**An Unusual Presentation of Ghost Cell Odontogenic Carcinoma: A Case Report with Review of Literature**

**Abstract**

Ghost cell odontogenic carcinoma (GCOC) is a malignant odontogenic epithelial tumor which is an exceedingly rare, highly aggressive, rapidly growing, and infiltrative tumor forming the malignant counterpart of long-standing benign cystic lesions coming in the spectrum of calcifying odontogenic cysts. To date, only a few cases have been reported in the medical literature. A case of unusual presentation of GCOC is presented and the clinical, histopathological, and immunohistochemical features are discussed along with a literature review. Our case report further emphasizes the bizarre biological behavior of this tumor and the need for strict long-term surveillance of the patients as metastasis to distant sites has been reported.

**Keywords:** Ghost cell odontogenic carcinoma, ghost cells, mandible

**Introduction**

Ghost cell odontogenic carcinoma (GCOC) is a malignant odontogenic epithelial tumor with features of calcifying cystic odontogenic tumor (CCOT) and/or dentinogenic ghost cell tumor (DGCT).[1] It is an exceedingly rare, highly aggressive, rapidly growing, and infiltrative tumor with increased risk of local recurrence and distant metastasis.[1] The first case of GCOC was reported in 1971 as a photograph in WHO monograph on odontogenic tumors but with no relevant clinical information.[2] The first well-documented case of a malignancy arising in a calcifying odontogenic cyst (COC) was reported by Ikemura et al. in 1985.[3] It constitutes about 0.37% to 2.1% of all odontogenic tumors.[4] Approximately, only 39 cases have been documented in English literature till date.

This article reports a new case of GCOC involving mandible of a 39-year-old male and reviews the features of this unusual and rare tumor.

**Case Report**

A 39-year-old man reported to our department complaining of a progressively enlarging painful swelling on the right side of the face of 3 months’ duration. The patient gave a history of similar recurrent painless swellings in the same site since childhood. However, he did not seek treatment as it caused little discomfort. He reported that 3 months before the visit, he had been experiencing pain in that region and consulted a dentist nearby and underwent an incision and drainage after which the lesion expanded enormously to the present size. Extraoral examination revealed a hard, tender immobile mass of size approximately 8 cm × 6 cm with soft fluctuant borders extending from corner of the mouth on the right side to angle of the mandible anteroposteriorly and from zygomatic process to lower border of mandible superoinferiorly. The overlying skin was smooth and normal with no surface ulceration and there was no evident lymphadenopathy [Figure 1]. Intraorally, diffuse firm swelling was seen extending lateral to the right mandibular central incisor up to retromolar trigone obliterating mucobuccal sulcus with lingual displacement of all teeth on the right side along with ulceration and superadded infection [Figure 2]. Panoramic radiograph showed an ill-defined unilocular radiolucency of size approximately 5 cm × 5 cm periapical to premolar-molar teeth, and root resorption of involved teeth was noted [Figure 3]. Computed tomography (CT) scan demonstrated a radiolucent lesion in the mandible with

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marked buccal expansion and buccal and lingual cortical break [Figure 4].

Ultrasonography (USG) of lesion was performed which disclosed a hypervascular lesion in the right side of the mandible suggestive of a benign vascular neoplasm. Based on clinical, radiographic, CT, and USG findings, a provisional diagnosis of vascular malformation or endotheliosarcoma was considered. Complete blood count was done and was within normal limits. Embolization of facial artery was done as a precautionary measure, and since embolization was an expensive procedure, complete excision of the lesion was done along with hemimandibulectomy, and entire specimen was submitted for histopathologic examination. Grossly, a fleshy soft tissue mass measuring 9 cm × 6 cm × 5 cm was present on the medial aspect of resected mandible of the right side extending from lower central incisor to the first molar with lingual displacement of all teeth. Expansion of the buccal cortical plate and breach of the buccal and lingual cortical plates were noticed [Figure 5].

Microscopically, proliferation of odontogenic cells with a dual pattern was seen. One set composed of round to ovoid cells with eosinophilic cytoplasm and hyperchromatic nuclei and the other population composed of basaloid cells with pale cytoplasm and vesicular large hyperchromatic nuclei with both types showing extensive nuclear and cellular pleomorphism, cellular atypia, and increased mitotic figures. Anucleate eosinophilic ghost cell aggregates were seen intermingling with the tumor cells in a moderately collagenous stroma with numerous multinucleated giant cells. Atypical dysplastic dentin formation was also seen [Figure 6a and b].

Van Gieson special staining was done to demonstrate dentinoid-like areas and ghost cells [Figure 7]. Immunohistochemical staining with a panel of antibodies demonstrated that neoplastic cells were strongly positive for cytokeratin and negative for vimentin, desmin, SMA,
and CD34 [Figure 8]. With the histopathologic findings and immunohistochemical staining profile, a final diagnosis of GCOC was made. The patient had to undergo extensive surgical resection of the mandible as the resected specimen margins were not free of tumor cells and also adjuvant radiotherapy. The patient is on regular follow-up thereafter, and no recurrence has so far been reported after 6 months of follow-up.

Discussion

GCOC is believed to be one end of the spectrum of a heterogeneous entity known as COC also known as Gorlin cyst, first identified by Gorlin in 1962.[5] In the initial years, COC was considered a nonneoplastic cyst. However, later, some of these lesions showed a solid component also. In 1981, Praetorius et al. classified COCs into cystic and neoplastic (solid) types.[6] In the new 4th edition of the WHO classification 2017, the consensus group agreed to revert back to the original terminology and classify the cyst as calcifying odontogenic cyst and the neoplasm as DGCT whereas GCOC is a malignant odontogenic epithelial tumor with features of one or both of these lesions.[7]

GCOC is an extremely rare malignant odontogenic tumor with only 40 cases reported till date. Review of the clinical features of previously reported cases of GCOC has shown that males are more commonly affected with male: female ratio of 3.4:1 [Table 1] which is a similar trend compared to its benign counterpart.[8] The mean age of occurrence occurred in the fourth decade (43.05 years) predominantly young and middle-aged adults with age ranging from 13 to 89 years [Table 1]. This is different from its benign neoplastic counterparts such as CCOT and DGCT which has a peak incidence in the second decade.[8] This difference may be attributable to the fact that majority of GCOC arises from malignant transformation of preexisting benign COC/CCOT/DGCT. More than half of the reported cases are from Asia (65%) when compared with other racial groups [Table 1]. The predominance of GCOC in Asians is in keeping with the demographics of the benign COC, which is also more common in Asians.[8,9] This suggests
that ethnic origin may play a role in the incidence of GCOC.\(^9\) Of the 40 cases reported, 27 cases (67.5\%) were in maxilla and 13 (32.5\%) in mandible [Table 1]. There was a clear predilection of GCOC in maxilla (2:1) which differs from the site distribution of benign COC that occurs equally in both maxilla and mandible. Only four cases, all in mandible, crossed the midline.

GCOC can appear as either “de novo” or as malignant transformation of a preexisting calcifying cystic odontogenic tumor (CCOT)/DGCT or other odontogenic tumors.\(^{10,11}\) GCOC is seen to arise from CCOT after multiple recurrences. More than half of the cases reviewed had a preexisting COC/CCOT/DGCT/other odontogenic malignancies to account for before malignant transformation to GCOC occurred [Table 1]. Eighteen of the reported cases gave an incidence of “de novo” origin of this tumor [Table 1]. In our case, history from the patient was inconclusive as the patient has not undergone any examination and related investigations for a similar lesion which is reportedly recurring at episodes in the same site. Hence, we are assuming it to be a benign cystic lesion which has undergone a malignant transformation to the present lesion. However, there was no evidence of any cystic epithelial lining and the lesion appeared as a solid tumor mass both macroscopically and microscopically.

Of the 40 cases reviewed, only 30 cases reported radiographic features. From them, most of the lesions (22 cases) showed mixed radiolucent–radiopaque features. Only 8 cases were totally radiolucent [Table 1]. However, radiographic features of GCOC are not specific and only a differential diagnosis of possible malignant tumors such as osteosarcoma/malignant ameloblastoma can be made based on radiographic features.

A diagnosis of GCOC is purely dependent on the histological examination of the tumor. According to the 2005 World Health Organization guidelines,\(^1\) GCOC is usually diagnosed on the basis of atypical histological features, groups of ghost cells, necrosis, prominent mitoses, infiltrative growth pattern, and aggressive behavior. The histological features of GCOC are an ameloblastoma-like epithelial proliferation, ghost cells that may be calcified, admixed with areas of atypical features such as increased cellularity, pleomorphism, mitosis, necrosis, and dentinoid formation.\(^9\) The accurate diagnosis of GCOC requires extensive sampling of the specimen as the features of malignancy can be focal and the other areas may show benign histology.

The immunocytochemical profile of aggressive GOCs has been first described by Scott and Wood where they reported anti-cytokeratin immunoreactivity in the “inclusions” noted in their case; the reactivity of the epithelium or ghost cells were however not commented upon.\(^{12}\) Folpe et al.\(^{13}\) studied extensively on the immunotyping of the tumor and reported that neoplasm had epithelial characteristics with squamous differentiation and showed high reactivity for high and low molecular weight cytokeratin, carcinoembryonic antigen, and mild reactivity for vimentin. They also commented that aggregates of intermediate filament material in a perinuclear distribution imparted the eosinophilia seen in the cytoplasm at the light microscopic level. Their study also found no immunohistochemical evidence of p53 overexpression. The proliferative rate was low, as assessed by immunoreactivity for proliferating cell nuclear antigen. However, recent studies reported higher number of cells expressing Ki-67 or proliferative cell nuclear antigen, overexpression of p53, and extensive expression of matrix metalloproteinase-9 in stromal cells indicative of the prognostic factor for cell

### Table 1: Consolidated data after reviewing literature of case reports of ghost cell odontogenic carcinoma

| Clinico-pathologic variables | Prevalence |
|-----------------------------|------------|
| Mean age at occurrence      | 43.05 years (13-89) |
| Gender (%)                  |            |
| Male                        | 31 (77.5)  |
| Female                      | 9 (22.5)   |
| Race (%)                    |            |
| Asian                       | 26 (65)    |
| White                       | 4 (10)     |
| Black                       | 5 (12.5)   |
| NA                          | 5 (12.5)   |
| Site (jaw) (%)              |            |
| Maxilla                     | 27 (67.5)  |
| Mandible                    | 13 (32.5)  |
| Crossing midline            | 4 (all in mandible) |
| Root resorption             |            |
| Yes                         | 14 (including our case) |
| No                          | 14         |
| NA                          | 12         |
| Tooth displacement/mobility |            |
| Yes                         | 10 (including our case) |
| No                          | 15         |
| NA                          | 15         |
| Radiographic feature        |            |
| Mixed radiolucent and radiopaque | 22         |
| Radiolucent                 | 8          |
| NA                          | 10         |
| Pattern of development      |            |
| De novo                     | 18         |
| After COC/CCOT/DGCT         | 10         |
| Other odontogenic tumors    | 4          |
| NA                          | 8 (including our case) |
| Follow-up                   |            |
| No recurrence               | 14         |
| Local recurrence            | 16         |
| Local recurrence followed by death | 3         |
| Distant metastasis          | 2          |
| Distant metastasis followed by death | 3         |
| NA                          | 2          |

COC=Calcifying odontogenic cyst, CCOT=Calcifying cystic odontogenic tumor, DGCT=dentinogenic ghost cell tumor, NA=Not available
proliferation and tumor invasion. This may be owing to the revised standardization of immunohistochemical procedure and improved sensitivity of antibodies used in the procedure.

Gene alterations were studied and reported by Rappaport et al.; mutation of the β-catenin gene was noted at codons 3, 4, 5, and 57 in all COCs, with the exception of GCOC, which was the only one to display a mutation at codon 33. They also reported of three genomic alterations: CTNNB1 S33C, CREBBP K1741*, and MLL2 S1997fs*44. An extensive integrative genomic and transcriptive analysis of GCOC studied by Bose et al. reported that there was homozygous deletion of RB1 locus, homozygous frameshift mutation in APC gene, and also a novel fusion involving the TCF4 and PTPRG genes. They also observed several alterations in the Sonic Hedge Hog gene (SHH) pathway including copy number gains in SHH and GLI1 genes accompanied by increased expression of these genes.

As the number of published cases is limited, clinical behavior of the tumor is yet to be established, local recurrences have been reported, but distant metastasis is extremely rare. Only five cases have been reported to cause cranial and pulmonary metastases. Although a recent report indicated that most cases of the COC have a benign course, 3 of 122 cases of COC were malignant (i.e. GCOC); hence, pathologists should be aware of this rare entity and its clinical course. The oncological prognosis shows a 5-year survival rate of 73%. A multidisciplinary team including a pathologist with expertise in evaluating odontogenic neoplasms is essential to provide proper treatment and optimal outcome, and wide excision with clear margins is highly recommended. GCOC being a rare and unpredictable odontogenic malignancy, long-term surveillance of patients is mandatory as metastasis to distant sites has been reported.

**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 identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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