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CASE REPORT

Ghost Cell Odontogenic Carcinoma: Case Series and Literature Review

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Abstract

Ghost cell odontogenic carcinoma (GCOC) is rare. These tumors can arise from odontogenic precursors or de novo, displaying a spectrum of clinical behaviors with potential for rapid local recurrence, distant metastasis, and death from disease. Considering limited data, we present two cases of GCOC in female patients and perform a comprehensive review of the literature related to GCOC with a focus on adjuvant therapies. The first case, a de novo occurrence, had an aggressive course, while the second, arising from an ameloblastoma, was more indolent. A review of 65 previously published cases revealed that 82% of GCOCs occurred in males. Recurrence rates were higher in cases arising from precursor lesions (64%) compared with de novo lesions (26%). Of the 59 patients who had documented follow-up, 37% had an isolated local recurrence, 3% had an isolated distant metastasis, and 5% had both a local recurrence and distant metastasis. Overall, GCOC is a rare but aggressive odontogenic carcinoma requiring a multidisciplinary approach. Radical surgical excision with clear margins remains the primary treatment. Adjuvant therapies, such as radiotherapy, are indicated for aggressive features like rapid growth, positive margins, and local recurrence. While both local and distant recurrences are a risk, local recurrence is the most common mode of treatment failure. Further research into prognostic markers such as *CTNNB1*, *p53*, and *Ki-67* may lead to more personalized therapies and improved outcomes. Additional research should also focus on intensifying adjuvant therapies to improve outcomes.

Keywords Ghost cell odontogenic carcinoma · Odontogenic cyst, calcifying · Odontogenic tumors · Jaw neoplasms · Malignant dentinogenic ghost cell tumor · Carcinoma

Introduction

Ghost cell odontogenic carcinomas (GCOCs) are a rare form of odontogenic malignancy [1, 2]. The tumor is within the category of mixed epithelial and mesenchymal tumors, most commonly reported among Asian males in the 5th to 7th decades of life [2, 3]. Due to the tumor's variable growth patterns and classifications, GCOCs have a highly unpredictable prognosis [1, 2, 4]. Despite their high recurrence rate, ranging from 40 to 63%, GCOCs have an estimated 73% 5-year survival rate [3, 5].

Tumors containing "ghost cells" represent a histologically distinct subset of neoplasms arising from epithelial and mesenchymal elements, in this setting from odontogenic origins. The term "ghost cell" refers to the aberrant, anucleated epithelial cells that can retain their cellular outline. Ghost cells can be seen in both benign and malignant lesions. Calcifying odontogenic cyst (COC) was one of the first lesions containing ghost cells to be described in literature [6]. GCOC, on the other hand, is an extremely rare malignant neoplasm that exhibits epithelial components and the presence of ghost cells. GCOCs were first introduced by the World Health Organization (WHO) in the 2005 classification as a malignant counterpart of COCs. Its histopathologic features are similar to dentinogenic ghost cell tumors (DGCT) when there are additional features of malignancy

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Table 1 Demographic summary of cases reported in the literature [3–5, 8–11, 13–15, 18, 19, 23, 24, 28, 29, 39, 41–77]

Demographic information		$N = 65$ total patients
Age (in years)	Mean	41.8
	Median	43
	Range	10–89
Sex	Male	53 (81.5%)
	Female	12 (18.5%)
Ethnicity	Asian	24
	African American/Black	8
	Caucasian	6
	Hispanic	1
	Not Reported	26
Precursor Lesion	Yes	22 (33.8%)
	No	43 (66.2%)
Presenting Symptoms	Pain	13
	Swelling	45
	Epistaxis	2
	Mass	5
Location	Mandible	28 (43.1%)
	Maxilla	37 (56.9%)
Laterality	Right	38
	Left	19
	Bilateral	4
	Central	3
	Not reported	1
Recurrence	No recurrence	36
	Isolated local recurrence	17
	Isolated distant metastasis	2
	Local and distant recurrence	3
	Recurrence data not reported	7

Table 2 Precursor lesions identified among reported cases in the literature

Precursor lesion	$N=22$
Calcifying cystic odontogenic tumor	12
Dentinogenic ghost cell tumor	3
Ameloblastoma	2
Dentigerous cyst	1
Odontogenic ghost cell tumor	1
Adenomatoid odontogenic tumor	1
Cholesterol granuloma	1
Ameloblastic carcinoma	1

[7, 8]. Due to its rarity, each new case and literature review is valuable for understanding the clinical behavior, histopathology, and prognosis of GCOCs.

A debated aspect of GCOC is its pathogenesis, particularly its relationship with precursor lesions. Existing literature suggests that GCOC can arise either de novo or from pre-existing odontogenic lesions, most commonly from COC or DGCT. To date, there have been roughly 65 cases reported in the English literature (Table 1), with most of the reported cases in males [9]. Of the reported cases, about 34% of GCOCs had an associated precursor lesion (Table 2), highlighting the importance of this potential malignant transformation [8]. The specific types of precursor lesions, other than the well-documented COCs, remain unconfirmed.

In this case series and literature review, we describe two cases of GCOC in female patients and analyze the clinical and histopathological features of 65 previously reported cases. Our paper aims to provide a comprehensive overview of this rare malignancy. Furthermore, we address a unique clinical presentation of GCOC arising from a pre-existing ameloblastoma in one of our cases. This finding contributes to the understanding of the pathogenesis of GCOC and prompts a re-evaluation of its potential origins from other odontogenic tumors.

Case Presentations

Case 1

A 46-year-old Southeast Asian female presented with progressive sinus pressure and congestion over three months. She was initially managed for presumed sinusitis with temporary, mild relief of symptoms, and thereafter referred to Head and Neck Surgery. Examination of the left nasal cavity demonstrated a friable, exophytic mass located on the medial wall anterior to the middle meatus with involvement of the floor and lateral wall. Biopsy of the mass demonstrated GCOC, felt to represent a de novo carcinoma. Imaging demonstrated a 40 mm enhancing destructive mass centered in the left nasal cavity (Fig. 1). There was no appreciable lymphadenopathy. The patient was discussed in a multidisciplinary tumor board with a recommendation for definitive surgical resection. She subsequently underwent left endoscopic resection with negative margins. Intraoperatively, the tumor did not invade the nasal septum, maxillary sinus, lamina papyracea, skull base, or nasal floor. After the procedure, the patient elected for observation after being offered adjuvant radiotherapy.

Two months later, she developed left nasal paresthesias, which then spread to her left cheek and under her left eye. Imaging workup demonstrated a 36 mm mass concerning for recurrence (Fig. 2). A PET scan did not show regional adenopathy or distant metastasis. Multidisciplinary evaluation recommended repeat surgical resection. She subsequently underwent left radical maxillectomy, ethmoidectomy, sphenoidotomy, orbital exenteration, unilateral cribriform resection, infratemporal fossa resection, and neck dissection of cervical levels I-III with free flap reconstruction. Pathology revealed a 35 mm GCOC involving the left nasal cavity, maxillary sinus, ethmoid sinus, and deep pterygoid muscle, invading through the orbital floor into the orbital tissue with

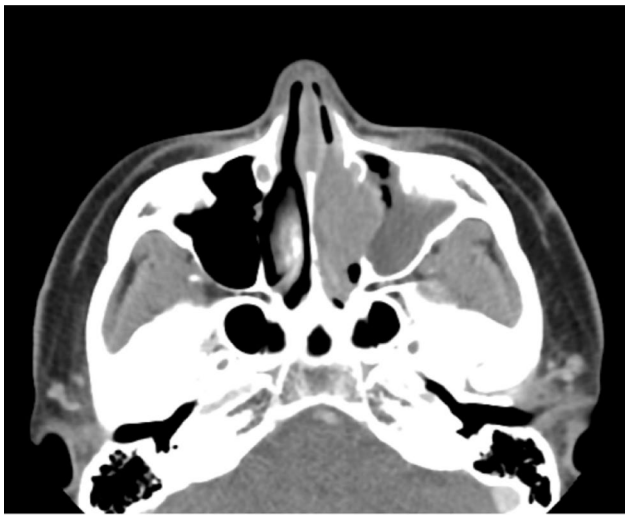

Fig. 1 A 40 mm enhancing destructive mass centered in the left nasal cavity with involvement of the left ethmoid sinus, abutment of the left cribriform plate, possible invasion into the nasal septum, erosion of the left ostiomeatal complex with involvement of the left maxillary sinus, erosion of the medial wall of the left orbit without orbital extension, and posterior extension to the sphenopalatine foramen without involvement of the pterygopalatine fossa

a positive lateral bone margin at the zygoma, with perineural and lymphovascular invasion. Twenty-one lymph nodes were negative. Considering her locally advanced disease with rapid recurrence and a positive margin, she then underwent adjuvant chemoradiotherapy. She received 66 Gy in 33 fractions to the tumor bed postoperatively using intensity modulated radiation therapy (IMRT; Fig. 3) with concurrent tri-weekly cisplatin (100 mg/m^2/kg).

During the last two weeks of chemoradiotherapy, she developed progressive left lower extremity pain and weakness. PET scan revealed a 90 mm left posterior pelvis mass invading the psoas muscle and eroding into L4 and L5, which was later biopsy-proven to be metastatic GCOC. Her pain improved with 5-fraction palliative radiotherapy. She additionally developed liver, skin, and soft tissue metastases. Molecular sequencing revealed a *CTNNB1* mutation. She started on everolimus, an *mTOR* inhibitor, but enrolled in hospice and passed away 6 months after the diagnosis of metastatic disease, 11 months after salvage surgical resection, and 15 months after initial surgery.

Histopathologic Features

Histologically, the invasive carcinoma was composed of several cell components, blended, but showing basaloid, squamous, ameloblastic, and ghost cell populations (Figs. 4b-d and 5a-c, and 6c). The tumor was destructively infiltrative into bone and soft tissues, with a desmoplastic stromal reaction to the tumor. The ghost cells presented as anucleate epithelial cells with swollen homogeneous pale eosinophilic cytoplasm and pale to clear central areas, which were once occupied by the nucleus (Fig. 5b-c). No precursor lesion or cyst was identified. There was well-developed tumor comedonecrosis and easily identified cellular pleomorphism (Figs. 5a and 6c). Increased and atypical mitoses were noted. The basaloid appearance was prominent,

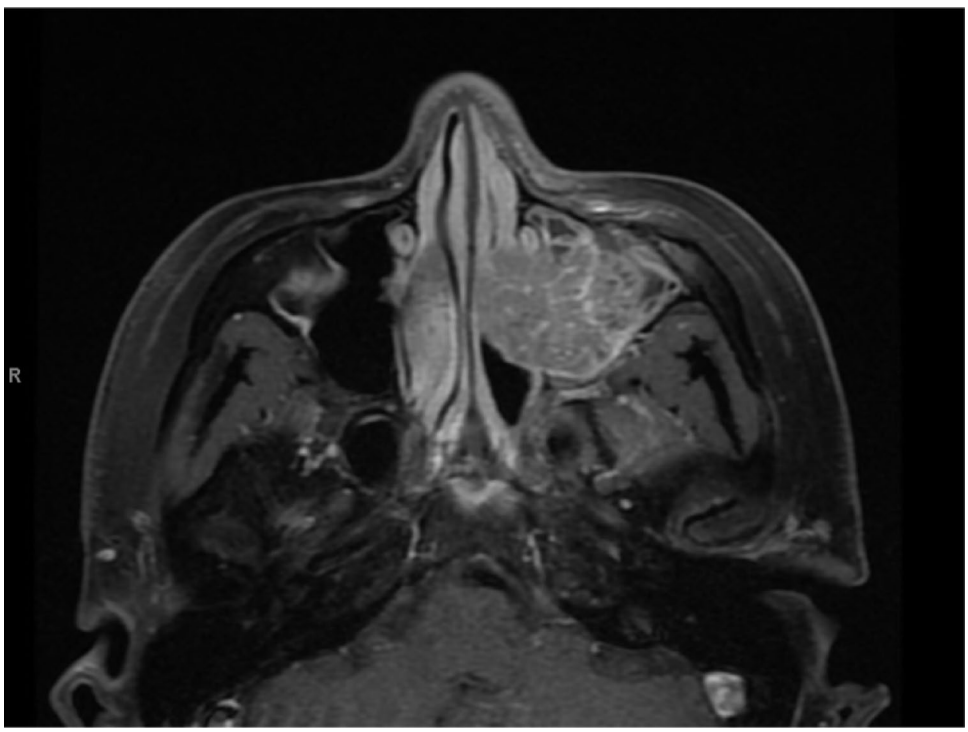

Fig. 2 MRI imaging demonstrating a 36 mm enhancing mass centered in the left maxillary sinus with extension into the nasal cavity and orbital floor

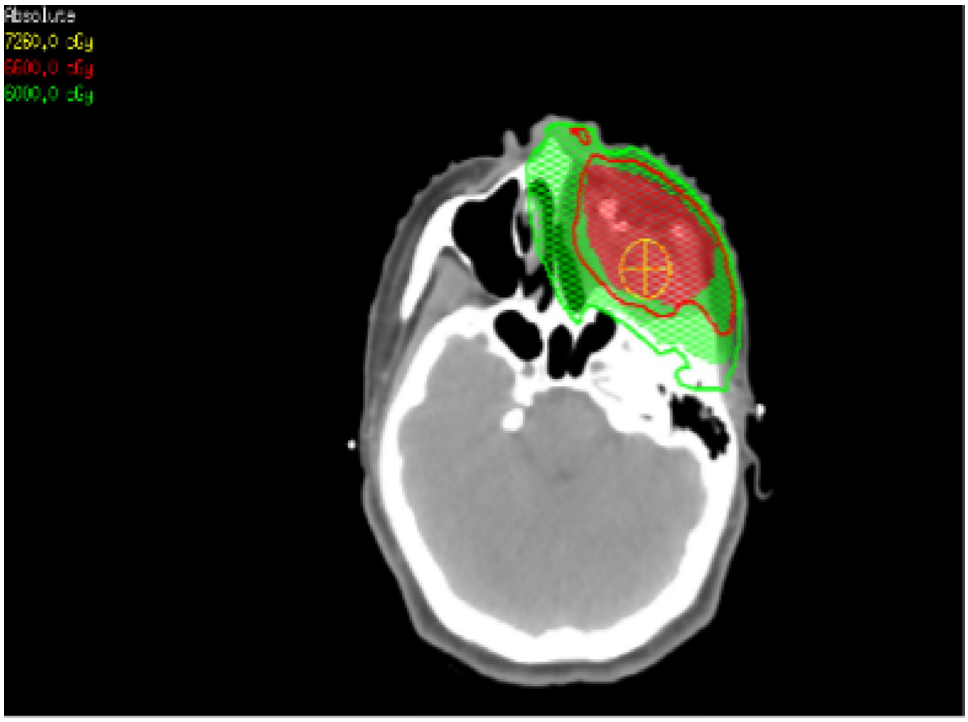

Fig. 3 Adjuvant radiotherapy plan with 66 Gy in red and 60 Gy in green

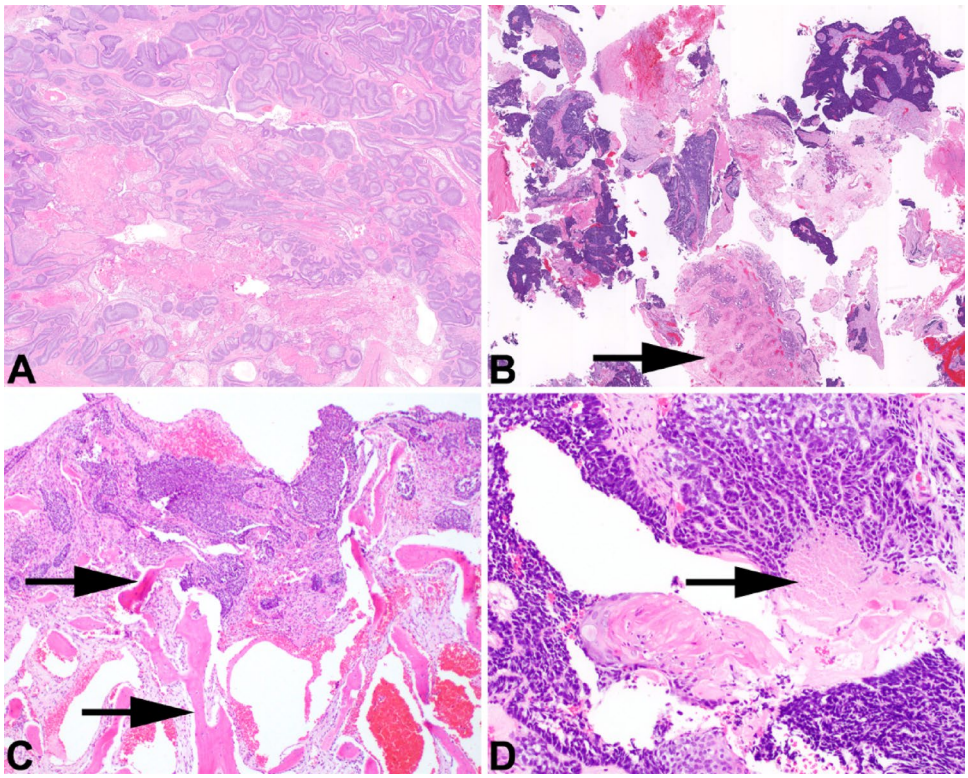

Fig. 4 Odontogenic ghost cell carcinoma: **A** A destructively infiltrative pattern of ameloblastic epithelium is noted with large areas of ghost cells (case 2). **B** This tumor has a very basaloid appearance as fragments are noted in the sinonasal tract epithelium (black arrow)(case 1). **C** The neoplastic cells destructively infiltrate the bone (black arrow)(case 1). **D** Comedonecrosis (black arrow) is noted adjacent to ghost cells (case 1)

with cells having a high nuclear to cytoplasmic ratio and scant cytoplasm. A syncytial appearance was noted in areas. Abrupt areas of squamous differentiation were noted, associated with the ghost cell population.

Case 2

A 40-year-old Caucasian female presented with a right anterior mandibular gingival growth along the suture line of a prior ameloblastoma, resected two years earlier. Biopsy of

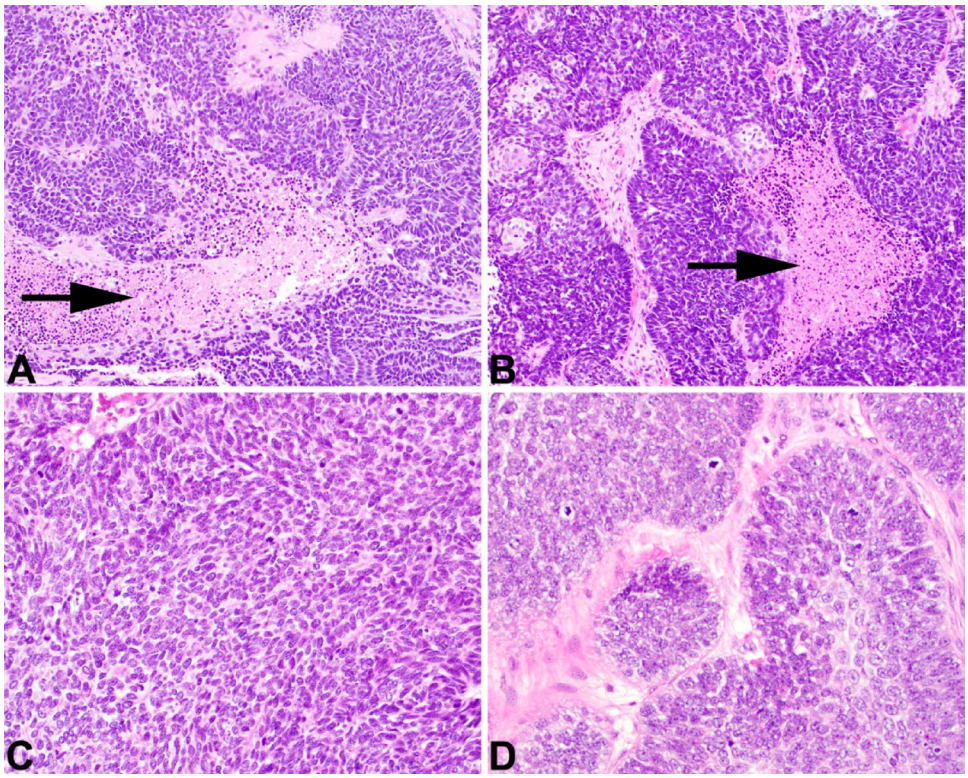

Fig. 5 Malignant features of odontogenic ghost cell carcinoma: **A** Comedonecrosis (black arrow) in the central area of a basaloid neoplasm (case 1). **B** The basaloid neoplastic cells have a high nuclear to cytoplasmic ratio and isolated areas of squamoid differentiation, along with tumor necrosis (black arrow)(case 1). **C** The neoplastic cells have an extremely high nuclear to cytoplasmic ratio, coarse chromatin, and increased mitoses (case 1). **D** The peripheral palisading of more columnar cells is noted, with areas of subnuclear clearing (vacuolization), along with numerous mitoses (including atypical forms)(case 2)

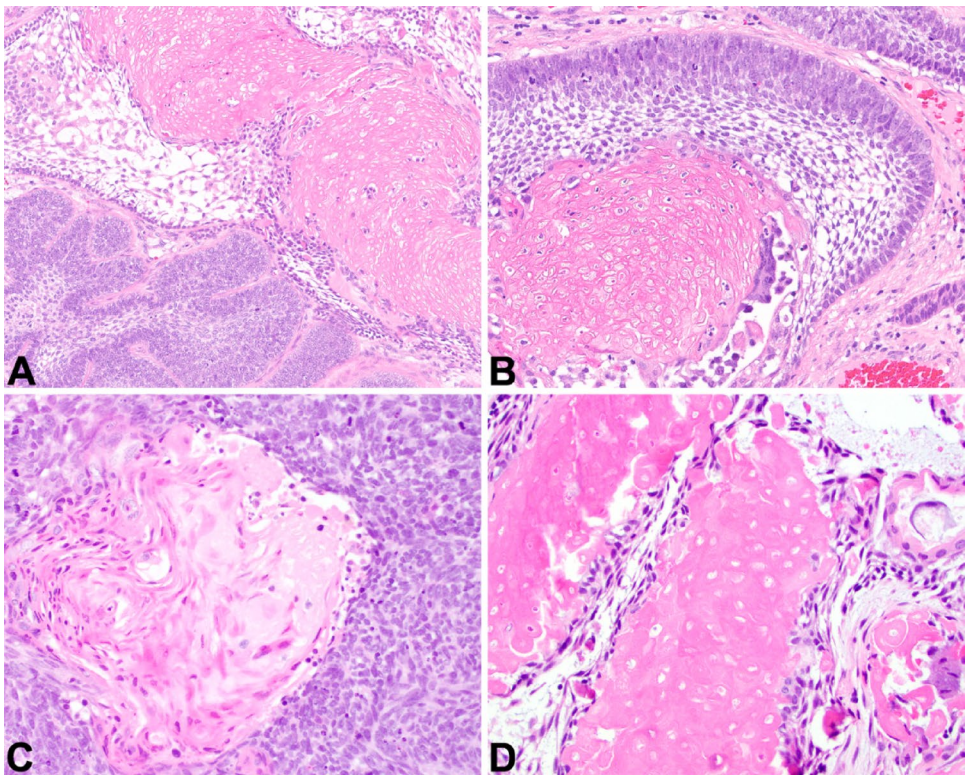

Fig. 6 Ghost cells are one of the most unique features of ghost cell odontogenic carcinoma. **A** Stacks of ghost cells with absent nuclei (case 2). **B** Ghost cells are noted, surrounded by a stellate-reticulum like proliferation and columnar cells that have easily identified mitoses (case 2). **C** A primitive epithelium abruptly associated with keratinization and ghost cells (case 1). **D** The ghost cells lack any nuclei, with a very bright hypereosinophilic appearance (case 2)

the soft tissue mass demonstrated recurrent ameloblastoma. CT imaging showed a 34 mm soft tissue mass extending from the right mandibular defect of her prior surgery to the adjacent right buccal mucosa and labial soft tissue (Fig. 7).

She underwent an excisional biopsy with pathology revealing a high-grade GCOC with margin involvement. A subsequent staging CT revealed no evidence of cervical adenopathy or distant metastasis. She was seen in a

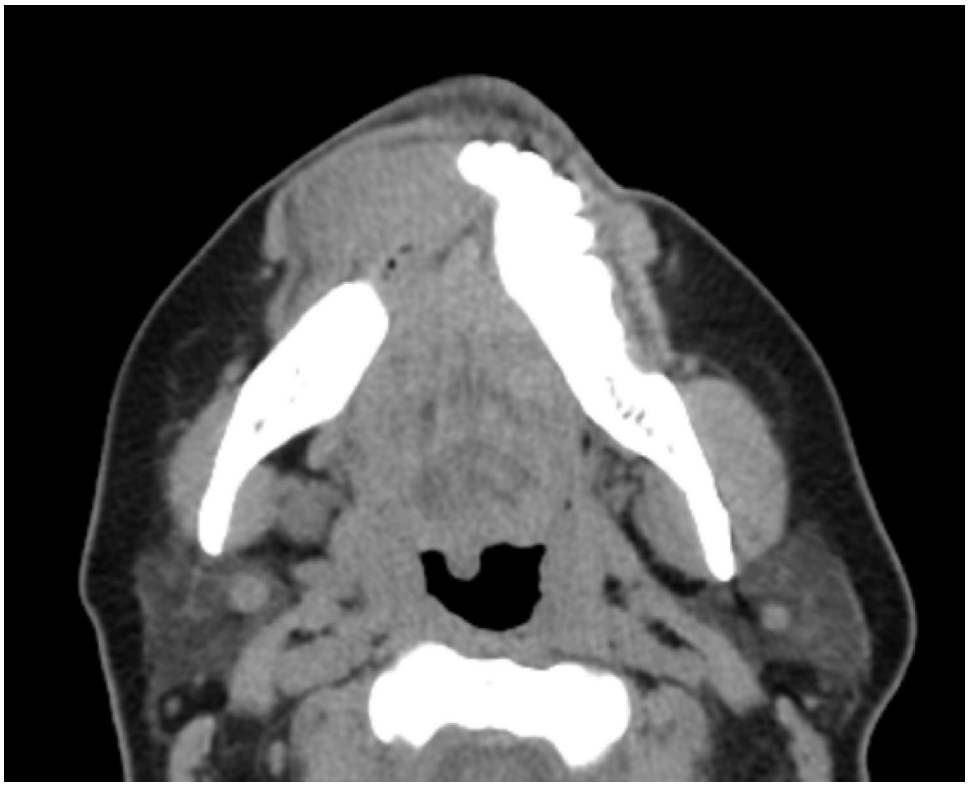

Fig. 7 CT imaging showed a 34 mm soft tissue mass extending from the right mandible to the adjacent right buccal mucosa and labial soft tissue (Case 2)

multidisciplinary tumor board with a recommendation for definitive surgical management.

She underwent mandibular resection, selective neck dissection of lymph node levels I-III, and free flap reconstruction. No residual carcinoma was identified in the mandibular specimen, and 47 lymph nodes were negative. No adjuvant therapy was recommended, and she remains disease-free without evidence of recurrence three years after surgery.

Histopathologic Features

The neoplastic cells were identified in proliferating sheets, nests, and islands of anastomosing cords of primitive appearing basaloid odontogenic to squamoid cells surrounded by columnar to cuboidal cells with reverse polarization, the latter representing ameloblastic epithelium (Figs. 4a and 5d, and 6), and ameloblastoma. Central areas of cystic change were seen, frequently associated with tumor cell necrosis (Figs. 5d and 6a). Easily identified mitoses, including atypical forms, were noted throughout (Fig. 5d). A stellate reticulum was noted (Figs. 4a and 5d). Vascular invasion was noted, but perineural invasion was not identified. The neoplastic cells showed a remarkably high nuclear to cytoplasmic ratio, nuclear hyperchromasia, and pleomorphism (Figs. 5d and 6b). Dystrophic calcifications were noted along with destructive infiltration into the adjacent bony interstices in several areas (Fig. 4a). Seen to a variable degree throughout the tumor were ghost cells (Figs. 4a, 5d and 6b, and 6d). These are defined by large, ovoid to polygonal, pale epithelial cells showing aberrant eosinophilic cytoplasmic keratinization that results in the loss of their nuclei with retained cellular shape that gives them a "ghostly" or "ghost cell" appearance. There is a faint outline of the nuclear membranes, with some isolated pyknotic debris (Fig. 6d). The cellular membranes were well developed, although blurred and fused to form groups of stacked cells (sometimes called "wet keratin"). Given the differential diagnostic consideration, a few pertinent negatives deserve mention: no osteoid or dentinoid material was identified. There was no tumor cell spindling; no rhabdomyoblastic differentiation; no glandular differentiation; no pigmentation; and no osteoid material.

Literature Review

Clinical Features

GCOCs can arise from precursor benign odontogenic lesions such as odontogenic cysts, including calcifying odontogenic cysts or dentinogenic ghost cell tumors, as well as ameloblastoma. However, GCOCs more frequently arise de novo [10]. In our review of literature, recurrence rates are greater in individuals with GCOCs that arise from precursor lesions (50%) in comparison to de novo lesions (26%), suggesting possibly more aggressive behavior in GCOCs that arise

from precursor lesions (Table 1). However, our first case was de novo disease and demonstrated aggressive natural history, while our second case arose from ameloblastoma and had a more indolent course. In our review of literature, 34% of patients with GCOC had a precursor lesion. Of these patients, calcifying cystic odontogenic tumors consisted of 54.5% of precursor lesions (Table 2). The second most common precursor lesion, occurring in 13.6% of the reported cases, was dentinogenic ghost cell tumors (Table 2). All other precursor lesions occurred less frequently (Table 2).

Clinically, these tumors exhibit locally destructive behavior with potential for recurrence and metastasis [10]. In the reviewed cases, GCOCs most often presented with symptoms of painful or painless swelling (N = 45), a mass ($N = 5$), and occasionally epistaxis ($N = 2$) (Table 1). Of the 65 patients reviewed, 82% were male, with the median age of all cases at time of diagnosis 43 years. The age range of GCOCs was 10–89 years. Of the cases that reported ethnicity ($N = 39$), 61.5% were Asian, 20.5% were black, 15.4% were Caucasian, and 2.6% were Hispanic. The site was maxilla in 56.9% and mandible in 43.1%. Lesions occurred on the right in 58.5% of patients, left in 29.2%, and central in 4.6%; with 6.2% bilateral (Table 1).

Of the 58 patients who had documented follow-up, 29% had an isolated local recurrence, 3% had an isolated distant metastasis, and 5% had both a local recurrence and distant metastasis (Table 1).

GCOCs exhibit several different radiological features. In most patients, tumors have both radiolucent and radiopaque lesions whose borders are often poorly defined [11–13]. Occasionally, in advanced cases, destructive bone invasion was seen [12–14]. Additional findings on imaging include tooth displacement and root resorption [15] (Table 1).

Histopathologic Features

Histologically, GCOCs are characterized by pleomorphism in the odontogenic epithelium, ghost cells (required), tumor necrosis, large cells with vesicular chromatin, and possibly dentinoid deposits [1, 11]. On hematoxylin and eosin (HE) stained sections, ghost cells appear as swollen epithelial cells with eosinophilic cytoplasm and a lack of a nucleus [2, 10]. Ghost cells may be associated with calcification and keratin debris, accompanied by foreign-body giant cell reaction in some cases [7, 12, 14]. Typically, varying degrees of fibrous stroma as well as mitoses are also observed [10]. 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 only a precursor lesion. Some tumors demonstrate areas of malignant transformation from pre-existing calcifying odontogenic cyst (COC) or dentinogenic ghost cell tumors (DGCT), into cytologically malignant regions, supporting a neoplastic spectrum [1, 16], 17]. Peripheral infiltration, perineural invasion, and vascular invasion have also been documented and are indicative of the tumor's aggressive potential [18].

There is no significant role for immunohistochemistry, as the odontogenic epithelial cells express various keratins along with p40/63, while the ghost cells show reduced or absent staining. While there is a reduced Ki-67 proliferation index in the ghost cells (they are terminal), there is generally a high proliferation index in the carcinoma component, frequently in contrast to the precursor lesion (if present) [19], often more than 75% There is a well-established association with *CTNNB1* mutations, and thus nuclear localization of β-catenin is commonly observed [1, 20–22].

The likelihood of metastasis or recurrence is determined by several factors, including histopathological characteristics, tumor location and size, lack of adjuvant therapy, Ki-67, *TP53*, and *CTNNB1* [1, 2, 23, 24]. Furthermore, there is often p53 overexpression reflecting *TP53* mutations.

Immunohistochemical and Genetic Markers

Genetic mutations, particularly the *CTNNB1* gene encoding β-catenin, have been frequently observed in GCOC and its benign precursors, such as COCs and DGCTs [21, 25]. β-catenin plays a vital role in both cell adhesion as well as signal transduction [26, 27]. β-catenin is a major component in the Wnt signaling pathway, which regulates gene transcription.

Additionally, Ki-67, a proliferation marker, and p53, a differentiation marker, provide insights into the aggressive behavior of GCOC. High Ki-67 proliferation indices, often exceeding 75% [28–29], have been shown to be significantly higher in GCOC compared to benign odontogenic tumors [28], such as ameloblastoma with a mean proliferation index of 4.4% or 0.9% for adenomatoid odontogenic tumors [30]. *TP53* plays a role in epithelial differentiation and proliferation, both of which are key features of GCOC and other odontogenic lesions [18, 31].

Differential Diagnosis

Ghost cell lesions encompass a wide variety of neoplastic and non-neoplastic lesions, in addition to both non-odontogenic and odontogenic neoplasms (Fig. 8). No matter where they fit, these rare lesions are united by the presence of shadow cells, "wet keratin," or "ghost cells." These are epithelial cells usually with ample eosinophilic cytoplasm with distinct cell borders, but lacking central nuclei (anucleated), while still showing the outline of where the nucleus was. Because there is cytoplasmic keratinization, it preserves the

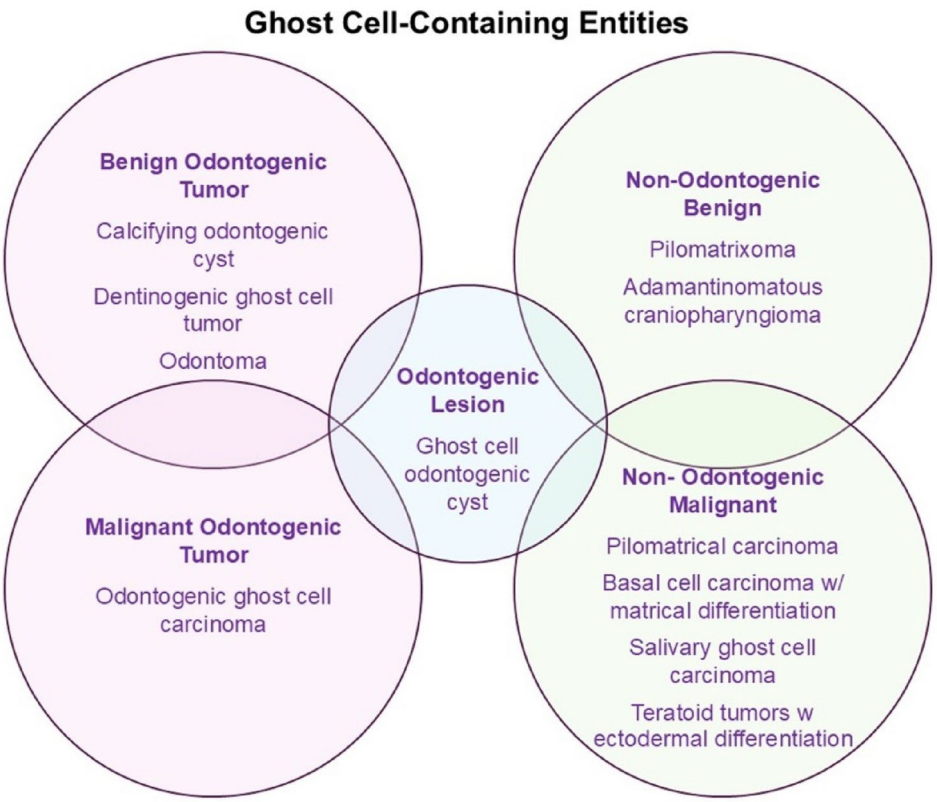

Fig. 8 A diagram showing ghost cell-containing entities, separated between odontogenic and non-odontogenic, then by lesion or benign or malignant neoplasm

location of the nucleus and thus further degradation is not seen, even though it is thought that ischemia plays a role in ghost cell development [32]. These ghost cells may undergo calcification or mineralization.

Within the head and neck, pilomatrixoma (calcifying epithelioma of Malherbe) is a relatively common skin tumor that develops most commonly in children and young adults, showing ghost cells in the central component [25]. Cutaneous cysts may have matrical differentiation, although exceptionally rare and usually sporadic [33]. Pilomatrix carcinoma, basal cell carcinoma with matrical differentiation, and teratoid tumors with ectodermal differentiation can show ghost cells but are all skin adnexal-based lesions [34, 35], so not usually a significant differential when the centering of the tumor is considered. The recently described salivary ghost cell tumor [36] is a proposed entity with similar histological features but a unique site of involvement. Craniopharyngioma develops from Rathke's pouch and is usually a midline neoplasm affecting the nasopharynx or sellar regions. The histological features of adamantinomatous craniopharyngioma are histologically identical to odontogenic ameloblastoma counterparts, and it is only the anatomic centering of the tumor that aids in correct classification [37].

The most common odontogenic lesions in the differential diagnosis include calcifying odontogenic cyst, dentinogenic ghost cell tumor, and odontoma, with ghost cell odontogenic carcinoma the only significant malignancy [36]. These lesions are typically found in the jaws and exhibit varying degrees of aggressiveness and recurrence. Calcifying odontogenic cyst (COC, also known as calcifying cystic odontogenic tumor and Gorlin cyst) is a simple developmental odontogenic cyst that shows stratified epithelium often with ameloblastoma-like areas, with characteristic ghost cells which frequently calcify [7]. Dentinogenic ghost cell tumor is a benign but locally infiltrative odontogenic tumor with ameloblastomatous epithelium, dentinoid material, and ghost cells (sometimes considered a solid subtype of COC) [7]. Odontoma and ameloblastic fibro-odontoma can have ghost cells within these hamartomatous proliferations, but the other components and architectural arrangements help to make such a separation [32, 38].

GCOC is rare, showing destructive invasion into the adjacent soft tissues and bone, malignant cytological features, tumor necrosis, increased mitoses, including atypical forms, and, of course, the presence of ghost cells. It is characterized histologically by a biphasic pattern comprising proliferative odontogenic epithelium and aberrant keratinizing ghost cells. NUT carcinoma can have areas of abrupt keratinization and squamous pearl formation, but tends to have acute inflammatory cells, cellular monotony, without showing peripheral palisading, ameloblastoma differentiation, and ghost cells with dystrophic calcifications. NUT immunohistochemistry is a confirmatory study that is easily performed if the differential arises [18].

Treatment

In the majority of cases, treatment for GCOC begins with oncologic surgical resection with clear margins [7, 12, 14]. Obtaining clear margins, even if requiring re-resection, remains the cornerstone of management [2, 7, 12]. Adjuvant therapies, such as radiation or systemic therapy, have also been variably utilized, particularly in recurrent, metastatic, or inoperable instances [7, 13]. Occasionally, combined therapy with adjuvant chemoradiotherapy has been used and can effectively prevent recurrence and metastasis [23]. The decision to proceed with adjuvant therapy is often based on aggressive features and oncologic principles such as rapid growth, positive lymph nodes, concern for residual microscopic disease, and recurrence after excision of the initial tumor [29, 39, 40]. In our literature review, GCOCs arising from precursor lesions had higher rates of recurrence and could be considered as another factor for adjuvant treatment. Often, patients are treated with a stepwise approach that includes an initial diagnostic surgery such as surgical enucleation or wide local excision, followed by definitive surgery such as partial mandibulectomy or total mandibulectomy, and then adjuvant radiation and/or chemotherapy depending upon clinical or histological risk factors of recurrence [29].

For adjuvant radiation therapy, review of the literature demonstrates doses ranging between 50 and 62 Gy. Eleven cases with adjuvant therapy are summarized in Table 3. Adjuvant radiation is used much more frequently than adjuvant chemotherapy (11/11 cases vs. 5/11 cases, respectively). Platinum-based concurrent chemotherapy has shown promising results when combined with radiation, as extrapolated from the treatment of other head and neck cancers [39]. Concurrent weekly docetaxel has also been used as a radiosensitizer with efficacy [23].

Out of the 11 cases treated with adjuvant therapy, six (55%) patients recurred, with five (45%) patients having local recurrence (LR) and three (27%) patients with distant metastasis (DM). Two patients developed both LR and DM, with the rest of the cases showing only isolated recurrence. Despite all patients receiving adjuvant radiotherapy, LR occurred in almost half of the cases and is the main mode of treatment failure. These findings suggest that LR remains a significant challenge in this disease, indicating a potential need for treatment intensification or alternative strategies to improve local control, especially in high-risk cases. Of note, some cases of isolated LR after adjuvant treatment have been successfully salvaged [41, 42].

Three of six (50%) patients who did not receive chemotherapy developed LR versus 2/5 (40%) patients who did receive chemotherapy. 50% of patients who did not receive chemotherapy developed DM, while no patients who received chemotherapy developed DM. 40% of patients who had LR developed DM, while 1/6 (17%) of patients who did not have LR developed DM. Although the sample size is too small to reach significance, chemotherapy may reduce DM, and having LR may be associated with the development of DM.

Targeted therapies for specific tumor mutations have also shown efficacy, such as *EGFR*-directed therapy [39]. Immunotherapy, such as the use of cetuximab, in combination with chemotherapy, has also demonstrated significant radiographic and clinical response for locally invasive primary inoperable odontogenic carcinomas [39]. Due to the unpredictable nature of these tumors, long-term follow-up is highly recommended regardless of initial treatment [43].

In conclusion, GCOC is a rare but aggressive odontogenic carcinoma requiring a multidisciplinary approach for management. Radical surgical excision, followed by adjuvant therapies as pathologically indicated, remains the primary treatment modality. Indications for adjuvant therapies such as radiotherapy include rapid preoperative growth, the presence of a precursor lesion such as ameloblastoma, positive lymph nodes, positive margins, and recurrence after excision of the initial tumor. While GCOC is prone to both local and distant recurrences, LR appears to be the primary mode of treatment failure. Advances in molecular genetics, particularly regarding the role of *CTNNB1*, *TP53*, and increased Ki-67 proliferation index, may pave the way for more personalized therapies, improving patient outcomes. Further research should therefore investigate the various roles these genetic markers play in the pathogenesis, recurrence rates, and potential for metastasis in GCOC. Additional research should continue to focus on the intensification of adjuvant therapies after oncologic resection to improve outcomes for these patients.

Table 3 Characteristics of patients treated with adjuvant therapy

Author	Year	Age/Sex	Tumor site	Initial treatment	LR	DM	Recurrence Details	Salvage treatment	Follow-Up
Grodjesk [52]	1987	46/M	R Maxilla	R maxillectomy + adjuvant RT (62 Gy to right maxilla, 50 Gy to neck)	Yes	Yes	LR 5 mo later; DM (lung) 6 mo later	No	Dead, 1 day after presenting with DM
Folpe [42]	1998	20/M	R Maxilla	Resection x3, adjuvant RT (60 cGy*) after last recurrence	Yes	No	LR 6 years later	Right radical maxillectomy; Intraoperative ^{125}I seeds in cavernous sinus	NED 1.5 years
Martos-Fernandez [18]	2014	70/F	R Maxilla	Extended maxillectomy + adjuvant RT (52 Gy)	No	No	N/A	N/A	NED 1 year
Rappaport [69]	2015	64/F	R Mandible	Resection x2, adjuvant RT (after recurrence, +PNI, multiple margins involved)	Yes	Yes	DM (pleura) 1 year later	None (due to medical comorbidities)	No follow-up after DM
Ali EAM [41]	2015	21/M	L Maxilla	Resection, adjuvant CT; RT for infraorbital positive margin (50 Gy/25 fx)	Yes	No	LR infraorbital area	Resection	NED 1 year
Ahmed [39]	2015	10/M	R Maxilla	Right maxillectomy/ palatectomy/neck dissection with 7/38 LN+, negative margins, EGFR+; adjuvant CT, RT (60 Gy with concurrent carboplatin), adjuvant cetuximab x9	No	No	No	N/A	NED 1.2 years
Namana [9]	2017	37/M	R Mandible	Hemimandibulectomy/radical neck dissection, adjuvant RT	Yes	Yes	Simultaneous LR and DR 1 year later (pleural and lung nodules)	Patient expired before salvage treatment	Dead after recurrence
Qin [23]	2018	41/M	R Maxilla	Radical resection x2, adjuvant therapy for recurrence (docetaxel/cisplatin x2, CT, RT 60 Gy with concurrent weekly docetaxel)	Yes	No	N/A	N/A	NED 1.7 years
Panprasit [67]	2021	43/M	L Maxilla	Resection x2, adjuvant therapy for recurrence (CT, RT)	Yes	No	N/A	N/A	NED 2 years
Al-Sammak [44]	2023	37/M	R Maxilla	Right maxillectomy with close posterior margin, adjuvant CT, RT (40 Gy) with persistent disease	Yes	No	Persistent disease	Declined radical resection, underwent palliative RT 30 Gy/10 fractions for intracranial extension of disease	No follow-up after palliative RT
Filali [10]	2023	19/F	L Mandible	Excision with 10 mm margin, adjuvant RT (50 Gy/25 fractions)	No	No	N/A	N/A	NED 1.5 years

M: male; F: female; L: left; R: right; LR: local recurrence; DM: distant metastasis; mo, months; N/A: not applicable, NED: No evidence of disease; RT: radiation therapy; Gy: gray; CT: chemotherapy; *As reported in text, unclear if typographical error and should be 60 Gy instead

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Declarations

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References

1. De Souza Vieira G, de Pinho Montovani P, Rozza-de-Menezes RE et al (2021) Comparative analysis between dentinogenic ghost cell tumor and ghost cell odontogenic carcinoma: a systematic review. Head Neck Pathol 15:1265–1283
2. Oliveira Santos P, Cabrera R, Vilares M, Borges A (2021) Ghost cell odontogenic carcinoma of the left maxilla. BMJ Case Rep 14(4):e242445
3. Goldenberg D, Sciubba J, Tufano RP (2004) Odontogenic ghost cell carcinoma. Head Neck 26:378–381
4. Attouchi I, Oualha L, Belkacem Chebil R, Ben Youssef S (2024) Calcifying odontogenic cyst associated with complex odontoma: report of a rare case. Clin Med Insights 17:11795476241277660
5. Nakhla MN, Richards PQ, Miller JE et al (2023) Ghost cell odontogenic carcinoma: a case report and literature review. Laryngoscope 133(4):830–833
6. Gorlin RJ, Pindborg JJ, Clausen FP, Vickers RA (1962) The calcifying odontogenic cyst–a possible analogue of the cutaneous calcifying epithelioma of Malherbe. An analysis of fifteen cases. Oral Surg Oral Med Oral Pathol 15:1235–1243
7. De Arruda JAA, Monteiro JLGC, Abreu LG et al (2018) Calcifying odontogenic cyst, dentinogenic ghost cell tumor, and ghost cell odontogenic carcinoma: a systematic review. J Oral Pathol Med 47(8):721–730
8. Zhu ZY, Chu ZG, Chen Y et al (2012) Ghost cell odontogenic carcinoma arising from calcifying cystic odontogenic tumor: a case report. Kor J Pathol 46(5):478–482
9. Namana M, Majumdar S, Uppala D, Avv A, Rao AK (2017) Ghost cell odontogenic carcinoma arising Denovo with distant metastasis: a case report and review of literature. J Clin Diagn Res 11(8):ZD01–ZD03
10. Filali H, Khalfi S, Lahmar S et al (2023) Ghost cell odontogenic carcinoma of the mandible: case report and review of literature. World J Adv Res Rev 18(02):375–380
11. Ghita I, Nagai MY, Lubek JE et al (2022) Ghost cell odontogenic carcinoma arising in a previous calcifying odontogenic cyst: a case report and review of literature. Head Neck Pathol 16:828–835
12. Lu Y, Mock D, Takata T, Jordan R (1999) Odontogenic ghost cell carcinoma: report of four new cases and review of the literature review. J Oral Pathol Med 28(7):323–329
13. Zhang L, Xu Q, Feng Z (2024) Comprehensive clinical, genome and transcriptomic analysis of primary ghost cell odontogenic carcinoma. Oral Oncol 148:106616
14. Cheng Y, Long X, Li X, Bian Z, Chen X, Yang X (2004) Clinical and radiological features of odontogenic ghost cell carcinoma: review of the literature and report of four new cases. Dent Max Radiol 33(3):152–157
15. Kim HJ, Choi SK, Lee CJ, Suh CH (2001) Aggressive epithelial odontogenic ghost cell tumor in the mandible: CT and MR imaging findings. AJNR 22(1):175–179
16. Lee SK, Kim YS (2014) Current concepts and occurrence of epithelial odontogenic tumors: II. calcifying epithelial odontogenic tumor versus ghost cell odontogenic tumors derived from calcifying odontogenic cyst. Korean J Pathol 48(3):175–187
17. Tarakji B, Ashok N, Alzoghaibi I et al (2015) Malignant transformation of calcifying cystic odontogenic tumour—a review of literature. Cont Oncol 19(3):184–186
18. Martos-Fernández M, Alberola-Ferranti M, Hueto-Madrid JA, Bescós-Atín C (2014) Ghost cell odontogenic carcinoma: a rare case report and review of literature. J Clin Exp Dent 6(5):e602–e606
19. Wader J, Gajbi N (2013) Neoplastic (solid) calcifying ghost cell Tumor, intraosseous variant: report of a rare case and review of literature. J Clin Diagn Res 7(9):1999–2000
20. Oh KY (2024) β-catenin nuclear translocation and WNT pathway mutations in ghost cell odontogenic carcinoma: a literature review and proposal of a new molecular-based classification WNT pathway-altered malignant odontogenic tumor. Oral Oncol 155:106907
21. Oh KY, Kim JH, Yoon HJ (2024) Calcifying odontogenic cyst demonstrates recurrent WNT pathway mutations and So-Called adenoid Ameloblastoma-Like histology: evidence supporting its classification as a neoplasm. Mod Pathol 37(6):100484
22. Oh KY, Kim JH, Yoon HJ (2025) Diagnostic utility of SATB2, CDX2, CD10, and β-Catenin immunohistochemistry in WNT pathway-altered odontogenic tumors. Arch Pathol Lab Med 149(11):1027–1032
23. Qin Y, Lu Y, Zheng L, Liu H (2018) Ghost cell odontogenic carcinoma with suspected cholesterol granuloma of the maxillary sinus in a patient treated with combined modality therapy: a case report and the review of literature. Medicine 97(7):e9816
24. Seki-Soda M, Sano T, Matsumura N et al (2022) Ghost cell odontogenic carcinoma arising in dentinogenic ghost cell tumor with next-generation sequencing cancer panel analysis: a case report. Oral Surg Oral Med Oral Pathol Oral Rad 134(3):e58–65
25. Schwarz Y, Pitaro J, Waissbluth S, Daniel SJ (2016) Review of pediatric head and neck Pilomatrixoma. Int J Ped Otorhinolaryngol 85:148–153
26. Novak A, Dedhar S (1999) Signaling through beta-catenin and Lef/Tcf. Cell Mol Life Sci 56(5–6):523–537
27. Valenta T, Hausmann G, Basler K (2012) The many faces and functions of β-catenin. EMBO J 31(12):2714–2736
28. Gomes da Silva W, Ribeiro Bartholomeu Dos Santos TC, Cabral MG, Azevedo RS, Pires FR (2014) Clinicopathologic analysis and syndecan-1 and Ki-67 expression in calcifying cystic odontogenic tumors, dentinogenic ghost cell tumor, and ghost cell odontogenic carcinoma. Oral Surg Oral Med Oral Pathol Oral Rad 117(5):626–633
29. Sakamoto S, Ando T, Mizuta K et al (2023) Ghost cell odontogenic carcinoma arising in dentinogenic ghost cell tumor, peripheral: a case report. Pathol Int 73(8):367–372
30. Jabbarzadeh M, Hamblin MR, Pournaghi-Azar F, Vakili Saatloo M, Kouhsoltani M, Vahed N (2021) Ki-67 expression as a diagnostic biomarker in odontogenic cysts and tumors: a systematic review and meta-analysis. J Dent Res Dent Clin Dent Prospects 15(1):66–75
31. Argyris PP, Malz C, Taleb R, Koutlas IG (2018) Benign and malignant odontogenic neoplasms of the jaws show a concordant nondiscriminatory P63/P40 positive immunophenotype. Oral Surg Oral Med Oral Pathol Oral Rad 126(6):506–512
32. Garg A, Malhotra R, Urs AB (2022) Ghost cells unveiled: a comprehensive review. J Oral Biosci 64(2):202–209
33. Bach CLT, Tallet A, Bonenfant C et al (2025) Cutaneous hybrid cysts with matrical differentiation are mostly sporadic and related to CTNNB1 mutation. Virch Archiv 486(5):1023–1032
34. Herrmann JL, Allan A, Trapp KM, Morgan MB (2014) Pilomatrix carcinoma: 13 new cases and review of the literature with emphasis on predictors of metastasis. J Am Acad Dermtol 71(1):38–43
35. Kyrpychova L, Carr RA, Martinek P et al (2017) Basal cell carcinoma with matrical differentiation: Clinicopathologic, Immunohistochemical, and molecular biological study of 22 cases. Am J Surg Pathol 41(6):738–749
36. Ide F, Kikuchi K, Miyazaki Y, Kusama K, Saito I, Muramatsu T (2015) The early history of odontogenic ghost cell lesions: from Thoma to Gorlin. Head Neck Pathol 9(1):74–78

37. Roberts KF, Dahiya SM (2024) Neuropathology entities involving the sinonasal tract. Surg Pathol Clin 17(4):733–748
38. Gwartzman B, Trinh K, Hassan A, Philipone E (2023) Dentinogenic ghost cell tumor associated with odontoma: report of a rare case and review of literature. Quin Int 54(8):652–657
39. Ahmed SK, Watanabe M, de Mello DE, Daniels TB (2015) Pediatric metastatic odontogenic ghost cell carcinoma: a multimodal treatment approach. Rare Tum 7(2):5855
40. Scott J, Wood GD (1989) Aggressive calcifying odontogenic cyst–a possible variant of ameloblastoma. Br J Oral Max Surg 27(1):53–59
41. Ali EA, Ali Karrar M, El-Siddig AA, Gafer N, Abdel Satir A (2015) Ghost cell odontogenic carcinoma of the maxilla: a case report with a literature review. Pan Afr Med J 21:260
42. Folpe AL, Tsue T, Rogerson L, Weymuller E, Oda D, True LD (1998) Odontogenic ghost cell carcinoma: a case report with immunohistochemical and ultrastructural characterization. J Oral Pathol Med 27(4):185–189
43. Sukumaran R, Somanathan T, Kattoor J (2015) Odontogenic ghost cell carcinoma with pulmonary metastasis. J Oral Maxillofac Pathol 19(3):371–374
44. Al-SammakA, Rezki O, Pennington M et al (2023) Treatment challenges of persistent ghost cell odontogenic carcinoma: a case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol 136(4):e123–e132
45. Alcalde RE, Sasaki A, Misaki M, Matsumura T (1996) Odontogenic ghost cell carcinoma: report of a case and review of the literature. J Oral Max Surg 54(1):108–111
46. Arashiyama T, Kodama Y, Kobayashi T et al (2012) Ghost cell odontogenic carcinoma arising in the background of a benign calcifying cystic odontogenic tumor of the mandible. Oral Surg Oral Med Oral Pathol Oral Rad 114(3):e35–40
47. Castle JT, Arendt DM (1999) Aggressive (malignant) epithelial odontogenic ghost cell tumor. Ann Diagn Pathol 3(4):243–248
48. Del Corso G, Tardio ML, Gissi DB, Marchetti C, Montebugnoli L, Tarsitano A (2015) Ki-67 and p53 expression in ghost cell odontogenic carcinoma: a case report and literature review. Oral Max Surg 19(1):85–89
49. Ellis GL, Shmookler BM (1986) Aggressive (malignant?) epithelial odontogenic ghost cell tumor. Oral Surg Oral Med Oral Pathol 61(5):471–478
50. Fitzpatrick SG, Hirsch SA, Listinsky CM, Lyu DJ, Baur DA (2015) Ameloblastic carcinoma with features of ghost cell odontogenic carcinoma in a patient with suspected Gardner syndrome. Oral Surg Oral Med Oral Pathol Oral Rad 119(4):e241–e245
51. Gomes JP, Costa AL, Chone CT, Altemani AM, Altemani JM, Lima CS (2017) Three-dimensional volumetric analysis of ghost cell odontogenic carcinoma using 3-D reconstruction software: a case report. Oral Surg Oral Med Oral Pathol Oral Rad 123(5):e170–e175
52. Grodjesk JE, Dolinsky HB, Schneider LC, Dolinsky EH, Doyle JL (1987) Odontogenic ghost cell carcinoma. Oral Surg Oral Med Oral Pathol 63(5):576–581
53. Hu SS, Yang J, Zhang HF et al (2024) Challenging pitfalls in frozen section pathology: a case of mandible ghost cell odontogenic carcinoma and the literature review. BMC Oral Health 24(1):450
54. Ihrler S, Mollenhauer M, Weitmayr B, Haas CJ (2020) Salivary ghost cell carcinoma: case report and proposal of a new entity. Virch Archiv 476(3):465–468
55. Ikemura K, Horie A, Tashiro H, Nandate M (1985) Simultaneous occurrence of a calcifying odontogenic cyst and its malignant transformation. Cancer 56(12):2861–2864
56. Jia MQ, Jia J, Wang L, Zou HX (2019) Ghost cell odontogenic carcinoma of the jaws: report of two cases and a literature review. World J Clin Cases 7(3):357–365
57. Kamijo R, Miyaoka K, Tachikawa T, Nagumo M (1999) Odontogenic ghost cell carcinoma: report of a case. J Oral Max Surg 57(10):1266–1270
58. Kasahara K, Iizuka T, Kobayashi I, Totsuka Y, Kohgo T (2002) A recurrent case of odontogenic ghost cell tumour of the mandible. Int J Oral Max Surg 31(6):684–687
59. Kim J, Lee EH, Yook JI, Han JY, Yoon JH, Ellis GL (2000) Odontogenic ghost cell carcinoma: a case report with reference to the relation between apoptosis and ghost cells. Oral Surg Oral Med Oral Pathol Oral Rad Endo 90(5):630–635
60. Li BB, Gao Y (2009) Ghost cell odontogenic carcinoma transformed from a dentinogenic ghost cell tumor of maxilla after multiple recurrences. Oral Surg Oral Med Oral Pathol Oral Rad Endo 107(5):691–695
61. Li BH, Cho YA, Kim SM, Kim MJ, Hong SP, Lee JH (2011) Recurrent odontogenic ghost cell carcinoma (OGCC) at a reconstructed fibular flap: a case report with immunohistochemical findings. Med Oral Pathol Oral Cir Buc 16(5):e651–e656
62. Li TJ, Yu SF (2003) Clinicopathologic spectrum of the so-called calcifying odontogenic cysts: a study of 21 intraosseous cases with reconsideration of the terminology and classification. Am J Surg Pathol 27(3):372–384
63. McCoy BP, O Carroll MK, Hall JM (1992) Carcinoma arising in a dentinogenic ghost cell tumor. Oral Surg Oral Med Oral Pathol 74(3):371–378
64. Motosugi U, Ogawa I, Yoda T et al (2009) Ghost cell odontogenic carcinoma arising in calcifying odontogenic cyst. Ann Diagn Pathol 13(6):394–397
65. Nazaretian SP, Schenberg ME, Simpson I, Slootweg PJ (2007) Ghost cell odontogenic carcinoma. Int J Oral Max Surg 36(5):455–458
66. Ohata Y, Kayamori K, Yukimori A et al (2018) A lesion categorized between ghost cell odontogenic carcinoma and dentinogenic ghost cell tumor with CTNNB1 mutation. Pathol Int 68(5):307–312
67. Panprasit W, Lappanakokiat N, Kunmongkolwut S et al (2021) Ghost cell odontogenic carcinoma: a case report. Img Sci Dent 51(2):203–208
68. Park SY, Park J, Kwon DH et al (2017) Ghost cell odontogenic carcinoma on right mandible and its respective surgical reconstruction: a case report. J Kor Ass Oral Max Surg 43(6):415–422
69. Rappaport MJ, Showell DL, Edenfield WJ (2015) Metastatic ghost cell odontogenic carcinoma: description of a case and search for actionable targets. Rare Tum 7(3):5813
70. Remya K, Sudha S, Nair RG, Jyothi H (2018) An unusual presentation of ghost cell odontogenic carcinoma: a case report with review of literature. Indian J Dent Res 29(2):238–243
71. Roh GS, Jeon BT, Park BW et al (2008) Ghost cell odontogenic carcinoma of the mandible: a case report demonstrating expression of tartrate-resistant acid phosphatase (TRAP) and vitronectin receptor. J Cranio Surg 36(7):419–423
72. Sun ZJ, Zhao YF, Zhang L, Li ZB, Chen XM, Zhang WF (2007) Odontogenic ghost cell carcinoma in the maxilla: a case report and literature review. J Oral Max Surg 65(9):1820–1824
73. Vijayakumar G, Kamboj M, Narwal A, Devi A (2021) Ghost cell odontogenic carcinoma of anterior mandible: a rare case report with review of literature. J Oral Max Pathol 25(Suppl 1):S99–108
74. Xia Y, Song Z, Zhang X et al (2023) Ghost cell odontogenic carcinoma: a rare case report and review of literature. Medicine 102(38):e35225
75. Aravind S, Jose J, Nayanar SK, Sajith Babu TP (2023) Ghost cell odontogenic carcinoma with sarcomatous transformation: report of a rare case with review of literature. Gulf J Oncol 1(41):111–116

76. Du W, Aladimi MT, Zhang Z et al (2017) Mandibular ghost cell odontogenic carcinoma: a case report and review of literature. Int J Clin Exp Med 10:8325–8330
77. Nel C, Robinson L, van Heerden WFP (2021) Ghost cell odontogenic carcinoma arising in the background of a calcifying odontogenic cyst. Oral Rad 37(3):537–542