Ghost cell odontogenic carcinoma of anterior mandible: A rare case report with review of literature

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Abstract

A 24-year-old male reported to the outpatient department with a complaint of swelling of the anterior lower jaw region for 9 months with history of traumatic injury and extraction of teeth from the same region, a month before the onset of swelling. Swelling was obvious extra- and intraorally which on examination presented as a soft to firm non-tender and non-fluctuant mass with an approximate size of 4 cm × 3 cm, extending from 34 to 43 region with obliteration of labial vestibule. Panoramic radiograph and cone-beam computed tomography showed a well-defined radiolucency in the mandibular anterior region crossing the midline with erosion of labial bony plates and root of 42 along with a tooth-like radiopaque mass within the lesion. Provisional diagnoses of odontogenic keratocyst, ameloblastomas, central giant cell granuloma and calcifying epithelial odontogenic tumor were listed. The histopathological and immunohistochemical examination of lesion followed by the biopsy confirmed the diagnosis of Ghost cell odontogenic carcinoma.

Keywords: Dentinogenic ghost cell tumor, ghost cell odontogenic carcinoma, ghost cells,
Personal and family history
The personal and family history was not relatable to the present condition.

Physical examination
Extraoral examination revealed a single large asymptomatic firm swelling approximately measuring 4 cm × 4 cm in the mandibular midline. The overlying skin showed scar of the previous trauma. Intraorally, the swelling was soft to firm, nontender and nonfluctuant of approximately size 4 cm × 3 cm, extending from 34 to 43 region with obliteration of labial vestibule [Figure 1b and c]. The mucosal surface was normal in color without signs of any drainage. Anterior mandibular teeth 41, 31, 32 and 33 were missing due to previous trauma while 42 showed grade II mobility.

Imaging examinations
Orthopantomogram (OPG) showed well-defined unilocular radiolucency in the mandibular anterior region crossing the midline and root resorption of 42 along with a tooth-like radiopaque mass within the lesion [Figure 2a]. Cone-beam computed tomography (CBCT) showed a round unilocular lesion with complete destruction of labial bony plate and irregular resorption front towards lingual side [Figure 2b]. Non uniform resorption of bone and a tooth-like calcification was evident in the 3D reconstruction image of CBCT [Figure 2c].

Laboratory examinations
The routine blood examinations showed no alterations.

Cytology findings
The thick yellow fluid discharge at the time of incision biopsy on H&E-stained smear showed population of large oval to round cells with vesicular as well as hyperchromatic nuclei within a background of red blood cells.

Histopathologic findings
Microscopically, unencapsulated sheets of proliferating odontogenic epithelial cells were seen with a dual cellular pattern. Few cells were round to ovoid with eosinophilic cytoplasm and hyperchromatic nuclei and the other composed of basaloid cells with pale cytoplasm and large vesicular hyperchromatic nuclei [Figure 3a-c]. Areas of calcifications were seen close to few tumor islands and within the ghost cell clusters [Figure 3d]. The tumor cells showed extensive nuclear and cellular pleomorphism, cellular atypia and increased mitotic figures (>6/HPF) [Figure 4a-c]. Features of ghost cell keratinization were evident at many focuses as large round pale eosinophilic malignant epithelial cells which lack nuclear features [Figures 3c and 4d]. Multinucleated giant cells were evident at places were the ghost cell interacted with overlying connective tissue stroma [Figure 5a]. The possibility of any odontogenic cyst, COC, ameloblastomas and calcifying epithelial odontogenic tumor (CEOT) were ruled out narrowing down the differential diagnosis to GCOC and DGCT. The presences of dentinoid in
such calcifications were ruled out using Van Gieson’s staining [Figure 5b]. Subsequent immunohistochemical examination using Ki67 (>60%) [Figure 5c] showed a high malignant potential of tumor while higher p53 expression, [Figure 5d] both favored a malignant ghost cell lesion the GCOC over the benign DGCT. Correlating the clinical, radiological, histopathological and IHC expressions the final diagnosis was GCOC.

DISCUSSION

The calcifying odontogenic cyst (COC), DGCT and GCOC makes up a spectrum of lesions characterized by odontogenic epithelium with ghost cell keratinization and calcifications. The cystic entity among these known as COC also known as Gorlin cyst, first identified by Gorlin in 1962 and was considered a nonneoplastic cyst. In 1981, Praetorius et al. classified COCs into cystic and neoplastic (solid) types. In the new 4th edition of the WHO classification 2017, the consensus group reverted the terminology and mentioned the cyst as calcifying odontogenic cyst and the neoplasm as DGCT. The malignant variant of with features of one or both of these lesions where termed GCOC.

GCOC is an extremely rare malignant odontogenic tumor with only 50 cases reported in literature till date with histopathological evidence [Table 1]. This appears to be more common in Asian population with a male predilection (male:female ratio of 3.4:1). The age of occurrence is variable from 10 to 89 but with a peak incidence in the fourth decade of life (mean age-43.4 years). GCOC occurs more frequently in the maxilla than the mandible with a usual presentation of a painful swelling with local paresthesias. Of the 51 cases reviewed, 31 cases (62%) were in maxilla and 19 (38%) in mandible. The size of swelling is variable from 3 mm to a maximum of 10 cm with local destructive features. Most cases showed recurrence at least once and few were with multiple recurrences as well as distant metastasis. Few cases were severe enough to lead to death of patient all of which denotes the malignant potential of the tumor. The consolidated data of literature till date is tabulated in Table 2.

Origin

GCOC can appear as either “de novo” or as malignant transformation of a preexisting COC, CCOT, DGCT or other odontogenic tumors. A careful patient history and clinical data is mandatory to ensure the origin of GCOC. In literature 28 cases found to be de novo in origin whereas 15 cases had previous history of ghost cell lesion spectrum COC, CCOT or DGCT. Three cases had history
of ameloblastoma where as a non odontogenic cyst and CEOT constituted one each.\textsuperscript{11,14,22} One case reported recurrent maxillary GCOC with suspected cholesterol granuloma of the maxillary sinus, which was improperly diagnosed as CEOT [Table 2].\textsuperscript{46} In our case, history from the patient was inconclusive as the patient has not undergone any examination and related investigations for a similar lesion in the same site before the trauma. We assume that the trauma may have aggravated a preexisting lesion but lack of histopathological evidence of such a lesion concludes the origin to be de novo.

**Radiology**

GCOC in most cases shows a mixed radiolucent and radiopaque pattern with poorly defined borders, with or without root resorption and tooth displacement. The radiographic differential diagnosis thus can include other mixed tumors such as a malignant bone tumor (osteosarcoma) or other odontogenic tumors (ameloblastomas, CEOT). Of the 51 cases reviewed, 45 cases reported radiographic features. Most cases had OPG and CT findings while 4 cases had positron emission tomography (PET) scan findings. Few cases had radiographic details of unspecified imaging modality. Most cases were radiolucent lesions to mixed radiolucent–radiopaque lesions while few were radiopaque. Four cases reported with computed tomography CT) scan image revealed hypermetabolic lesion [Table 2]. However, radiographic features of GCOC are not specific and only a differential diagnosis of possible malignant tumors.

**Histology**

According to the 2017 World Health Organization guidelines the diagnosis of GCOC is purely dependent on the histological examination of the tumor. This guideline is followed for the diagnosis of GCOC as well as to rule out its histological differential diagnosis DGCT [Table 3].\textsuperscript{4,8} The histological features mainly include groups of ghost cells, necrosis, prominent mitoses, infiltrative growth pattern and aggressive behavior.\textsuperscript{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. Two cases reported as GCOC in in literature was avoided from the data as the histopathological features did not show any features of malignancy to be diagnoses as GCOC.\textsuperscript{2}

**Special stains**

The use of various special stains are reported in demonstrating ghost cells and differentiating dentinoid material in ghost cell lesions In a study by Sun ZJ elt al the ghost cells were stained red and the dentinoid material was stained blue by Heidenhain–Azan stain.\textsuperscript{24} The individual cell disintegration (ghost cell keratinization), extracellular amorphous eosinophilic material (dentinoid) and calcifications can be distinguished by Van Gieson’s stain.\textsuperscript{4} The stain differentiates the dentinoid (pink) with ghost cells (yellow), collagen and other calcifications.

**Immunohistochemistry**

The immunohistochemical analysis of GCOCs was first described by Scott and Wood proving the epithelial origin by a positive anti-cytokeratin expression.\textsuperscript{11} Folpe \textit{et al}. studied extensively on immunohistochemical expression of the tumor and reported that it had epithelial characteristics with squamoid differentiation. According to their study GCOC showed high reactivity for high and low molecular weight cytokeratin, carcinoembryonic antigen, mild reactivity for vimentin, low immunoreactivity for proliferating cell nuclear antigen and no immunohistochemical evidence of p53 overexpression.\textsuperscript{16} Later, in study by Lu \textit{et al}. three cases expressed high molecular weight keratin but were negative for CEA, vimentin, S-100 and synaptophysin and showed variable staining for neuron-specific enolase. However, the proliferation index, as assessed by p53 and Ki67 staining showed higher positive expression.\textsuperscript{19} The pleomorphic tumor cells were focally positive, and nucleated cells adjacent to the ghost cells were positive for cytokeratins and involucrin. Bcl-2 immunostaining was found negative whereas Bcl-XL was demonstrated in
| Years | Author | Age/sex | Presenting complaint | Site | Treatment | Origin | Recurrence and follow-up |
|-------|--------|---------|----------------------|------|-----------|--------|------------------------|
| 1985  | Ikemura et al. | 48/F | Swelling of upper gingiva and hard palate on left side | Maxilla | Surgery | De novo | 1 recurrence and no evidence of disease after follow-up |
| 1986  | Ellis et al. | 64/M | Painful Swelling in anterior mandible | Mandible | Surgery | OPG-Mixed | 1 recurrence death by intracranial extension |
| 1986  | Ellis et al. | 17/M | Ulcerated mass | NA | Not specified-Mixed | De novo | 1 recurrence |
| 1987  | Godbole et al. | 46/M | Painless swelling of the mid right maxilla and bleeding from site | Maxilla | Surgery | OPG and waters mixed | Free of tumor after 10 years |
| 1989  | Scott and Wood | 30/M | Swelling, left lacrimation and nasal blockage | Maxilla | Surgery | OPG-Mixed | 4 recurrences and lost to follow-up |
| 1992  | McCary et al. | 13/F | Extraction site that had not healed in 2 years | Maxilla | Surgery | OCC | No recurrence and no evidence of disease after follow-up |
| 1993  | Dubiel-Bigaj et al. | 42/F | A massive, ulcerative and rapidly growing tumor | Maxilla | Surgery | OPG-Mixed | 2 recurrences. Alive with residual tumor for 3 years |
| 1994  | Star and Ng | 39/M | A swelling on the right side of the face | Maxilla | Surgery | OPG-RL | 3 recurrences. No evidence of disease after follow-up |
| 1996  | Alcayde et al. | 7/F | Painless swelling from infraorbital region to the left mandible | Maxilla | Surgery | OPG-RL | 1 recurrence death by intracranial extension |
| 1998  | Falge et al. | 26/M | A progressively enlarging right cheek mass | Maxilla | Surgery | OPG-Mixed | 1 recurrence and no recurrence after 6 years |
| 1999  | Carle and Arendt | 57/M | Difficulty in breathing and swelling of the upper lip | Maxilla | Radiation Therapy | OPG-Mixed | No recurrence after 7 years |
| 2000  | Kim et al. | 33/M | Mandibular swelling | Mandible | Surgery | OPG-Mixed | 2 recurrences. Alive with and no evidence of disease after follow-up |
| 2002  | Kashiya et al. | 59/M | A painless swelling on the right side of the mandible | Mandible | Surgery | OPG-RL | 4 recurrences and lost to follow-up |
| 2004  | Cheng et al. | 36/M | A painless swelling in the right maxilla | Maxilla | Construction View | OPG-Mixed | No recurrence after 7 years |
| 2005  | Cheng et al. | 35/M | A painless swelling in the right maxilla | Maxilla | Surgery | OPG-Mixed | No recurrence after 7 years |

Table 1: List of case reports on ghost cell odontogenic carcinoma with its significant features. Contd....
| Presenting complaint | Site | Treatment | Size (cm) | Age (male/female) | Years | Recurrence and follow-up | Origin | Imaging (modality-finding) |
|----------------------|------|-----------|-----------|------------------|-------|--------------------------|--------|---------------------------|
| Pain in the right maxillary mass | Mandible | Surgery | 4×2×2 | 44/M | 2004 | 1 recurrence | COC | OPG-RL |
| Tenderness and swelling of the face | Mandible | Surgery | 2×1 | 36/M | 2004 | No evidence of disease after 18 months | COC | CT-lytic lesion |
| A painful swelling in the right maxilla | Maxilla | Surgery | 3×3 | 40/M | 2007 | Recurrence after 1 year | De novo | OPG-Mixed |
| A painful swelling in the maxilla | Maxilla | Surgery | 10×10 | 61/M | 2004 | No evidence of disease after 6 months | NA | CBCT |
| A slowly growing, painful and tender swelling on the right side of the face | Maxilla | Surgery | 2×1 | 68/M | 2007 | 1 recurrence | COC | OPG-RL |
| A slowly growing mass in the right maxilla | Mandible | Surgery | 10×10 | 23/F | 2009 | Recurrence after 1 year | De novo | CBCT |
| A painful swelling on the right mandible | Mandible | Surgery | 10×10 | 2009 | 2009 | 1 recurrence | De novo | CBCT |
| A maxillary swelling with local paraesthesia in the left side of the face | Mandible | Surgery | 2×1 | 51/M | 2010 | No evidence of disease after 18 months | COC | OPG-RL |
| A gingival swelling in area of previously treated cyst | Mandible | Surgery | 3×2 | 36/M | 2009 | 2 recurrence | De novo | OPG-RL |
| A painful swelling in the left maxilla | Maxilla | Surgery | 4×2 | 44/M | 2010 | 2 recurrence within 22 months | COC | OPG-RL |
| A gingival swelling | Mandible | Surgery | 4×3 | 23/F | 2010 | 1 recurrence | De novo | OPG-RL |
| A slowly growing painless mass in the right maxilla | Maxilla | Surgery | 3.5×2.5×2 | 38/M | 2009 | No evidence of disease after 1 year | COC | OPG-RL |
| A slowly growing, painful and tender swelling on the right side of the face | Maxilla | Surgery | 4×2×2 | 54/M | 2011 | No evidence of disease after 1 year | COC | OPG-RL |
| A slowly growing mass in the right mandible | Mandible | Surgery | 3×3 | 47/F | 2010 | 1 recurrence | COC | OPG-RL |
| A painless swelling in the region | Mandible | Surgery | 3×2×2 | 40/M | 2011 | No evidence of disease after 1 year | COC | OPG-RL |
| A slowly growing mass in the lower right jaw | Mandible | Surgery | 5×4 | 30/M | 2011 | 1 recurrence and no recurrence after 4 years | COC | OPG-RL |
| Recurrence of previous swelling of the left mandible | Mandible | Surgery | 1×1 | 70/F | 2011 | No evidence of disease after 1 year | De novo | OPG-RL |
| A gingival swelling | Mandible | Surgery | 4×3 | 23/F | 2010 | 1 recurrence | De novo | OPG-RL |
| A slowly growing, painless mass in the right maxilla | Maxilla | Surgery | 3×2×2 | 51/M | 2010 | No evidence of disease after 1 year | COC | OPG-RL |
| A slowly growing, painful mass in the right maxilla | Mandible | Surgery | 2×1 | 36/M | 2011 | 1 recurrence | De novo | OPG-RL |
| A recurrence at 7th month | Mandible | Radiotherapy | De novo | 89/M | 2010 | No evidence of disease after 1 year | De novo | OPG-RL |
| A maxillary mass in area of the previously treated cyst | Maxilla | Surgery | 2×1 | 47/F | 2009 | 3 recurrence | De novo | OPG-RL |
| A gingival swelling | Mandible | Surgery | 2×1 | 23/F | 2011 | 1 recurrence | De novo | OPG-RL |
| A painless swelling in the region | Mandible | Surgery | 3×2×2 | 36/M | 2011 | No evidence of disease after 1 year | COC | OPG-RL |
| A gingival swelling | Mandible | Surgery | 2×1 | 23/F | 2011 | 1 recurrence | De novo | OPG-RL |
| A gingival swelling | Mandible | Surgery | 2×1 | 23/F | 2011 | 1 recurrence | De novo | OPG-RL |
| A painless swelling in the region | Mandible | Surgery | 3×2×2 | 36/M | 2011 | No evidence of disease after 1 year | COC | OPG-RL |
| n  | Years | Author                        | Age/sex (male/female) | Presenting complaint                                           | Size (cm) | Site     | Imaging (modality-finding) | Treatment       | Origin     | Recurrence and follow-up                                                                 |
|----|-------|-------------------------------|-----------------------|---------------------------------------------------------------|-----------|----------|----------------------------|----------------|------------|------------------------------------------------------------------------------------------|
| 42 | 2015  | Renu Sukumaran et al.         | 54/M                  | Pain in the left malar prominence and epistaxis              | 4.6×4.5×3.8 | Maxilla | NA                         | Surgery, radiotherapy | De novo   | Metastasis to lung in 2 years                                                             |
| 43 | 2015  | Safia K. Ahmed et al.         | 10/M                  | Fluctuant mass in the right maxilla                          | 5.3cms long | Maxilla | CT-soft tissue lesion PET-FDG | Surgery, radiotherapy | De novo   | No evidence of disease after 1.2-year follow-up                                          |
| 44 | 2017  | Gomes et al.                  | 45/F                  | Abnormality on the maxillary right gingiva                  | 3×2.5×1.7 | Maxilla | 3D CT-soft tissue lesion OPG-RL PET | Surgery | De novo | No evidence of disease after 2-year follow-up                                           |
| 45 | 2017  | Namana M et al.               | 37/M                  | Pain in the lower right back tooth region                   | NA        | Mandible | CT-soft tissue lesion MRI-mixed | Surgery | De novo       | Recurrence after 1 year with lung metastasis 3 recurrence 10th, 22nd, 28th months, patient died 3 years and 10 months after initial diagnosis. Under follow-up |
| 46 | 2017  | Miwako S et al.               | 65/M                  | Painful swelling of the left maxilla                         | 4 cms long | Maxilla | CT-soft tissue lesion MRI-mixed | Surgery, chemotherapy Radiotherapy | From CCOT |                                             |
| 47 | 2017  | Sang Yoon Park et al.         | 53/M                  | Slow growing painless swelling and bleeding from right mandible | 6.4×6.1×5.9 | Mandible | OPG-RL CT-RL PET | Surgery | De novo       |                                             |
| 48 | 2018  | Remya et al. (India)          | 39/M                  | Painful swelling on the right side of the face of 3 months' duration | 9×6 × 5 | Mandible | OPG-RL CT-RL PET | Surgery | De novo       | no recurrence after 6 months                                                             |
| 49 | 2018  | Ohata et al.                  | 44/M                  | Swelling in the left maxilla                                 | 3×2.5    | Maxilla | CT-mixed lesion PET-FDG     | Surgery | From unknown cyst | Free from recurrence and metastasis for 3 years after surgical resection No evidence of recurrence or metastasis after the 20-month                |
| 50 | 2018  | Qin et al.                    | 41/M                  | Bloody purulent rhinorrhea with a peculiar smell in the right nasal cavity | 3.5×2.5×2.9 | Maxilla | MRI-soft tissue mass | Surgery, Chemotherapy Radiotherapy Incision Biopsy | From cholesterol granuloma of the maxillary sinus De novo | Under chemotherapy and follow-Up |
| 51 | 2019  | Present case (India)          | 23/M                  | Swelling on anterior jaw region                             | 4×3       | Mandible | OPG-RL CT-Lytic lesion      | Surgery |                                             | Under chemotherapy and follow-up |

M: Male, F: Female, OPG: Orthopathamogram, CT: Computed tomography, MRI: Magnetic resonance imaging, RL: Radiolucent, RO: Radiopaque
malignant epithelial cells but ghost cells were faintly positive for Bcl-XL. Bax positivity was expressed in ghost cells and in nucleated cells adjacent to ghost cells, but it was not found in pleomorphic tumor cells. Nucleated cells immediately adjacent to ghost cells and pleomorphic epithelial cells had a positive reaction in Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling assay used to detect cells undergoing apoptosis.\[29\] In a study by Roh et al. the osteoclast-related cytokines, Tartrate resistant acid phosphatase and vitronectin receptor were detected in the ghost cells, but they were not expressed in the tumor cells.\[25\] Recent studies reported higher number of malignant epithelial cells expressing cytokeratin, Ki-67 and p53.\[24,29,34,38,43,45,48\] In cases reported by Zhu et al. the positive expression rate of Ki-67 was 61.8% which indicates that cell proliferation activity is significantly higher. Only a few ghost cells were positive for MMP-9 while all were negative for Ki-67.\[51\] In one study, tumor cells were positive for cytokeratin and p63 and were negative for TTF1 and CK7.\[39\] Expression of Syndecan-1 was also observed in one study in which it was frequently expressed in the cells resembling the stellate reticulum and ameloblastomatous proliferation but the stromal cells were negative for Syndecan-1.\[48\]

### Genetic background

Gene alterations in GCOC were first studied and reported by Rappaport et al. Mutation of the β-catenin gene was noted at codons 33. They also reported of three genomic alterations: CTNNB1 S33C, CREBBP K1741* and MLL2 S1997fs*44.\[34\] An extensive integrative genomic and transcriptomic analysis of GCOC studied by Bose et al. reported numerous genomic alterations. There was homozygous deletion of RB1 locus, homozygous frame shift 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.\[49\] However, the exact genetic background of the tumor is yet to be established by further studies.

### Recurrence, metastasis and survival

A recurrence rate of 63.4% has been reported in literature.\[47\] The prognosis shows a 5-year survival rate of 73%.\[6,19\] GCOC being a rare and unpredictable odontogenic malignancy, long-term surveillance of patients is mandatory as metastasis to distant sites has been reported. In literature review of 51 cases, 13 cases showed no recurrence after surgical excision but 18 cases had local recurrence once after initial treatment and 9 cases had multiple recurrence. Five cases showed distant metastasis, and in seven cases, tumor leads to death of patients [Tables 1 and 2].

### 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.

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Conflicts of interest
There are no conflicts of interest.

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