Case Report

Dentinogenic ghost cell tumor: Case report of a rare central variant and literature review

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Abstract

The dentinogenic ghost cell tumor (DGCT), a solid variant of the calcifying odontogenic cysts, is an uncommon odontogenic neoplasm which is aggressive and has a propensity for recurrence. It accounts for <0.5% of all odontogenic tumors which can exhibit intraosseous (central) or extraosseous (peripheral) localization. Till today, only 39 cases of central DGCT have been reported in English literature according to WHO 2017 Classification. Therapeutic intervention of central variant should be aggressive, local resection with adequate safety margins and monitoring the patient for recurrence as the lesions show recurrence rate up to 71%. The purpose of this paper is to describe a rare case report of central DGCT in a 57-year-old female patient with a brief review of literature which provides an update on the epidemiology, diagnostic and clinicopathological characteristics of the published cases.

Keywords: Calcifying odontogenic cyst, case report, dentinogenic ghost cell tumor, odontogenic neoplasm, recurrence, World Health Organization

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Submitted: 02-Jun-2021, **Revised:** 23-Nov-2021, **Accepted:** 24-Nov-2021, **Published:** 28-Feb-2022

INTRODUCTION

Calcifying odontogenic cysts (COCs), dentinogenic ghost cell tumors (DGCTs) and ghost cell odontogenic carcinomas (GCOCs) represent a group of odontogenic ghost cell lesions (OGCLs) of the jaws.[1] COC which represents 1%–2% of all odontogenic neoplasms is an entity well known to clinicians and pathologists and was first described by Gorlin *et al.* It was described as a likely analog of the "calcifying epithelioma of Malherbe" (also termed pilomatricoma or pilomatrixoma) in a study by Gorlin; therefore, the eponym of "Gorlin cyst" is frequently used[2,3] Gold in 1963 named the lesion as "Keratinizing calcifying odontogenic cyst."[4] In 1971, World Health Organization (WHO) defined it as a nonneoplastic cystic lesion and named it as COC (calcifying odontogenic cyst).[4] Fejerskov and Krogh in 1972 called it "Calcifying ghost cell odontogenic tumor," whereas Freedman *et al.* in 1975 suggested the name "Calcifying cystic odontogenic tumor (CCOT)."[5] COC's were classified into cystic and solid neoplastic type (termed as DGCT) by Praetorious *et al.*[6] The term dentinoameloblastoma was coined by Shear due to its resemblance to the ameloblastoma with dentinoid production.[7] In 1992, WHO classified it as a benign odontogenic tumor, with the SNOMED code 9301/0, but did not change its name.[8] In 1998, Toida

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_174_21

How to cite this article: Reddy V, Wadhwan V, Singh R, Bansal V. Dentinogenic ghost cell tumor: Case report of a rare central variant and literature review. J Oral Maxillofac Pathol 2022;26:S68-72.

suggested that the terms "cystic" or "neoplastic" were not appropriate because the former term described the morphology while the later defined the biological behavior of the lesion.[4] Controversy prevails as to whether COC is a cyst or a tumor as the biological behavior of all lesions is often not compatible with a cyst.[9] Classification of COCs has been put forward as monistic and dualistic concepts.[4] The monistic concept by the WHO classification, postulates that all COCs are neoplastic in nature, even though the majority are cystic in architecture and appear to be nonneoplastic.[8] The dualistic concept was favored by most researchers, proposes that COCs contain two different entities, a cyst and a neoplasm.[10] This conundrum was solved by WHO classification in 2005 which included both type of COC under tumors, renamed COC as CCOT and DGCT for the neoplastic.[11] According to the WHO, the spectrum of odontogenic ghost cell tumors comprises CCOT, DGCT and ghost cell odontogenic carcinoma.[12] Cystic lesions are termed as "calcifying cystic odontogenic tumors" and "DGCT" for neoplastic entities by Singhaniya *et al*.[13] WHO classification in 2017, the consensus group classifies the cyst as calcifying odontogenic cyst and the neoplasm as DGCT and has described it under mixed (epithelial-mesenchymal) origin tumors.[14]

DGCT is an extremely rare neoplasm which accounts for less than 0.5% of all odontogenic tumors.[15] WHO (2005) defined DGCT as a locally aggressive tumor that is histologically characterized by strands and islands of ameloblastoma-like epithelial cells infiltrating into mature connective tissue with aberrant keratinization in the form of ghost cells with some undergoing calcification and variable amounts of dysplastic dentin production.[13] DGCT may show extraosseous (peripheral) and intraosseous (central) localization. Intraosseous variant exhibits highly aggressive behavior showing infiltrative growth patterns and a high recurrence after resection.[16] Few cases of distant metastasis have also been reported in central DGCT. In contrary, the peripheral variant is relatively dormant. DGCT transforming into squamous cell carcinoma and GCOC has also been reported.[17]

To the best of our knowledge, only 57 cases (39 were central type and 18 were peripheral variants) reevaluated using the WHO 2017 classification for odontogenic tumors have been reported till date.[17] Here with, we present a case of intraosseous DGCT located in a left mandibular region in a 57-year-old female patient highlighting the importance of clinical, radiological, histopathological and histochemical profile in understanding the behavior of these lesions compared with the existing literature.

CASE REPORT

A 57-year-old female reported with a complaint of swelling in the lower left side of the jaw for 6–7 months. As reported by the patient, the swelling had started following the extraction of teeth, which gradually increased in size since its onset. There was no history of trauma or pain, but the swelling was associated with discharge for 1–2 months. Medical, surgical, dental, family and personal histories were not relevant. On extraoral examination, facial asymmetry was noted with noticeable solitary diffuse swelling on left facial region, approximately 4 cm × 5 cm in size extending from the left corner of the mouth till 2 cm from the left ear and superoinferiorly from line joining the corner of the mouth till inferior border of the mandible [Figure 1]. Overlying skin appeared normal with the local rise in temperature. Swelling was firm to hard in consistency and nontender on palpation. Submandibular, sublingual and cervical lymphnodes were palpable. Examination of the intraoral region revealed a bony hard solitary swelling 4 cm × 4 cm in size extending from 35 till ramus of the mandible. Buccal and lingual cortical plate expansion with perforation was noticed [Figure 2]. The swelling was tender on palpation. On the basis of clinical examination, provisional diagnosis of ameloblastoma was given. Differential diagnosis of central giant cell granuloma, fibrous dysplasia and calcifying epithelial odontogenic cyst was made. Orthopantomograph (OPG) revealed a multilocular radiolucency extending from left lower second premolar to left ramus with a remarkable bony expansion toward buccal and lingual sides and inferiorly to the lower border of the mandible [Figure 3]. An incisional biopsy of the lesion was performed, and on examination, tissue revealed islands and nests of odontogenic epithelium with cystic degeneration at areas. The odontogenic epithelium was lined by peripheral tall columnar ameloblast-like cells with hyperchromatism, reverse polarity and central stellate reticulum-like cells. Aggregates of ghost cells with eosinophilic cytoplasm were appreciated scattered within the epithelium. Basophilic calcifications in the ghost cells were are also seen. Areas of eosinophilic material represented by dysplastic dentin were seen adjacent to epithelial component. The histopathological impression was obvious of DGCT [Figure 4] but, it can be confused with ameloblastoma, COC and GCOC. COC was excluded in the present case because of high amount of dentinoid which accounted for the solid structure of a DGCT. The presence of dysplastic dentin and ghost cells differentiated it from ameloblastoma. The absence

Figure 1: Extraoral photograph of the patient showing swelling in the lower left premolar and molar region

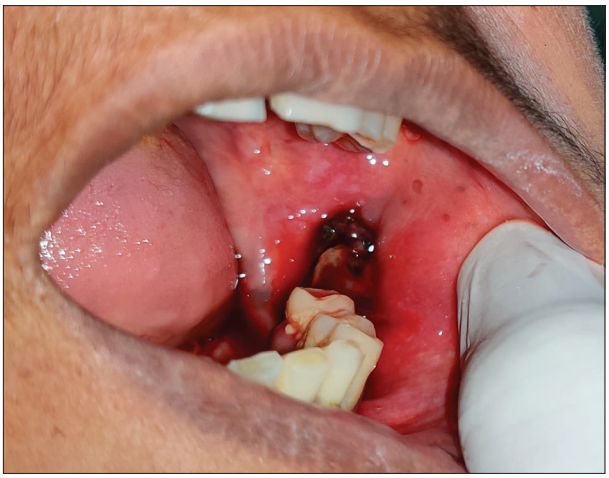

Figure 2: Intraoral view shows a swelling of approximately 4 cm × 5 cm in size over left side of the mandible

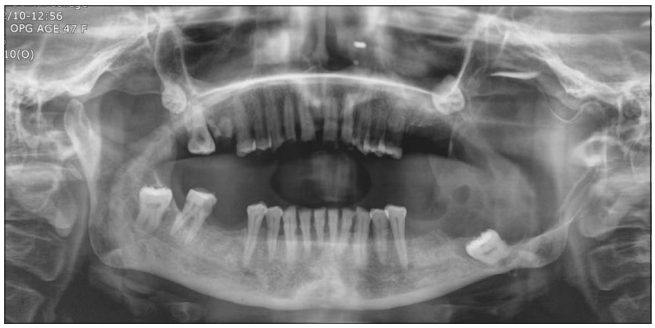

Figure 3: Panoramic radiograph revealed radiolucent lesion extending from left mandibular second premolar till ramus of the mandible

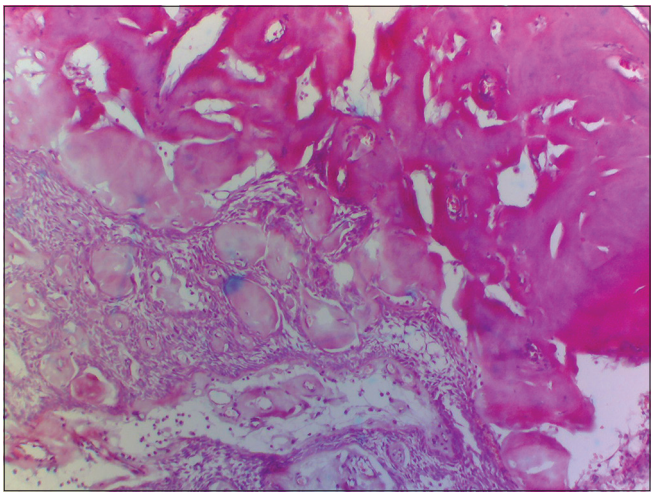

Figure 4: Photomicrograph of the lesion showing foci of ghost cells and eosinophilic dentinoid like material interspersed in proliferating sheets of odontogenic epithelium (H and E, ×10)

of hypercellular proliferation of small cells with scanty cytoplasm, hyperchromatic nuclei and brisk mitotic activity ruled out the diagnosis of GCOC. Van Gieson and Masson trichrome staining were done where ghost cells were stained yellow/red whereas dentinoid like areas appeared pink/blue respectively which further confirmed the nature of ghost cells and dentinoid like areas [Figures 5 and 6]. Based on the histopathological features, findings of histochemistry and the final diagnosis of intraosseous DGCT were given. The patient was treated with segmental mandibulectomy followed by rib grafting, and no recurrence was noted 6-month follow-up.

DISCUSSION

The term DGCT was first proposed for the neoplastic variety of COC (Type 2 COC) by Praetorius *et al*.[6] Odontogenic ghost cell tumor was coined by Colmenero *et al*.[18] DGCT is an extremely rare odontogenic tumor and exists both as a central and a peripheral type. According to the available literature on central DGCTs, only 39 cases have been reported.[17] Buchner *et al*. in their update, reported 66% of DGCT in the Asian population.[19] Extraosseous lesions exhibit limited growth potential and usually occur in sixth decade of life, with an age range of 10–92 years whereas intraosseous DGCT are locally invasive and age ranges from 12 to 75 years with a peak in 4th decade of life.[20] The lesions are predominantly seen in males with equal distribution between the maxilla and mandible.[18] Extraosseous lesions present as firm, painless nodules on gingival or alveolar mucosa with predilection for anterior regions (usually in the edentulous areas), whereas intraosseous lesions present as painless bony swelling in canine to first molar region with obvious facial asymmetry due to expansion of the jaw and occasionally accompanied by pus discharge, tooth displacement or mobility.[6,16,21] In general, these tumors do not exceed 6.5 cm, with a mean of 4.28 cm, although rare cases have shown larger growth occupying almost the entire mandible.[22] Despite the growth pattern, the tumor is asymptomatic in 33% of cases and is often identified

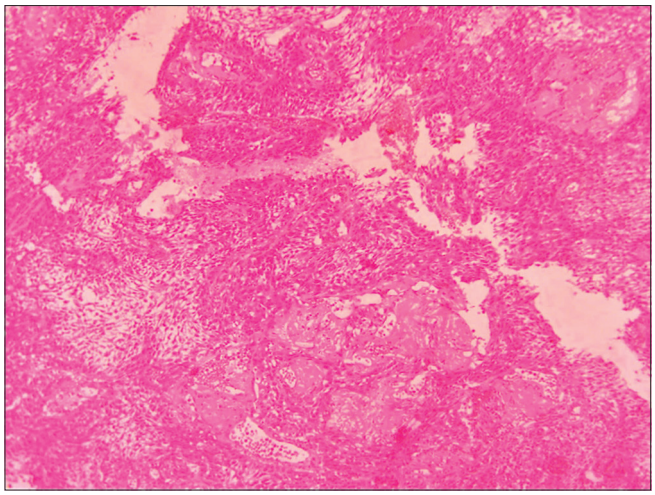

Figure 5: Positive Van Gieson stain showing odontogenic epithelium and ghost cells (yellow color) and dentinoid material (Pink) (Van Gieson stain, ×40)

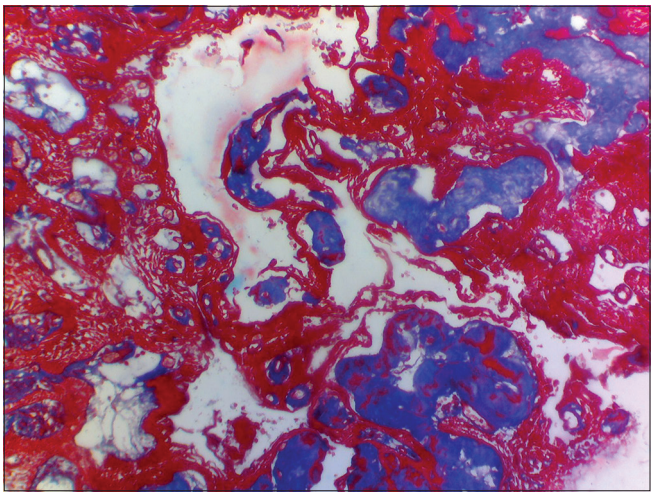

Figure 6: Positive Masson trichrome stain showing odontogenic epithelium and ghost cells (reddish color) and dentinoid material (blue) (Masson trichrome stain, ×40)

during the routine radiographic investigation which is in contrast to a study reported by Buchner *et al*. where the lesion presents with dull, mild pain in 52% of the cases.[19] The present case was seen in a 57-year-old female patient in the left mandibular region which presented as a diffuse extraoral bony hard painless swelling of 4 cm × 5 cm size which was uniform throughout for 6 months.

DGCTs on panoramic radiographs may appear as radiolucent, radiopaque or mixed lesion depending on the amount of calcifications. It may be either unilocular or multilocular presentation with either well-defined or ill-defined margins. The presence of impacted teeth and displacement and/or root resorption of adjacent teeth have also been reported in some cases.[23] OPG of the present case revealed a multilocular radiolucency with displacement of left mandibular third molar and missing first and second molars. These findings were in accordance with the literature review carried out by Konstantakis *et al*. in 2013.[21]

The histogenetic derivation of DGCT has been attributed to cell rests of Serres or the surface epithelium but currently remains unclear. Missense mutation on codon 3 suggests that β-catenin plays an important role in the tumorigenesis of DGCT by an improper differentiation process coordinated by Wnt signaling pathway.[24]

Histopathologically, both intraosseous and extraosseous variants of DGCT are characterized by sheets and islands of odontogenic epithelium with ameloblastic differentiation occasionally undergoing cystic degeneration in a mature connective tissue stroma. A central component of the epithelial islands bares resemblance to the stellate reticulum of the enamel organ.[24] Scattered among the odontogenic epithelium are ghost cells which appear as enlarged, ellipsoidal, eosinophilic epithelial cells which have lost their nuclei and often undergo calcification, which appear as fine basophilic granules or coarser basophilic masses. They are thought to result from squamous metaplasia with secondary calcification due to ischemia/result of apoptotic process/aberrant keratinization/coagulative necrosis. Production of dysplastic dentin or dentinoid which appears as amorphous masses of eosinophilic material containing widely separated cell bodies may be seen in association with the tumor epithelium.[25] The rationale for the formation of dentinoid material has been considered to represent an inflammatory response of the body tissue toward masses of ghost cells or masses of "ghost cells" induce granulation tissue to lay down juxtraepithelial osteoid which may calcify. On the other hand, it was hypothesized that it might be an inductive phenomenon or a metaplastic change in the connective tissue.[12] According to the WHO, the proportion of ghost cells (>1%–2%) and dentinoid is vital for the diagnosis of DGCT as seen in the present case.[8]

The treatment is different for both variants of DGCT due to the difference in recurrence rate and malignant potential.[16] The treatment of choice for peripheral DGCT is local excision and is not thought to recur. Central DGCTs are aggressive neoplasms that show locally invasive behavior and recurrence rates of up to 71% and are reported not only following local excision/enucleation but also 1–5 years after segmental mandibular resection and partial maxillectomy.[26] Malignant transformation of a DGCT into an odontogenic ghost cell carcinoma has also been reported.[19] Recurrent DGCT tumors have shown to exhibit malignant characteristics diagnosed as GCOC. GCOC is a particularly rare malignant counterpart of

DGCT. About 32.5% of GCOCs are derived from DGCT or COC.[17] The present case was treated by segmental resection with safety margin of 0.5 cm and showed no recurrence till date.

CONCLUSION

DGCT is a rare odontogenic tumor with distinctive histological features and aggressive biological behavior. Differentiating this lesion from other odontogenic lesions histologically is important for the appropriate management. Given the rarity, atypical histological characteristics and malignant potential of DGCT, it may be necessary for a long period of clinical, radiographic and histopathological follow-up. Recurrence is relatively more common in central DGCT, especially in cases, which are treated conservatively. Thus, it is vital that central DGCTs are diagnosed early and are treated aggressively to prevent a recurrence. We hope that additional case reports in future will contribute to determining the best treatment options for DGCT in this line, as well as a better explanation of the precise histopathological, biological and clinical development of DGCT and to definitively determine whether aggressive resection is the best treatment for DGCT.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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