Case Report

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,

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INTRODUCTION

Ghost cell odontogenic carcinoma (GCOC) is a rare malignancy of odontogenic epithelium described first by Ikemura *et al.* in 1985.[1] The origin of GCOC is thought to be either *de novo* (55% cases) or may arise from a preexisting tumor (45% cases) like calcifying cystic odontogenic tumor (CCOT) or from dentinogenic ghost cell tumor (DGCT).[2] The progression and aggressiveness of GCOT is uncertain as it may vary from a slow growing mass to rapid destructive lesion. It constitutes about 0.37% to 2.1% of all odontogenic tumors.[3,4] Entities such as CCOT and DGCT manifest similar clinical and radiological criteria as that of GCOC making the diagnosis challenging. In literature till date only few cases of GCOT have been reported. Here we report a case of GCOC with the clinical, radiological, histopathological and immunohistochemical features along with detailed review of literature.

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CASE REPORT

Chief complaint

A 24-year-old male reported to the outpatient department with complaint of swelling of the anterior lower jaw region for 9 months. He had a history of traumatic injury and extraction of teeth from the same region around a month before the onset of swelling [Figure 1a].

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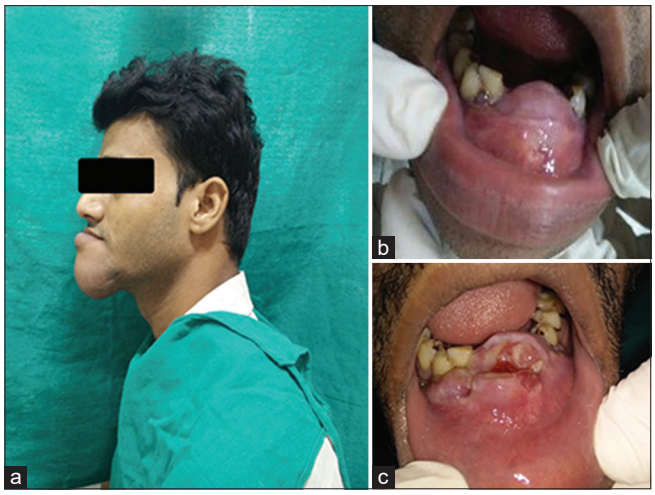

Figure 1: Clinical presentation of present case (a): Swelling of the anterior lower jaw region (b): Intraoral swelling with obliteration of labial vestibule (c): Intraoral swelling with site of incision biopsy

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 approximate 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

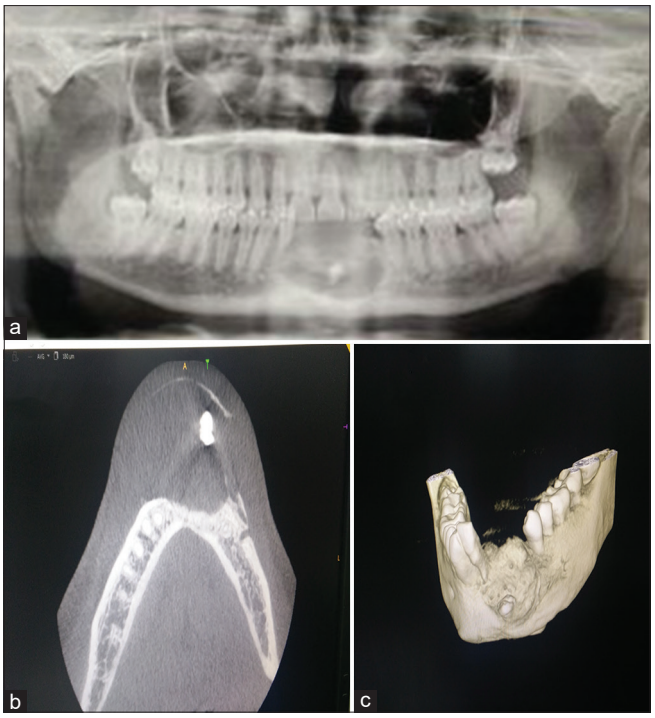

Figure 2: Radiograph of present case (a): Orthopathamogram showing well-defined unilocular radiolucency in the mandibular anterior region crossing the midline and root resorption of 42 along with a tooth-like radiopaque mass within the lesion (b): Cone-beam computed tomography showing round unilocular lesion with complete destruction of labial bony plate and irregular resorption front towards lingual side (c): Three-dimensional reconstruction of cone-beam computed tomography showing non uniform resorption of bone and a tooth-like calcification

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 keratiniation 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

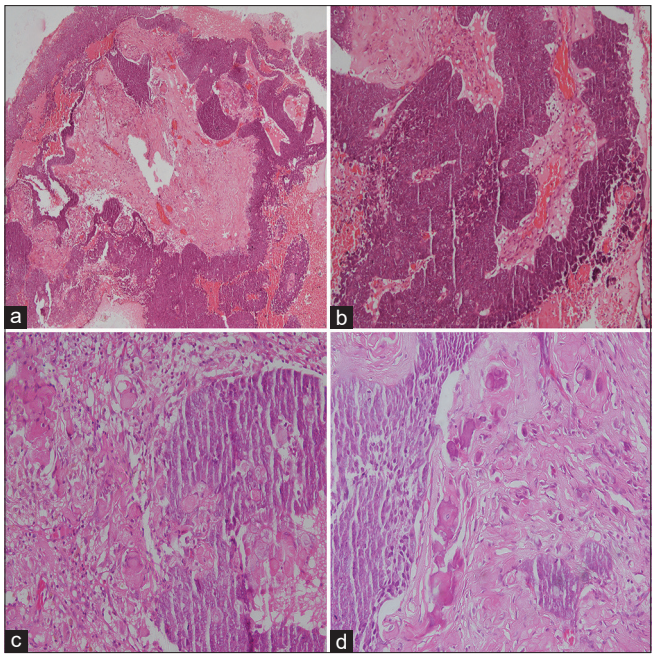

Figure 3: Photomicrograph of present case showing, (a): unencapsulated sheets of proliferating odontogenic epithelial cells in fibro cellular stroma (×40) (b): proliferating sheets of odontogenic epithelial cells (×100) (c): Tumor Island showing ghost cell changes and clusters of Ghost cells (×100) (d): Ghost cell changes and calcifications close to the tumor island (×100)

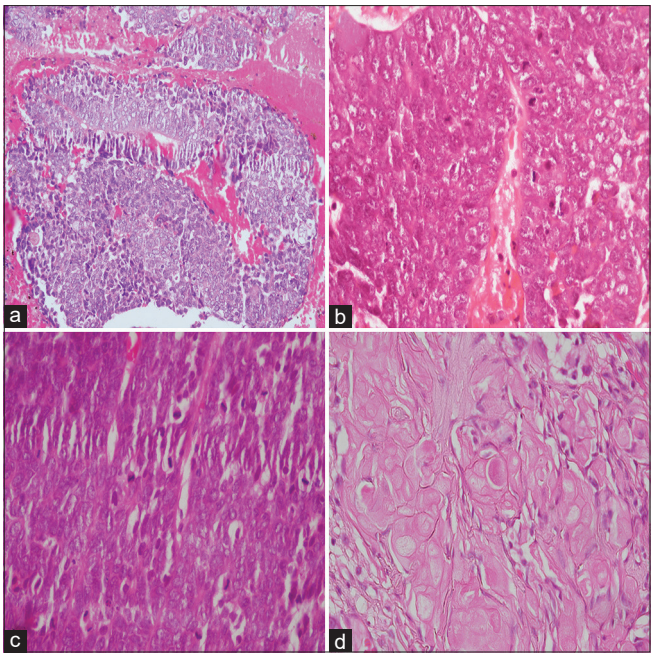

Figure 4: Photomicrograph showing (a): pleomorphism of cells within the tumor island (population of cells with vesicular nuclei and round to oval hyperchromatic nuclei with scanty cytoplasm) (×200) (b): Tumor Island with peripheral columnar cells having vesicular nuclei and absence of ameloblastomas like areas (×400) (c): Abnormal mitotic figures (>6/HPF) (×400) (d): cluster of eosinophilic cells with lack of nuclear detail (Ghost cell keratinization) (×400)

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.[5] 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 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.[7,8]

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).[4,47] 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.[2,4,47] 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

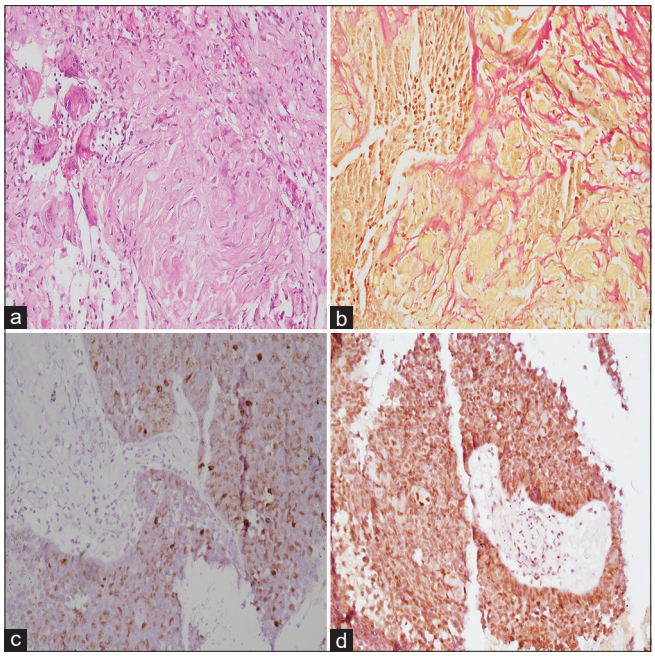

Figure 5: Photomicrograph showing (a): Giant cell reaction within the connective tissue in reaction to the ghost cells (×200) (b): Van Gieson's stain to differentiate calcification from dentinoid material, ghost cells (yellow) and collagen (×200) (c): Ki67 expression in epithelial cells within tumor island (>60%) (×200) (d): Strong p53 expression within epithelial tumor island (×200)

of ameloblastoma where as a non odontogenic cyst and CEOT constituted one each.[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].[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].[4,8] The histological features mainly include groups of ghost cells, necrosis, prominent mitoses, infiltrative growth pattern and aggressive behavior.[8] 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.[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.[24] The individual cell disintegration (ghost cell keratinization), extracellular amorphous eosinophilic material (dentinoid) and calcifications can be distinguished by Van Gieson's stain.[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.[11] Folpe *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.[16] Later, in study by Lu *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.[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

Table 1: List of case reports on ghost cell odontogenic carcinoma with its significant features

n	Years	Author	Age/sex (male/female)	Presenting complaint	Size (cm)	Site	Imaging (modality-finding)	Treatment	Origin	Recurrence and follow-up
1	1985	Ikemura *et al*.[1]	48/F	Swelling of upper gingiva and hard palate on left side	4×6	Maxilla	Not specified-mixed	Surgery Radiotherapy Chemotherapy	*De novo*	1 recurrence death by intracranial extension
2	1986	Ellis *et al*.[9]	64/M	Painful Swelling in anterior mandible	5×3	Mandible	Occlusal-RL	Surgery	From COC	1 recurrence death by bronchopneumonia
3	1986	Ellis *et al*.[9]	17/M	Ulcerated mass	NA	Maxilla	Not specified-Mixed	Surgery	*De novo*	1 recurrence Free of tumor after 6 years
4	1986	Ellis *et al*.[9]	46/M	Painless swelling of the mid right maxilla	5×5	Maxilla	Not specified-mixed	Surgery	*De novo*	No recurrence Free of tumor after 6 years
5	1987	Grodjesk *et al*.[10]	46/M	Swelling of right maxilla and bleeding from site	NA	Maxilla	OPG and waters view- mixed	Surgery Radiotherapy	*De novo*	Death from lung metastasis
6	1989	Scott and Wood[11]	33/M	Swelling, left lacrimation and nasal blockage	6 cm long	Maxilla	Occipitomental view-RO	Surgery Radiotherapy	From ameloblastoma	2 recurrences. Alive with residual tumor for 3 years and lost to follow-up
7	1992	McCoy *et al*.[12]	13/F	Extraction site that had not healed in 2 years	6×4	Maxilla	OPG-mixed CT-tumor mass	Surgery	From a cyst	No evidence of disease after 7 Years
8	1993	Dubiel-Bigaj *et al*.[13]	42/F	NA	NA	NA	NA	NA	*De novo*	NA
9	1994	Siar and Ng[14]	39/M	A massive, ulcerative and rapidly growing tumor	0.3×0.3	Maxilla	NA	Surgery	From ameloblastoma	4 recurrences and lost to follow-up
10	1996	Alcalde *et al*.[15]	72/F	Painless swelling from the left orbital rim to the left cheek	5×4.5	Maxilla	OPG-mixed CT-lytic lesion	Surgery, radiotherapy	*De novo*	No evidence of disease after 10 years
11	1998	Folpe *et al*.[16]	20/M	A progressively enlarging right cheek mass	8.8×4.5×4.4	Maxilla	NA	Surgery, radiotherapy	*De novo*	3 recurrences. No evidence of disease after 1.5 years
12	1999	Castle and Arendt[17]	57/M	Difficulty in breathing and swelling of the upper lip	3×3	Maxilla	CT-lytic lesion	Incisional biopsy	*De novo*	Patient refused further treatment
13	1999	Kamijo *et al*.[18]	38/M	Swelling of the right cheek from infraorbital region to the upper lip	NA	Maxilla	Waters -mixed CT-RO lesion	Surgery, radiotherapy	From COC	1 recurrence and no evidence of disease after 1 year
14	1999	Lu *et al*.[19]	24/M	Painful mass	7×5 × 3	Maxilla	Waters view-mixed	Surgery	From COC	4 recurrences and lost to follow-up
15	1999	Lu *et al*.[19]	31/F	A swelling on the right side of the face	3×3	Maxilla	OPG-RL	Surgery	*De novo*	1 recurrence and no evidence of disease after 14 months
16	1999	Lu *et al*.[19]	19/M	A swelling in the right mandible	10×10×5	Mandible	OPG-mixed	Surgery	*De novo*	Died of local tumor extension in 2 years
17	1999	Lu *et al*.[19]	39/M	A mass in the right mandible with paresthesia of the lower lip	NA	Mandible	Not specified-RL	Surgery	*De novo*	1 recurrence and no evidence of disease after 28 years
18	2000	Kim *et al*.[20]	33/M	Mandibular swelling	7.5×6.5×5.5	Mandible	CT and MRI- ill-defined mass	Surgery	*De novo*	No evidence of disease after 2.5 years
19	2002	Kasahara *et al*.[21]	59/M	A painless swelling on the right side of the mandible	6×5	Mandible	OPG-Mixed CT-tumor mass	Surgery	*De novo*	1 recurrence
20	2004	Cheng *et al*.[22]	36/M	A painless swelling in the anterior mandible	7×5 × 2	Mandible	Cephalogram-mixed	Surgery	From COC	1 recurrence
21	2004	Cheng *et al*.[22]	35/M	A painless swelling in the right maxilla	10×6 × 5	Maxilla	Waters view-RL CT-lytic lesion	Surgery	From ameloblastoma	1 recurrence and died of cranial metastasis

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Table 1: Contd.....

n	Years	Author	Age/sex (male/female)	Presenting complaint	Size (cm)	Site	Imaging (modality-finding)	Treatment	Origin	Recurrence and follow-up
22	2004	Cheng *et al.*[22]	33/M	Tender swelling on the right side of the face	4×2 × 2	Maxilla	Waters view-RL Occlussal-RL	Surgery	From COC	1 recurrence
23	2004	Cheng *et al.*[22]	44/M	A painless swelling in the right mandible	3×2 × 2	Mandible	OPG-RL	Surgery	From CEOT	4 recurrences in 1st, 4th ,8th 13th year
24	2004	Goldenberg *et al.*[3]	36/M	Painful swelling and cyst formation in the right maxilla	NA	Maxilla	OPG-mixed CT-lytic lesion	Surgery	From COC	1 recurrence and no evidence of disease after 18 months
25	2007	Nazaretian *et al.*[23]	40/M	Pain in the right maxillary region	NA	Maxilla	OPG-RO CT-tumor mass	Surgery	*De novo*	NA
26	2007	Sun *et al.*[24]	30/M	A rapidly growing mass in the right maxilla	5×4 × 2.5	Maxilla	Waters view-RL	Surgery	*De novo*	No evidence of disease after 1 year
27	2008	Roh *et al.*[25]	55/M	A painful swelling with local paraesthesia in the left side of the mandible	4.5×3.5×2	Mandible	OPG-RL CT-Lytic lesion	Surgery	*De novo*	No evidence of disease after 1.8 Years
28	2009	Li *et al.*[26]	53/M	A slowly growing painless mass in the left maxilla	3×3 × 2.5	Maxilla	Not specified- RL	Surgery	From DGCT	5 recurrences 4th, 12th, 17th, 18th, 21st year
29	2009	Motosugi *et al.*[27]	17/M	A maxillary mass in area of previously treated cyst	NA	Maxilla	CT-solid lesion	Surgery	From COC	2 recurrences 3rd and 4th year
30	2010	Slama A *et al.*[28]	89/M	swelling of the left mandible and gums	6 cm long	Mandible	CT-lytic lesion	surgery	*De novo*	Recurred 2 months later and the patient died 6 months after surgery
31	2011	Li *et al.*[29]	47/F	A slow-growing, painful and swelling mass in the right mandible	6.5×5.5	Mandible	OPG-RL CT-soft tisuue mass	Surgery	From DGCT	1 recurrence at 7th month and no evidence of disease after 4 years
32	2012	Arashiyama *et al.*[30]	68/M	A gingival swelling	3.5×2.5×2	Mandible	OPG-RL CT-lytic lesion	surgery	From CCOT	1 recurrence and no recurrence after 4 years
33	2012	Zhu *et al.*[31]	51/M	A slow growing, painful mass in the right maxilla	3×3 × 3	Maxilla	OPG-RL	Surgery	From CCOT	Recurrence after 1 year
34	2013	Wader and Gajbi[32]	61/M	A painful swelling in the lower right jaw	2×1	Mandible	Radiology-mixed lesion	Surgery	*De novo*	NA
35	2014	Martos-Fernández *et al.*[33]	70/F	Pain and rapid expansion of a mass on alveolus	4×3.2×3.4	Maxilla	OPG-Mixed MRI	Surgery, radiotherapy	*De novo*	no evidence of disease on 1-year follow-up
36	2014	Del Corso *et al.*[34]	86/M	An asymptomatic swelling of the left mandible	NA	Mandible	OPG-RL CT-lytic lesion	Surgery	*De novo*	NA
37	2014	Fitzpatrick *et al.*[35]	37/M	A slowly growing mass in the right anterior maxilla	5cms long	Maxilla	OPG-Mixed CBCT	Surgery	From COC	Lost to follow-up
38	2014	Mohamed Ali *et al.*[36]	21/M	Swelling at the left side of the maxilla	10× 10	Maxilla	CT-Mixed lesion	Surgery, radiotherapy Chemotherapy	*De novo*	Recurrence after 5 months One year later, the patient passed away
39	2015	Fitzpatrick *et al.*[35]	70/F	Maxillary pain	3.9×3.5	Maxilla	NA	Surgery, radiotherapy	NA	disease free in 6-month follow-up
40	2015	Ismerim *et al.*[37]	23/F	Swelling of symphysis	NA	Mandible	Not specified-RL	Surgery	From CCOT	Recurrence later 3 years
41	2015	Rappaport *et al.*[38]	64/F	Recurrence of previous cystic lesion on right mandible	NA	Mandible	NA	Surgery radiotherapy	From DGCT	3 recurrence within 22 years

Contd.....

Table 1: Contd.....

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.*[39] (India)	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.*[40]	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.*[41]	45/F	Abnormality on the maxillary right gingiva	3×2.5×1.7	Maxilla	3D CT-soft tissue lesion	Surgery	*De novo*	No evidence of disease after 2-year follow-up
45	2017	Namana M *et al.*[42] (India)	37/M	Pain in the lower right back tooth region	NA	Mandible	OPG-RL PET	Surgery	*De novo*	Recurrence after 1 year with lung metastasis
46	2017	Miwako S *et al.*[43]	65/M	Painful swelling of the left maxilla	4 cms long	Maxilla	OPG-RL CT-soft tissue lesion MRI-mixed	Surgery, chemotherapy Radiotherapy	From CCOT	3 recurrence 10th, 22nd, 28th months, patient died 3 years and 10 months after initial diagnosis.
47	2017	Sang Yoon Park *et al.*[44]	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*	Under follow-up
48	2018	Remya *et al.*[4] (India)	39/M	Painful swelling on the right side of the face of 3 months' duration	9×6 × 5	Mandible	OPG-RL CT-RL	Surgery	*De novo*	no recurrence after 6 months
49	2018	Ohata *et al.*[45]	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
50	2018	Qin *et al.*[46]	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	From cholesterol granuloma of the maxillary sinus	No evidence of recurrence or metastasis after the 20-month
51	2019	Present case (India)	23/M	Swelling on anterior jaw region	4×3	Mandible	OPG-RL CT-Lytic lesion	Incision Biopsy Chemotherapy	*De novo*	Under chemotherapy and follow-up

M: Male, F: Female, OPG: Orthopathamogram, CT: Computed tomography, MRI: Magnetic resonance imaging, RL: Radiolucent, RO: Radio-opaque

Table 2: Consolidated data after reviewing literature of case reports of ghost cell odontogenic carcinoma

Clincopathological parameters	Result
Total number of cases (including present)	51 cases
Mean age of occurrence (years)	43.47 (age range 10-89)
Male	40 cases
Female	11 cases
Male:female	3.63:1
Site	
Maxilla	31 cases (61.7%)
Mandible	19 cases (38.2%)
Size	
Mean diameter of lesion (cm)	4.9 (range from 0.3 to 10)
Radiology	
OPG	21 cases
Radiolucent	19 cases
Radiopaque	14 cases
Mixed	2 cases
Computed tomography findings	24 cases
Magnetic resonance findings	4 cases
Positron emission tomography finding	4 cases
Other imaging modalities (occlusal/ waters)	16 cases
Origin	
De novo	28 cases
Preexisting COC/CCOT/DGCT	15 cases
Preexisting ameloblastoma	3 cases
Other preexisting lesions	5 cases
Follow-up	
No recurrence	13 cases
Single recurrence	18 cases
Multiple recurrence (>1)	9 cases
Distant metastasis	5 cases
Death of patient	7 cases

OPG: Orthopantomogram, DGCT: Dentinogenic ghost cell tumor, COC: Cell odontogenic carcinoma, CCOT: Calcifying cystic odontogenic tumor

Table 3: Diagnostic criteria of ghost cell odontogenic carcinoma in comparison to dentinogenic ghost cell tumor according to the World Health Organization

Diagnostic criteria	DGCT	GCOC
Areas resembling ameloblastoma	Main H/P feature	Not shown
Hyperchromatic isomorphic cells	Present	Present
Cellular pleomorphism	Not shown	Present
Abnormal mitotic activity	Not shown	Present
Necrosis	Not shown	Present
Calcifications	Occasional	Occasional
Infiltrative growth	Not shown	Present
Ghost cell keratinization	Present	Present
Giant cells	Tissue response	Not mandatory
Dentinoid formation	Present	Not mandatory
Stroma	Fibrous	Fibrous/hyalinized
P53 expression	Less	High
Ki67 expression	Less (<5%)	High

DGCT: Dentinogenic ghost cell tumor, GCOC: Ghost cell odontogenic carcinoma

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.[20] 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.[31] In one study, tumor cells were positive for cytokeratin and p63 and were negative for TTF1 and CK7.[39] Expression of Syndcan-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.[38] 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%.[4,19] 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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