# Metastatic ghost cell odontogenic carcinoma: description of a case and search for actionable targets

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## Abstract

Ghost cell odontogenic carcinoma (GCOC) is an exceedingly rare malignant tumor on the spectrum of already uncommon odontogenic or dentinogenic tumors. We describe here the case of metastatic GCOC in a patient with a history of recurrent dentinogenic ghost cell tumor of the mandible, now presenting with bilateral pleural effusions. We will discuss typical histopathologic and histochemical features of GCOC, along with results of genomic testing and their role in directing therapy.

## Introduction

The ghost cell odontogenic carcinoma (GCOC) is a rare malignant tumor most commonly arising in maxillary bones.[1] These malignant neoplasms are considered to be derived from the calcifying odontogenic cysts (COC) or *de novo.* COCs can be subdivided into two benign variants; the dentinogenic ghost cell tumor (DGCT) as well as the calcifying cystic odontogenic tumor (CCOT).[2] These tumors have a mean age of 40 years, with a male predominance (2:1) and a tendency to affect patients of Asian descent disproportionately.[1,2] In general, these neoplasms have a very unpredictable course that ranges from indolence to potential fatality.[1,3,4]

Dentinogenic ghost cell tumors are benign, locally invasive neoplasms found in men more commonly than women and between 12 and 75 years of age. They are found equally in the maxilla and the mandible and are usually asymptomatic. They are divided into intraosseous or central and extraosseous or peripheral subtypes. Intraosseous DGCT may be aggressive and local resection with wide margin, although attempted, was never obtained in our case. There are previous reports of documented transformation into GCOC, as appears to be demonstrated with our current case report.[2,5]

According to literature, approximately 33 cases of GCOC have been reported prior to this case report. Of these cases of GCOC, two have been metastatic, one to the brain and one to the lung.[1,6] We describe here a case of GCOC with metastasis to bilateral lungs and malignant pleural effusions; the primary, in the right mandible, had recurred locally twice before.

## Case Report

A 64 year-old black female was seen in office after hospital discharge during which she received tissue diagnosis of a well differentiated metastatic odontogenic carcinoma. She has a history of a previous right mandibular cyst resected May 1990 with histopathology reported DGCT with the caveat that review of histopathology not available for review. In August 2009 she had local recurrence with histopathologic diagnosis of atypical DGCT with sections of epithelial tumor composed of islands of hyperchromatic odontogenic epithelial cells. This specimen was noted to be more cellular and mitotically active than the original tumor 19 years prior giving rise to the possibility that this lesion could represent an odontogenic ghost cell carcinoma. In July 2010, our patient again had local recurrence with histopathologic diagnosis of GCOC based on the rapid recurrence and increased proliferation index of 15-20% on Ki-67 staining. Recurrence occurred locally in May 2012 and histology was again consistent with a GCOC. Of note, in 2012 there was perineural invasion present and multiple margins involved, thus our patient underwent local radiation therapy from June through August 2012. Our patient's most recent recurrence was diagnosed by pleural biopsy in December 2013, with microscopic histopathology consistent with metastatic well-differentiated odontogenic carcinoma and similar to previous pathology without the *ghost cell* component (Figure 1). At the current time due to our patient's multiple complex medical co-morbidities that include ischemic congestive heart failure status post automatic implantable cardioverter defibrillator, pulmonary hypertension, end stage renal disease requiring hemodialysis, atrial fibrillation with atrial thrombus requiring chronic anticoagulation, hypertension, and previous stroke she is unable to be registered in any potential clinical trials. In addition, as there are no previously effective chemotherapy options, our patient will continue to be monitored clinically and treated symptomatically.

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## Discussion

The histopathology of GCOC commonly demonstrates prominent mitotic activity, nuclear atypia, cellular pleomorphism, necrosis, and occasionally scarce mineralized or dentin-like materials.[7] GCOC has an infiltrative growth pattern. It is felt to be a solid variant of the classic benign calcifying odontogenic cyst with ghost cells, as well as malignant features (*i.e.* calcifying rounded epithelial islands in a fibrous stroma).[2,8] As the tumor cells undergo malignant processes, ghost cells may be difficult to find, as occurred in our case.[9] GCOC can present *de novo*, however, it may also present as a malignant transformation of recurrent CCOT or DGCT.[3,4] The ability of CCOT or DGCT to transform into the malignant variant, GCOC, has been linked to level of expression of Ki-67, a biomarker of cell proliferation. In almost all reported studies, Ki-67 is weakly expressed in CCOT or DGCT, however, expression is strong in GCOC.[10-12] Similar overexpression patterns have been reported of p53 protein in odontogenic tumor cells.[8,12] Though immunohistochemical characterizations are frequently used, genomic screening, especially

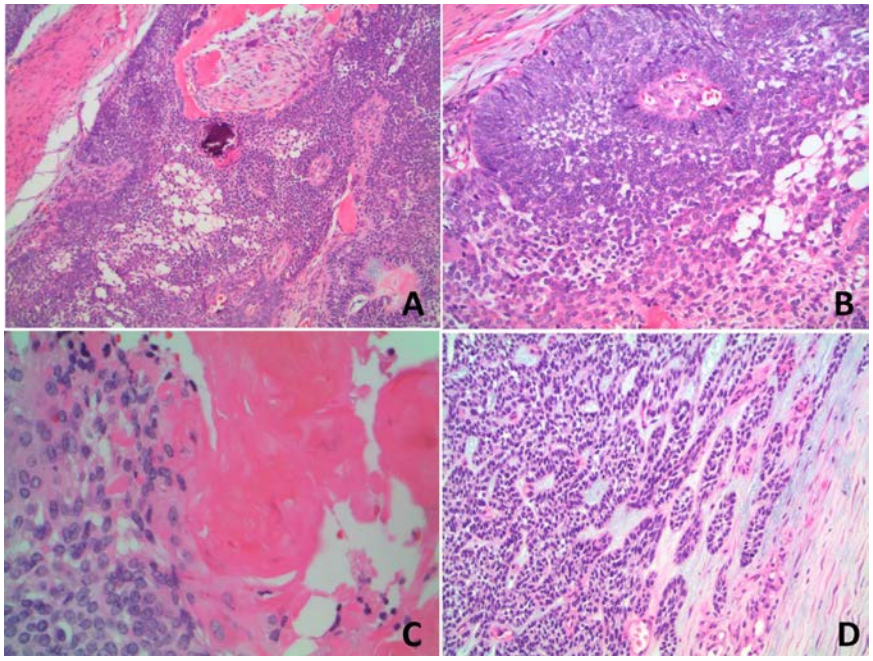


**Figure 1. Recurrent atypical odontogenic ghost cell tumor of right mandible in 2009 (A, 100× magnification; B, 200× magnification). C) 40× objective, 10× ocular magnification of ghost cells of right mandible pathology (in 2009); D) metastatic ghost cell odontogenic carcinoma to pleura in 2013 (200× magnification). The tumor displays sheets and islands of hyperchromatic, basaloid cells with increased mitotic activity. There is peripheral palisading with more central loose reticulum and areas of ghost cells and focal keratinization. This pattern was present in the original 1990 specimen (image not available) and within the right mandible recurrences from 2009 and 2010. The same pattern is recapitulated in the metastatic lesion from 2013.**

that useful to guiding therapy, is lacking. (paragraph moved from introduction)

Development of GCOC from a benign/cystic odontogenic mass, or de novo, is key in development of these tumors. Often the Wnt/β-catenin/TNF pathway is implicated in formation of odontogenic tumors; cystic, solid, malignant, and benign. Mutation of the β-catenin gene were noted at codons 3,4,5, and 57 in all COCs, with the exception of GCOC, which was the only to display a mutation at codon 33. The location of cellular β-catenin expression in tumors may help differentiate the true diagnosis of maxillary and mandibular masses. The patient in our case underwent genetic screening demonstrating three genomic alterations: CTNNB1 S33C, CREBBP K1741* and MLL2 S1997fs*44. Of these, *CTNNB1* gene alteration is the only with new directed agents in development. The CTNNB1 which encodes β-catenin, a downstream component of the WnT signaling pathway, interacts with cadherin to regulate cell-cell adhesion as well as assists in development, cell proliferation, and cell differentiation.[13]

## Conclusions

In summary, we have presented a rare case of GCOC with pulmonary metastasis. This tumor appears to have transformed from a recurrent DGCT, first diagnosed 23 years prior. Currently there are no approved therapies that target CTNNB1, beta catenin activation, or Wnt pathway all of which are common in GCOC development. Further evaluation of cellular expression of this and other associated genomic alterations may prove essential in determining actionable targets for these rare, aggressive tumors.

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