

# 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

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### Abstract

**Rationale:** Ghost cell odontogenic carcinoma (GCOC) is a rare malignant odontogenic tumor with aggressive growth characteristics.

**Patient concerns:** A 41-year-old Chinese male visited our hospital in 2013, with a 4-month history of bloody purulent rhinorrhea with a peculiar smell in the right nasal cavity.

**Diagnoses:** The patient suffered from recurrent GCOC with suspected cholesterol granuloma of the maxillary sinus. The patient was incorrectly diagnosed with a calcifying epithelial odontogenic tumor at his first recurrence. Physical examination, radiological examination, and histopathology were used to identify GCOC.

**Interventions:** Considering the recurrence of GCOC and poor effects of single surgery, postoperative adjuvant chemotherapy and concurrent chemoradiotherapy were performed after radical surgical excision.

**Outcomes:** So far, no significant evidence has suggested recurrence or metastasis after a long-term follow-up.

**Lessons:** We advocate wide surgery with clean margins at the first accurate diagnosis. Combined modality therapy could be taken for the recurrent GCOC. We expect to provide a new treatment strategy to prevent the growth of this neoplasm.

**Abbreviations:** CEOT = calcifying epithelial odontogenic tumor, CG = cholesterol granuloma, CGMS = cholesterol granuloma in the maxillary sinus, GCOC = ghost cell odontogenic carcinoma, MR = magnetic resonance, PTV = planning target volume.

**Keywords:** calcifying epithelial odontogenic tumor, cholesterol granuloma of the maxillary sinus, combined modality therapy, ghost cell odontogenic carcinoma, odontogenic tumor

## 1. Introduction

According to the latest World Health Organization classification in 2005, malignant odontogenic epithelium tumors consist of metastatic ameloblastoma, ameloblastic carcinoma, primary intraosseous carcinoma, ghost cell odontogenic carcinoma

(GCOC), and clear cell odontogenic carcinoma.<sup>[1]</sup> GCOC is defined as a malignant odontogenic epithelial tumor with the features of a calcifying cystic odontogenic tumor, a dentinogenic ghost cell tumor, or both.<sup>[1]</sup> GCOC has a wide spectrum of biological characteristics.<sup>[2,3]</sup> Here, we report a case of recurrent maxillary GCOC with suspected cholesterol granuloma of the maxillary sinus (CGMS), which was improperly diagnosed as calcifying epithelial odontogenic tumor (CEOT). We have described the clinical symptoms, radiographic features, histological characteristics, treatment, and follow-up.

## 2. Case report

A 41-year-old Chinese male visited our hospital in 2013, with a 4-month history of bloody purulent rhinorrhea with a peculiar smell in the right nasal cavity. We reviewed the patient's medical history. The patient had been referred to a hospital in Guangzhou in 2008 for a 3-year history of bloody rhinorrhea and nasal obstruction in the right nasal cavity. At that time, physical examination revealed congested mucous, enlarged inferior turbinate, enlarged middle nasal meatus, and markedly impaired sense of smell on the right side. Surgical resection was performed under general anesthesia. The lesion was histopathologically diagnosed as CGMS.

In 2012, nearly 4 years after the first treatment, the patient began to show nasal obstruction again and complained of no

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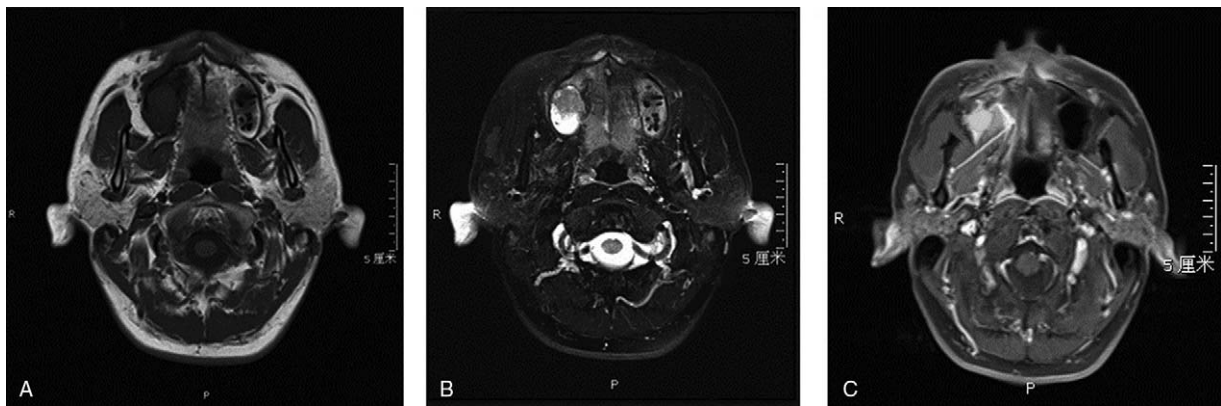
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**Figure 1.** MR showed a soft tissue mass. (A) T1-weighted image (axial). (B) T2-weighted image (axial). (C) Contrast-enhanced T1-weighted image (axial).

alleviation of bloody rhinorrhea since the first operation. The patient went to a hospital in Tianmen for help. According to his medical history and the results of radiological examinations, the patient underwent a radical operation. The pathologic diagnosis was CEOT.

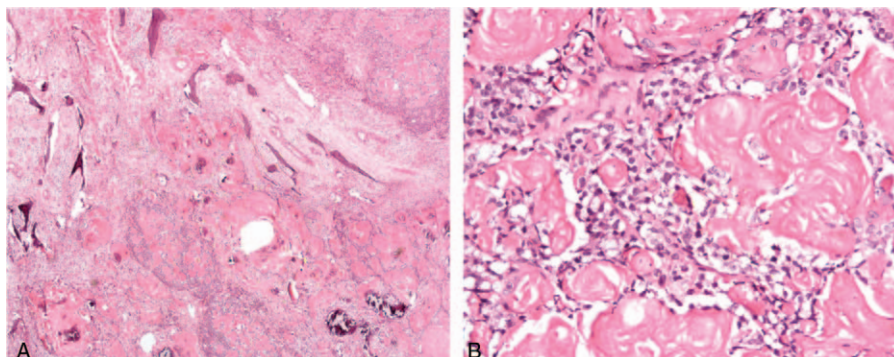
In 2013, 1 year after the second operation, the patient came to another hospital in Guangdong with a 4-month symptom of bloody purulent rhinorrhea accompanied by a peculiar smell in the right nasal cavity. It was proved pathologically to be keratinizing squamous cell carcinoma after biopsy. Without any further treatment, the patient came to our hospital in May 14, 2013. Magnetic resonance (MR) imaging revealed a soft tissue mass measuring  $3.5 \times 2.5 \times 2.9$  cm located in the right maxillary sinus, which presented mixed, slightly high signal intensity on a T1-weighted image and slightly high signal intensity on a T2-weighted image. This was surrounded by the liquid, high signal intensity on a T2-weighted image, and the lesion invaded all walls of the right maxillary sinus and adjacent zygoma, extending into the nasal cavity and ethmoidal sinus on the right side at the same time. The contrast-enhanced MR showed significant heterogeneous density (Fig. 1). Upon inspection of the emission computed tomography (CT) and lung CT, no evidence supported metastasis. Considering his medical history, we reviewed his hematoxylin and eosin stain slices in 2012. We revised the previous pathologic diagnosis as GCOC. Histopathologically, we observed the neoplastic nests. Parts of the tumor were calcified. The tumor also infiltrated the surrounding connective tissue and bone (Fig. 2A). It was surrounded by the deeply stained small

round cells, typical ghost cells in clusters or isolated with pale swollen homogeneous eosinophilic cytoplasm, which had lost their nuclei (Fig. 2B).

Under general anesthesia, a radical surgery was performed. Systemic chemotherapy by intravenous administration of docetaxel ( $75 \text{ mg/m}^2$  on day 1) and cisplatin ( $75 \text{ mg/m}^2$  on day 1) was carried out on May 31, 2013. After 2 cycles of chemotherapy, the patient received concurrent chemoradiotherapy (planning target volume [PTV<sub>1</sub>] 60 Gy/27F, PTV<sub>2</sub> 54 Gy/27F, PTV<sub>3</sub> 50 Gy/27F during weeks 1–5) using a 3-dimensional conformal radiation therapy technique together with 4 weekly docetaxel (40 mg). The adverse effects were decreased appetite, pigmentation of skin in radiation field, and bone marrow suppression, especially thrombocytopenia. At the end of the combined modality therapy, the patient showed good results without any residual neoplasm in radiography. The patient showed a good therapeutic result after the combined modality therapy. No evidence of recurrence or metastasis was observed after the 20-month follow-up, which lasted until May 2015. We will continue to focus on the patient's follow-up.

### 3. Discussion

GCOC is a rare malignant odontogenic tumor that was first described by Ikemura et al.<sup>[4]</sup> To our knowledge, 36 cases of GCOC have been reported in English-language literature (Table 1).<sup>[4–29]</sup> Three pathogenic mechanisms explain the origin of GCOC. The first one is that GCOC occurs secondary to



**Figure 2.** (A) Neoplastic nests are composed of small round cells and ghost cells. Calcification also can be founded (H&E stain, original magnification  $\times 20$ ); (B) Tumor is mixes with 2 kinds of components, which are deeply staining small round cells and ghost cells (H&E stain, original magnification  $\times 200$ ).

**Table 1****The clinical features of GCOC in English-language literature.**

Case	Author	Age	Sex	Location	Clinical presentation	Primary treatment	Treatment after recurrence or metastasis	Follow-up
1	Ikemura et al <sup>[4]</sup>	48	Female	Maxilla	Swelling of the upper gingiva and hard palate on the left side	Surgery	Radiotherapy, chemotherapy	1 recurrence and death of intracranial extension
2	Ellis et al <sup>[16]</sup>	55	Male	Mandible	Painful swelling of the anterior mandible	Surgery	Surgery	1 recurrence and death of bronchopneumonia
3	Ellis et al <sup>[16]</sup>	17	Male	Maxilla	Ulcerated mass	Surgery	Surgery	1 recurrence and no evidence of disease after 6 years
4	Ellis et al <sup>[16]</sup>	46	Male	Maxilla	Painless swelling of the mid-right maxilla	Surgery	No recurrence or metastasis	No evidence of disease after 6 years
5	Grodjesk et al <sup>[18]</sup>	46	Male	Maxilla	A large mass in the right maxilla accompanied by frequent, spontaneous bleeding	Surgery, postoperation radiotherapy	N/A	Death from lung metastasis
6	Scott and Wood <sup>[26]</sup>	33	Male	Maxilla	Swelling, left lacrimation, and nasal blockage	Surgery	Surgery, postoperation radiotherapy	2 recurrences. Alive with residual tumor for 3 years and lost to follow-up
7	McCoy et al <sup>[24]</sup>	13	Female	Maxilla	An extraction site that had not healed in 2 years	Surgery	N/A	No evidence of disease after 7 years
8	Dubiel-Bigaj et al <sup>[15]</sup>	42	Female	Maxilla	N/A	N/A	N/A	N/A
9	Siar and Ng <sup>[27]</sup>	39	Male	Maxilla	A massive, ulcerative, and rapidly growing tumor	Surgery	Surgery	4 recurrences and lost to follow-up
10	Alcalde et al <sup>[9]</sup>	72	Female	Maxilla	Painless swelling from the left orbital rim to the left cheek. Intraoral palatal ridge expansion	Surgery, postoperation radiotherapy	N/A	No evidence of disease after 10 years
11	Folpe et al <sup>[17]</sup>	20	Male	Maxilla	A progressively enlarging right cheek mass	Surgery	Surgery, radiotherapy	3 recurrences. No evidence of disease after 1.5 years
12	Castle and Arendt <sup>[13]</sup>	57	Male	Maxilla	Rhinobony and persistent swelling of the upper lip	Incisional biopsy and refuse further treatment	N/A	N/A
13	Kamijo et al <sup>[19]</sup>	38	Male	Maxilla	Swelling of the right cheek extending from the infraorbital region to the upper lip	Surgery	Surgery, postoperation radiotherapy	1 recurrence and no evidence of disease after 1 year
14	Lu et al <sup>[23]</sup>	24	Male	Maxilla	Painful mass	Surgery	Surgery	4 recurrences and lost to follow-up
15	Lu et al <sup>[23]</sup>	31	Female	Maxilla	A swelling on the right side of the face	Surgery	Surgery	1 recurrence and no evidence of disease after 14 months
16	Lu et al <sup>[23]</sup>	19	Male	Mandible	A swelling in the right mandible	Surgery	N/A	Died of local tumor extension in 2 years
17	Lu et al <sup>[23]</sup>	39	Male	Mandible	A mass in the right mandible associated with paresthesia of the right lower lip	Surgery	Surgery	1 recurrence and no evidence of disease after 28 years
18	Kim et al <sup>[21]</sup>	33	Male	Mandible	Mandibular swelling	Surgery	N/A	No evidence of disease after 2.5 years
19	Kasahara et al <sup>[20]</sup>	59	Male	Mandible	A painless swelling on the right side of the mandible	Surgery	Surgery	1 recurrence
20	Cheng et al <sup>[14]</sup>	36	Male	Mandible	A painless swelling in the anterior mandible	Surgery	Surgery	1 recurrence
21	Cheng et al <sup>[14]</sup>	35	Male	Maxilla	A painless swelling in the right maxilla	Surgery	Surgery	1 recurrence and died of cranial metastasis
22	Cheng et al <sup>[14]</sup>	33	Male	Maxilla	Tender swelling on the right side of the face	Surgery	Surgery	1 recurrence
23	Cheng et al <sup>[14]</sup>	44	Male	Mandible	A painless swelling in the right mandible	Surgery	Surgery	4 recurrences
24	Goldenberg et al <sup>[29]</sup>	36	Male	Maxilla	Painful swelling and cyst formation in the right maxilla	Surgery	Surgery	1 recurrence and no evidence of disease after 18 months
25	Nazaretian et al <sup>[25]</sup>	40	Male	Maxilla	Pain in the right maxillary region	Surgery	N/A	N/A
26	Sun et al <sup>[7]</sup>	30	Male	Maxilla	A rapidly growing mass in the right maxilla	Surgery	N/A	No evidence of disease after 1 year
27	Roh et al <sup>[10]</sup>	55	Male	Mandible	A painful swelling with local paraesthesia in the left side of the mandible	Surgery	N/A	No evidence of disease after 1.8 years
28	Li et al <sup>[22]</sup>	53	Male	Maxilla	A slowly growing painless mass in the left maxilla	Surgery	Surgery	5 recurrences and no evidence of disease after 6 months
29	Motosugi et al <sup>[12]</sup>	17	Female	Maxilla	A maxillary mass	Surgery	Surgery	2 recurrences
30	Li et al <sup>[22]</sup>	47	Female	Mandible	A slow-growing, painful and swelling mass in the right mandible	N/A	Surgery	1 recurrence and no evidence of disease after 4 years
31	Arashiyama et al <sup>[3]</sup>	68	Male	Mandible	A gingival swelling	Surgery	Surgery	1 recurrence and no evidence of disease after 4 years
32	Zhu et al <sup>[11]</sup>	51	Male	Maxilla	A slowly growing, painful mass in the right maxillary region	Surgery	Surgery	1 recurrence
33	Wader and Gajbi <sup>[28]</sup>	61	Male	Mandible	A painful swelling in the lower right jaw	Surgery	N/A	N/A
34	Martos-Fernández et al <sup>[30]</sup>	70	Female	Maxilla	Pain and rapid expansion of a mass	Surgery, postoperation radiotherapy	N/A	1 recurrence and no evidence of disease after 1 year
35	Del Corso et al <sup>[6]</sup>	86	Male	Mandible	An asymptomatic swelling of the left mandible	Surgery	N/A	N/A
36	Fitzpatrick et al <sup>[5]</sup>	37	Male	Maxilla	A slowly growing mass in the right anterior maxilla	Surgery	N/A	Lost to follow-up

N/A = not available.

calcifying cystic odontogenic tumors. The second is that GCOC is caused by dentinogenic ghost cell tumors. The last one is that it arises de novo.<sup>[3,30]</sup> A secondary onset from an undiagnosed primary lesion can be potentially considered the de novo type.<sup>[3]</sup> Owing to a suspected diagnosis as CGMS, this case seemed to fit the last one.

GCOC has a low incidence. In China, malignant odontogenic tumors account for 5.06% of all odontogenic tumors, which accounted for only 0.23% of GCOC.<sup>[31]</sup> GCOC appears to be more common in Asians and in males.<sup>[6,14,23]</sup> It can occur at any age with a peak incidence in the fourth decade of life.<sup>[6,14,32]</sup> GCOC occurs more frequently in the maxilla than the mandible.<sup>[6,14,23]</sup> The most common clinical symptom of GCOC is a painful swelling in jaws with local paresthesias.<sup>[14]</sup> The most typical radiological features of GCOC reveal a mixed radiolucent and radiopaque lesion pattern with poorly defined borders, with or without root resorption and tooth displacement.<sup>[14]</sup> In this article, a 41-year-old Chinese male came to our hospital with a maxillary lesion. The patient showed atypical symptoms of GCOC, such as bloody purulent rhinorrhea and peculiar smell in the right nasal cavity. The age of onset in this case was typical for GCOC. As far as we are concerned, his atypical clinical features may be attributable to the suspected CGMS.

CG is a foreign body reaction to the deposition of cholesterol crystals. It is usually associated with middle ear diseases.<sup>[1]</sup> It is a rare condition in the maxillary sinus. It was first reported by Graham and Michaels. The clinical features of CGMS are nonspecific. But the most common symptoms are nasal discharge, nasal obstruction and congestion, postnasal drip, facial pain and headache, and otalgia.<sup>[33]</sup> Although the exact mechanism of the development of CGMS is not clear, Chao<sup>[34]</sup> proposed probable mechanisms, specifically the obstruction of ventilation, hemorrhage, and impaired drainage. It seems that the appearance of CGMS and GCOC is irrelevant.

In the present case, the patient was diagnosed as CGMS after his first operation in 2008. We suspected this diagnosis may not have been accurate. It seems impossible that 2 kinds of rare tumors would occur in one individual. Because of the limited medical records of the first visit, especially the loss of pathological section, we cannot confirm whether the patient suffered CGMS before GCOC. The patient was diagnosed with CEOT nearly 4 years after his first operation in 2012. By reviewing his pathological section, we finally confirmed that the patient suffered GCOC rather than CEOT. Although GCOC and CEOT are odontogenic origin epithelial tumors producing calcifying materials from transformed epithelial tumor cells, CEOT is a benign odontogenic tumor, considerably different from the malignant GCOC.<sup>[35]</sup>

The diagnosis of odontogenic tumors should not be based solely on clinical symptoms or radiological examination, but must rely on histopathology. Here, we summarize the histopathological features of CGMS, CEOT, and GCOC. CGMS is characterized by a large number of cholesterol clefts surrounded by multinucleated giant cells, histiocytes, plasma cells, lymphocytes, and hemosiderin deposits.<sup>[34]</sup> CEOT represents retrogressive calcific changes, amyloid-like deposition, and clear cytoplasm.<sup>[1,35]</sup> Cheng et al<sup>[14]</sup> put forward histological diagnostic criteria for GCOC, which are an epithelial lining with a well-defined basal layer of columnar cells, a layer of cells resembling the stellate reticulum of the enamel organ, and masses of ghost cells that may be calcified or not, accompanied by atypical epithelial cell foci presenting mitosis, keratin pearls, necrosis, and so on. Some studies also point out that the expressions of

immunohistochemical biomarkers of Ki-67 and MMP-9, which are associated with tumor proliferation and invasion, are positive in GCOC.<sup>[36]</sup> As a result of the high levels of expression of those biomarkers, Ki-67 and MMP-9 can be helpful in the diagnosis and evaluation of the prognosis of GCOC.<sup>[6,11]</sup> In short, the pathologists should pay more attention to these histopathological features and provide the accurate pathology reports, which is important to the clinical doctors. Immunohistochemistry may help to determine the benign or malignant nature of odontogenic tumors.

The recommended treatment of GCOC is wide surgical excision with clean margins.<sup>[2,3,6]</sup> The use of postoperative adjuvant chemotherapy and chemoradiotherapy is controversial. Because of the recurrence of GCOC and poor effects of single surgery, we take comprehensive therapy in this case. Two cycles of chemotherapy and chemoradiotherapy together with 4 rounds of weekly chemotherapy after wide surgery were performed. The patient's symptoms showed significant improvement. Meanwhile, cervical lymph nodes were reduced after this therapeutic strategy. The overall 5-year survival rate is estimated to be 73%.<sup>[23]</sup> The recurrence of GCOC is possible. However, the metastasis is very uncommon. To date, only 2 cases have been reported to cause cranial and pulmonary metastases.<sup>[14,18]</sup>

In summary, GCOC is a rare malignant odontogenic tumor with a high rate of recurrence. We advocate wide surgery with clean margins at the first accurate diagnosis. Regarding recurrent GCOC, we were able to perform combined modality therapy, which combines surgery, postoperative adjuvant chemotherapy, and concurrent chemoradiotherapy. Long-term follow-up is important for observation of recurrence or metastases.

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