EOGCT C. Central EOGCT

Table.4. Classification scheme of so-called COC by Toida M

<p>1. Cyst: Calcifying ghost cell odontogenic cyst (CGCOC)</p> <p>2. Neoplasm:</p> <ul style="list-style-type: none"> A. Benign: Calcifying ghost cell odontogenic tumour (CGCOT) <ul style="list-style-type: none"> a. Cystic variant: cystic CGCOT b. Solid variant: solid CGCOT B. Malignant: malignant CGCOT <p>3. Combined lesion: each of the categories described above (CGCOC, CGCOT and malignant CGCOT) associated with the following lesions</p> <ul style="list-style-type: none"> α Odontoma β Ameloblastoma γ Other odontogenic lesions
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Table.5. Classification suggested by Reichart PA and Philipsen HP in 2004.

<p>1. Non-neoplastic (simple cystic) variants (CGCOC)</p> <ul style="list-style-type: none"> a. With nonproliferative epithelial lining b. With nonproliferative (or proliferative) epithelial lining associated with odontomas c. With proliferative lining d. With unicystic, plexiform ameloblastomatous proliferation of epithelial lining <p>2. Neoplastic variants</p> <ul style="list-style-type: none"> A. Benign type (CGCOT) <ul style="list-style-type: none"> a. Cystic subtype (cystic CGCOT) <ul style="list-style-type: none"> α SMA ex epithelial cyst lining b. Solid subtype (solid CGCOT) <ul style="list-style-type: none"> α peripheral ameloblastoma-like β SMA-like B. Malignant type (malignant CGCOT or OGCC) <ul style="list-style-type: none"> a. cystic subtype b. solid subtype <p>(Note: SMA- Solid multicystic ameloblastoma)</p>

Table 6. Classification of the odontogenic ghost cell lesions by Praetorius, 2006

<p>A. Group 1 : 'Simple' cysts</p> <ul style="list-style-type: none"> 1. Calcifying odontogenic cyst (COC) <p>B. Group 2: Cysts associated with odontogenic hamartomas or benign neoplasms: calcifying cystic odontogenic tumors (CCOT).</p> <ul style="list-style-type: none"> 1. CCOT associated with an odontome 2. CCOT associated with adenomatoid odontogenic tumor 3. CCOT associated with ameloblastoma 4. CCOT associated with ameloblastic fibroma 5. CCOT associated with ameloblastic fibro-odontoma 6. CCOT associated with odonto-ameloblastoma 7. CCOT associated with odontogenic myxofibroma <p>C. Group 3 : Solid benign odontogenic neoplasms with similar cell morphology to that in COC, and with dentinoid formation</p> <ul style="list-style-type: none"> 1. Dentinogenic ghost cell tumor <p>D. Group 4: Malignant odontogenic neoplasms with features similar to those of the dentinogenic ghost cell tumor</p> <ul style="list-style-type: none"> 1. Ghost cell odontogenic carcinoma
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and Hong et al. (**Table 3**)¹⁷ have also proposed classifications of COC based on the dualistic concept. Hong et al. (1991) supported the use of term "Epithelial Odontogenic Ghost Cell Tumor" based on the presence of odontogenic epithelial proliferations with some inductive activity and the formation of ghost cells.¹⁷ Hirshberg et al considered COC associated with odontomas to have clinical features sufficiently distinct to categorise them as a separate lesion and named them 'Odontocalcifying odontogenic cyst'.¹⁸ Langlais et al in 1995 proposed the term calcifying odontogenic lesion (COL), encompassing both the cystic and neoplastic forms as well as combined lesions containing elements of both.¹⁹ Toida M in 1998 suggested another classification based on the dualistic concept (**Table 4**).²⁰ Li and Yu classified the lesions into three categories- cysts, benign tumours and malignant tumours. They suggested that the term COC should be used specifically to designate the unicystic lesions, with or without an associated odontoma.²¹

This divergence on nomenclature is also reflected in the WHO classifications through the years, wherein in 1971 it recognised COC as a non-neoplastic lesion.²² In 1992, COC was placed in subgroup 1.1.2, even though the stroma was mature collagenous type and the lesion was said to be mostly non-neoplastic.¹⁰ In the WHO Histological Classification of Odontogenic Tumours of 2005, COC was re-named as calcifying cystic odontogenic tumour (CCOT), the benign solid type was referred to as DGCT and the cases previously reported as odontogenic ghost cell carcinoma (OGCC) and malignant epithelial odontogenic ghost cell tumours were re-named by the WHO as ghost cell odontogenic carcinoma (GCOC).³

Since then at least two more classification systems have been proposed. (**Table 5 and 6**).^{23, 24}

Calcifying cystic odontogenic tumor

The WHO in 2005, defined CCOT was defined as 'a benign cystic neoplasm of odontogenic origin, characterized by an ameloblastoma-like epithelium with ghost cells that may calcify'.³

CCOT is an uncommon lesion and represents about 0.03% of the biopsy lesions and less than 2% of all odontogenic cysts and tumours. Calcifying cystic

odontogenic tumour (CCOT) can occur intra or extraosseously and they can be further subdivided into⁴:

- **CCOT type 1:** Simple cystic CCOT (Includes pigmented and clear cell variants)
- **CCOT type 2:** Odontoma-associated CCOT
- **CCOT type 3:** Ameloblastomatous proliferating CCOT
- **CCOT type 4:** CCOT associated with benign odontogenic tumours other than odontoma.

CCOT has been reported to be associated with an odontome in 22-47% of cases. Hirshberg et al gave several possible explanations for this association. Firstly, that it could represent a coincidental juxtaposition of a COC and an odontoma. The second possibility was that odontoma could develop secondarily from the lining epithelium of COC. Towards this effect they referred to the lesion as 'Odontocalcifying odontogenic cyst'.¹⁸ A third explanation could be that this lesion represents a odontoma wherein the epithelial component not only initiates the odontoma but also at a certain stage forms an epithelial cyst lining which eventually envelopes the odontoma. The authors were of the opinion that the lesion be best considered as a variant of odontoma and be called as 'compound complex cystic ghost cell odontoma'.²³

The lesion occurs over a wide age range with preponderance for the second decade. There seems to be no gender predilection. The lesion is slowly expansile with anterior maxilla being the most common site of occurrence.⁴

Radiographically, CCOT with odontoma usually presents as well defined unilocular, mixed radiolucent-radiopaque lesion and in around 40% of cases is associated with an unerupted and /or impacted teeth. The present case too demonstrated comparable clinical features. Histologically, CCOT essentially is a unicystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer often many cells thick that may resemble the stellate reticulum and usually containing masses of ghost cells which may be located within the epithelial lining or in the fibrous capsule. Variable quantities of dentinoid or dentin-like material are laid down adjacent to the epithelial lining and on occasion dental hard tissues resembling odontome, especially the compound type are found in association.⁴

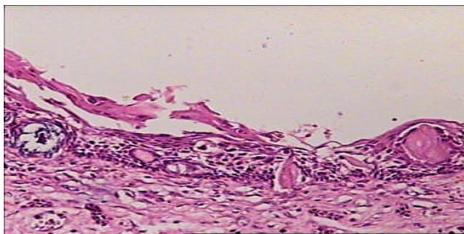


Fig 5: The photomicrograph shows cystic lining made up of ameloblast like cells and stellate reticulum-like cells. A few ghost cells and areas of calcification are seen. (H&E 40X).

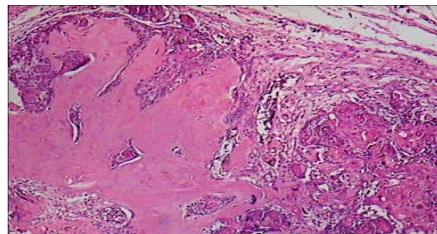


Fig 6: The photomicrograph shows dense collection of ghost cells in the stroma with deposition of large amount of dentinoid material in the cyst wall (H&E 40X).

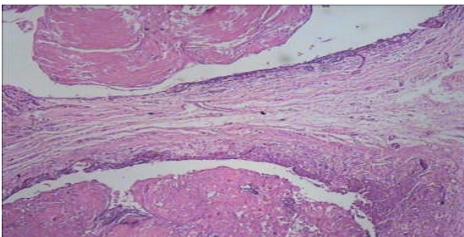


Fig 7: photomicrograph showing microcysts with enclosed ghost cell masses (H&E 40X)

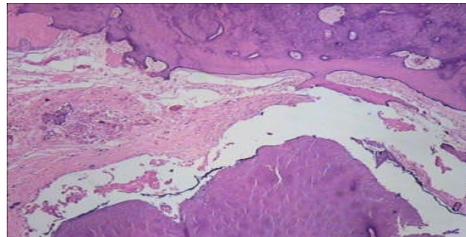


Fig 8: Another area of the tumor showing complex odontome (H&E 40X)

The present case had abundant dentinoid material and distinction from DGCT was made on the basis of presence of a macrocyst and several microcysts in the fibrous stroma. The presence of hard tissue containing dentin, cementum and pulp-like tissues arranged in an irregular haphazard architecture favoured the diagnosis of complex odontoma. The absence of primitive ectomesenchymal tissue ruled out the possibility of Ameloblastic fibro-odontoma. Intramural or luminal plexiform ameloblastomatous proliferations were also not found in any of the sections. Hence a final diagnosis of CCOT, multicystic variant associated with odontoma was arrived upon.

This case is unique due to the presence of multiple cysts and the rare association with a complex odontome. Buchner in an assessment of 217 cases recognized multicystic variant as a separate entity and incorporated in his classification. The occurrence of multicystic variety is rare when compared to the unicystic variant.¹⁶

In an analysis of 20 cases of COC with odontoma, the authors classified the lesion into two types. Type I represents an odontoma in a cyst and Type II, an odontoma outside a cyst. Type I occurred at a younger age group and type II

odontomas were larger in size, cysts being variable in size²⁴.

Immunohistochemical studies on CCOT have found ameloblastomatous, proliferative types and odontoma associated CCOT's to have higher expression of Ki 67. Increased expression of Ki 67 is seen as compared to DGCT or CCOT.²⁵ Bcl 2 positivity was found to be more in CCOT associated with odontoma than without.²⁶ The recommended treatment protocol for CCOT is conservative surgical enucleation. Since rare recurrences have been reported, a follow-up period of 10 years has been suggested²³.

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