

# Clear cell odontogenic carcinoma: Case report of a deceptive pathology

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## Abstract

Clear cells are associated with numerous physiological and pathological conditions. Odontogenic cysts and tumors can arise from physiological clear cells like rests of dental lamina. One such clear cell neoplasm is clear cell odontogenic carcinoma (CCOC) that is associated with aggressive clinical behavior, metastasis and low survival rate. With <80 cases reported so far, it is a rare entity. Initially described as a clear cell odontogenic tumor considering it as a benign but invasive neoplasm, it was later termed as CCOC owing to its infiltrative nature with a marked tendency for local recurrence, regional nodal spread and possible distant, mainly pulmonary, metastasis. Reported here is a case of CCOC affecting mandible of a 55-year-old female along with its immunohistochemical workup.

**Keywords:** Clear cell lesions, clear cell odontogenic carcinoma, pathogenesis, treatment

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## INTRODUCTION

Clear cell changes have been identified in various benign and malignant tumors of epithelial, melanocytic, mesenchymal and hematopoietic origin but are perceived as a rare occurrence in the head and neck region.<sup>[1]</sup> Clear cell tumors in the head and neck region constitute a diagnostic challenge to the pathologist since the prime features of malignant neoplasia along with cytological atypia are frequently absent even in aggressive variants thereby excluding reliance on histopathological hallmark for arriving at a diagnosis. Thus, definitive differential diagnosis of clear cell tumors must incorporate not only the benign but also malignant variants with phenotype of the cells seen on histopathology.<sup>[2]</sup> Here, we report a case

of clear cell odontogenic carcinoma (CCOC) affecting mandible of a 55-year-old female.

## CASE REPORT

A 55-year-old female reported with a chief complaint of pain in the lower right side of the face for 4 months and swelling in the same region for 2 months. She was prescribed analgesics and antibiotics by a local physician which did not provide any relief, and hence, she was referred to the institution for further treatment.

At the time of presentation, a 5 cm × 5.5 cm diffuse, irregular swelling was seen on the lower right side of her face extending from 2.5 cm above the inferior border of the mandible to 3 cm below the inferior border superoinferiorly

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and from parasymphysis region on the body of mandible anteroposteriorly.

Intraorally, a firm to hard swelling was seen causing expansion of buccal and lingual cortical plates between 43 and 46. Grade II mobility was seen with 46. 44 and 45 were extracted 2 years ago due to mobility. Radiographically, a 3 cm × 4 cm ill-defined destructive lesion was seen in the right body of the mandible extending from 43 to mesial aspect of 47 anteroposteriorly and between alveolar ridge and base of mandible superoinferiorly. Periphery of the lesion was partly corticated [Figure 1].

Incisional biopsy revealed the tumor to be composed of irregularly outlined nests of cells with intervening thick fibrovascular septa. Under higher magnification, biphasic population of cells was evident – a population of large cells with eccentric nucleus and clear cytoplasm as well as polygonal cells with hyperchromatic nucleus and eosinophilic cytoplasm [Figure 2]. A provisional diagnosis of clear cell malignant lesion was considered.

The tumor cells were periodic acid–Schiff (PAS) +ve and immunoreactive for 19 while cytokeratin 17 and carcinoembryonic antigen (CEA) expression were absent. More than 10% positivity for Ki-67 marker was observed. Finally, diagnosis of CCOC was established [Figure 3 and Table 1].

Hemimandibulectomy was performed along with resection of Ib cervical group of lymph nodes. Specimen of the



**Figure 1:** Clinical. (a) A 55-year-old female with swelling in the right parasymphysis region. (b) Swelling extending from 43 to 46 region. H/O extraction of 44 and 45 2 years ago. (c) Ill-defined radiolucency extending from 43 to mesial aspect of 47 causing thinning of lower border of the mandible

mandible with lump submitted for histopathological examination also included 4 lymph nodes which were found to be free of tumor and a 4 cm × 3 cm × 3 cm part of the mandible in which tumor tissue was approximately 3 cm × 2 cm × 1.5 cm grayish white region. The histopathological findings of the excisional biopsy specimen were consistent with the findings of incisional biopsy. The margins and lymph nodes were found to be free of tumor.

## DISCUSSION

Clear cells in a lesion are believed to stem from fixation artifacts, cytoplasmic accumulation of water, glycogen, lipids, mucins, hydropic degeneration of organelles, etc. Thus, when the histopathological picture shows an increased number of clear cells, the definitive diagnosis proves to be a challenge.<sup>[3]</sup>

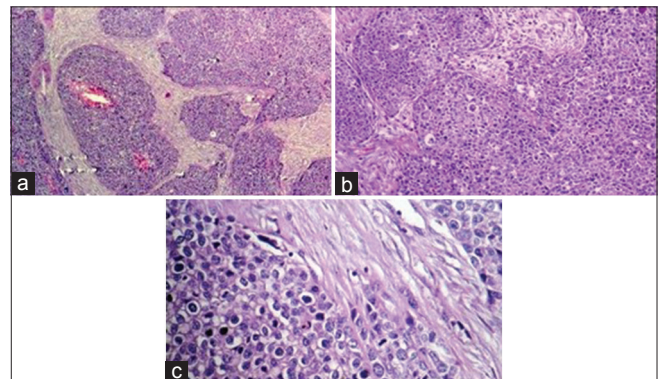
Hansen *et al.* first described the entity, clear cell odontogenic tumor (CCOT) in 1985 as a benign and locally aggressive neoplasm.<sup>[4]</sup> Since the malignant potential of CCOT had not been recognized till then, CCOT was included under benign neoplasm arising from odontogenic epithelium without odontogenic ectomesenchyme in 1992 WHO classification.<sup>[5]</sup>

**Table 1: Immunohistochemical analysis**

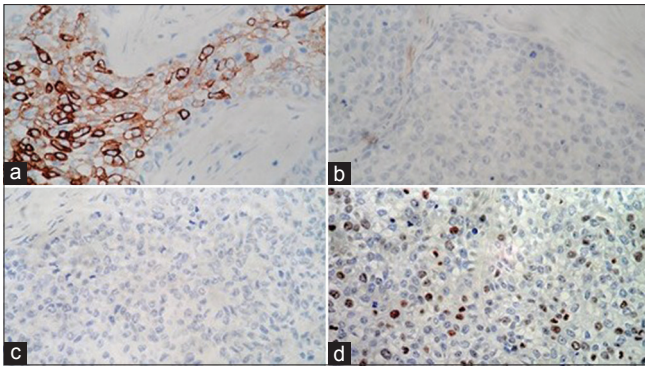
IHC marker	Significance	Expression in the present case
Ki-67	Cell proliferation marker	>10% +ve
CK 19	Expressed in odontogenic epithelium	+ve
CK 17	Basal cells' differentiation marker	-ve
CEA	Luminal cells of salivary gland	-ve

+ve indicates positive expression, -ve indicates negative expression.

IHC: Immunohistochemical, CEA: Carcinoembryonic antigen



**Figure 2:** Histopathological. (a) Incisional biopsy indicated that the tumor was composed of irregularly outlined lobules with intervening thick fibrovascular septa (H&E, ×40). (b) On higher magnification, the lobules were composed of a biphasic population of cells - round to oval cells with eccentric nucleus and clear cytoplasm and another group of polygonal cells with hyperchromatic nucleus and eosinophilic cytoplasm (H&E, ×100). (c) Cells were seen invading the fibrous septa (H&E, ×400)



**Figure 3:** Immunohistochemical analysis. (a) Tumor cells were positive for CK19 (×400). (b) Negative for CK17 (×400). (c) Negative for carcinoembryonic antigen (×400). (d) Ki67 >10% positivity (×400)

Bang *et al.* in 1989 employed the use of the term CCOC and reported cases with pulmonary and lymph node metastasis. They emphasized that it behaves in a more aggressive manner than other odontogenic tumors and calls for an early aggressive therapy. Hence, it was inappropriate to designate it as tumor. Piattelli *et al.* in 1994 supported the view that this tumor could behave in an aggressive way and has true metastatic potential despite the absence of malignant cellular features. This entity was considered distinct from clear cell variant of ameloblastoma which presents with similar clinical features.<sup>[6]</sup> Eversole in his review also held up the metastatic potential of CCOTs, and hence, the appellation should be employed as suggested by Bang *et al.* in 1989.<sup>[7]</sup>

Thus, owing to the aggressive behavior, predilection for local recurrence, evidence of distant metastasis and histologically distinct features, CCOT was designated as malignant tumor of odontogenic origin in 2005 WHO classification.<sup>[8]</sup>

Histopathological diagnoses need to exclude the following lesions having clear cell component [Table 2].

Clear cell ameloblastoma exhibits peripheral tall columnar cells with palisading and reverse nuclear polarity as well as immunopositivity for calretinin, CK8, CK13 and CK19.<sup>[9]</sup> In the present case, although CK19 positivity was seen, both the histopathological features were missing. CCOC manifests as one of the three histological variants (biphasic, monophasic and ameloblastomatous). In ameloblastomatous variant, tumor islands display peripheral ameloblastomatous palisaded columnar cells without any evidence of central stellate reticulum, squamous differentiation or cystic change which can be used to distinguish between clear cell ameloblastoma and CCOC.<sup>[10]</sup>

**Table 2: Clear cell lesions of head and neck**

Differential diagnosis	Distinguishing features
Odontogenic lesions	
Clear cell ameloblastoma	peripheral tall columnar cells with palisading and reverse nuclear polarity +ve calretinin, CK8, CK13, CK19
Clear cell calcifying epithelial odontogenic tumor	Liesgang's calcifications Amyloid deposits +ve Congo red
Salivary gland tumors	
Mucoepidermoid carcinoma	Presence of intermediate, epidermoid and mucous cells +ve Mucin
Myoepithelial carcinoma	Plasmacytoid, epithelioid and clear cells +ve calponin
Hyalinizing clear cell carcinoma	Stromal hyalinization with hyaline or myxoid degeneration +ve pancytokeratin and EMA
Metastatic lesions from	
Renal cell carcinoma	Intratumoral hemorrhage and sinusoidal vascularity +ve hepatocyte antigen
Ca thyroid	Thyroglobulin +ve
Ca prostate	High serum PSA
Melanotic tumor	
Balloon cell melanoma	Vertical growth phase melanoma with nodular proliferation of neoplastic balloon cells +ve Masson-Fontana stain, melan A and HMB-45

EMA: Epithelial membrane antigen, PSA: Prostate-specific antigen

Another CK19-positive lesion, i.e., clear cell CEOT has characteristic Liesgang's calcifications and amyloid deposits which stain with Congo red. The clear cell nests in CEOT are usually small, forming acinar-like clusters. The basement membrane may be thickened, or the cell islands may lie within a hyalinized stroma.<sup>[2]</sup> Positivity for PAS stain is seen.<sup>[11]</sup>

PAS +ve salivary gland tumors included in the differential diagnosis of clear cell malignant lesion also express positive CEA and CK 17 immunostain and PAS-positive cells which were absent in the present case. Myoepithelial carcinoma shows plasmacytoid, epithelioid and clear cells arranged in various patterns while clear cells in hyalinizing clear cell carcinoma illustrate clear cells arranged in anastomosing cords, sheets, trabeculae, nests and solid sheets. Mucoepidermoid carcinoma is manifested by the presence of intermediate, epidermoid and mucous cells along with clear cell component.<sup>[9,11]</sup>

Metastatic lesions with clear cells most commonly seen in mandibular region are from renal cell carcinoma. Intratumoral hemorrhage and sinusoidal vascularity are displayed by these lesions whereas positive expression of Masson-Fontana stain, S100 and HMB-45 is indicated by melanotic tumors.<sup>[9]</sup>

Based on the histopathological and immunohistochemical findings, the present case was diagnosed as CCOC. Radiographically, CCOC similar to other osteolytic lesions appears as a poorly delineated uni- or multilocular

radiolucent lesion that occurs with prominent bone destruction as seen in the present case.<sup>[5]</sup>

As supported by Maiorano *et al.*, the histogenesis of the tumor is from odontogenic epithelium.<sup>[12]</sup> Eversole drew similarities between the normal enamel organ and then known CCOT to prove that CCOC could arise from odontogenic epithelium.<sup>[11]</sup> Clear cells in odontogenic tumors are believed to originate from dental lamina recapitulating a phase of amelogenesis in which they accumulate glycogen. Eversole advocated these clear cells to be related to presecretory ameloblast and epithelial in nature, containing desmosomes and lacking secretory granules. Ultrastructurally, these are organelle poor cells containing lysosomes, mitochondria, tonofilament bundles and desmosomes.<sup>[13]</sup> The latter features point toward squamous differentiation.<sup>[14]</sup> Moreover, immunopositivity for CK19 established the odontogenic origin.

Ruhin-Poncet *et al.* studied the expression of Msx and Dlx homeobox genes in various odontogenic tumors including CCOC and observed a lack of Dlx2, Dlx3, Msx2 and Bmp2 expression, specifically in CCOC, compared to ameloblastomas and the physiological process of odontogenesis. Bmp2 is downregulated at the time of terminal differentiation of ameloblasts, suggesting that the differentiation process is affected in the CCOC cells. Bmp2 also stimulates expression of Msx1, Msx2, Dlx2 and Dlx3. The lack of Bmp2 may be responsible for the absence of these two homeobox genes in the case of CCOC, thus implying inability of cell differentiation of the preameloblasts. Furthermore, comparative genomic hybridization discloses consistent chromosomal aberrations in both primary and metastatic CCOC.<sup>[15]</sup>

Currently, treatment involves wide surgical resection with tumor-free margins and lymph node resection. The overall recurrence rate for these tumors was 55%, and local recurrence rates were higher (80%) for curettage alone than for resection alone (43%). Lymph node metastasis on initial presentation was rare (10%) but swiftly evolved in those with recurrent disease (33%). To diminish the risk of recurrence, the patient was treated with hemimandibulectomy with lymph node resection. The postoperative recovery was uneventful, and no recurrence has been observed in 1-year follow-up period.

Thus, we conclude that CCOC despite its rare occurrence should be considered in differential diagnosis of tumors affecting the jaws with prominent clear cell component. A long-term follow-up must be advised as these tumors may recur locally or with distant metastases.<sup>[16]</sup>

### 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 initials 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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