Clear Cell Odontogenic Carcinoma: Diagnostic Approach to Exclude the Unclear

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CASE REPORT

Clear Cell Odontogenic Carcinoma: Diagnostic Approach to Exclude the Unclear

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Abstract Clear cell odontogenic carcinoma (CCOC) is a rare malignant odontogenic neoplasm with about 110 reported cases to date. CCOC has a high recurrence and metastatic potential, and thus, needs to be diagnosed early for improved prognosis. However, the diagnosis of CCOC can be challenging as numerous other clear cell-rich entities present similar histological features. A final diagnosis of CCOC requires meticulous histopathological observation and a planned exclusion of other entities by employing special stains and immunohistochemistry. The present case report aims to add another case of the rare odontogenic malignancy to the literature as well as guide histopathologists regarding the approach to be taken when encountering a clear cell-rich lesion.

Keywords Odontogenic tumors · Immunohistochemistry · Mandible

Introduction

Clear cell odontogenic carcinoma (CCOC) is described by the WHO as an odontogenic carcinoma characterized by sheets and islands of vacuolated and clear cells [1]. About only 110 cases of CCOC have been reported to date ever since the first case reported by Hansen et al. in 1985 [1, 2]. They used the term 'clear cell odontogenic tumor' (CCOT) and described it as a benign odontogenic neoplasm with aggressive potential.

Owing to its locally destructive nature, and a high potential for lymph node metastasis and recurrence, the WHO re-classified CCOC as a malignant odontogenic neoplasm in 2005 [3]. Various authors have previously used the terms CCOT and 'clear cell ameloblastoma' (CCAM) for tumors exhibiting similar histopathological features. However, both terms are now obsolete and the use of the term CCOC has been recommended by WHO in 2017 [1].

CCOC most commonly occurs as an asymptomatic intraosseous lesion that has a predilection for the mandibular posterior region. Most of the cases reported have a preponderance in females of older age groups, particularly, in the 5th to 7th decades. [1, 4]. Even so, the information pertaining to clinicopathological aspects of CCOC is derived from the limited number of reported cases and the actual incidence of the entity is still unknown. Herein, we report one such case of the rare malignant odontogenic neoplasm with emphasis on its histopathological and immunohistochemical aspects.

Case Report

A 45-year-old female complained of a painless swelling in the left lower jaw region since five months. The patient's medical and family history were unremarkable. On inspection, a diffuse swelling of size 4 × 3 cm was noted extraorally in the mandibular left posterior region (Fig. 1). On palpation, the swelling was non-tender, non-fluctuant, and firm in consistency The cervical lymph nodes were non-palpable and non-tender. Intraorally, no specific findings were noted except for slight obliteration of the buccal vestibule in the mandibular left molar region (Fig. 1). The mandibular left

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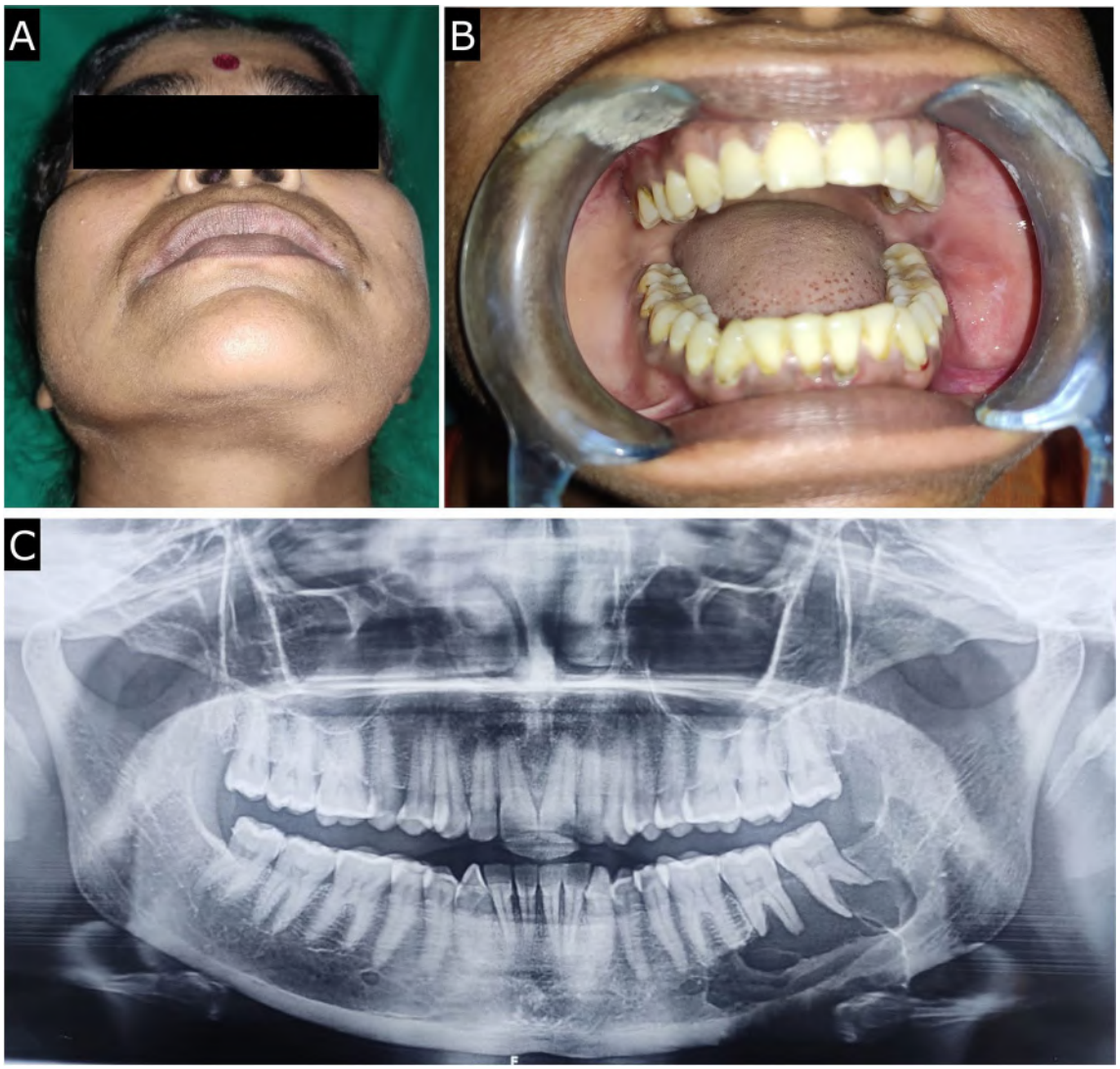

Fig. 1 **A** Extraoral swelling in the lower left region of the face; **B** Obliteration of buccal vestibule in the left mandibular posterior region intraorally; **C** Orthopantomogram exhibiting partially well-defined multilocular radiolucent lesion in the mandibular left molar region

second and third molars exhibited Grade I mobility without any tenderness on percussion.

Orthopantomogram (OPG) revealed an extensive multilocular radiolucency extending from the mesial root of mandibular left first molar to the distal portion of third molar. The borders of the lesion were partially well-defined and corticated. Thinning of the inferior border of the mandible with loss of continuity was noted. The roots of all the three mandibular left molars exhibited spiked irregular resorption.

The clinical and radiographic findings were suggestive of an aggressive benign or malignant neoplasm. The differential diagnosis included ameloblastoma, odontogenic keratocyst, central giant cell granuloma, aneurysmal bone cyst, and odontogenic myxoma. Malignant odontogenic tumors or metastatic tumors from other organs were also considered in the differential diagnosis owing to the aggressive destruction of bone and spiked resorption of the roots in the mandible which is a common mode of presentation of such tumors. No fluid could be elicited from the lesion on aspiration and an incisional biopsy was obtained under local anesthesia.

Microscopically, the tissue demonstrated a predominantly biphasic population of epithelial cells proliferating in the form of lobular sheets, nests, cords and islands within a fibrocellular connective tissue stroma (Fig. 2). Areas of cystic degeneration could be noted occurring centrally within the epithelial sheets and islands. Under higher magnification, one population comprised of clear cells having a polygonal outline with well-demarcated cell membranes, and hyperchromatic nuclei that varied in size and shape. A basaloid, non-vacuolated cell population having small, dark, hyperchromatic nuclei in an eosinophilic cytoplasm was noted almost always towards the periphery of the clear cells.

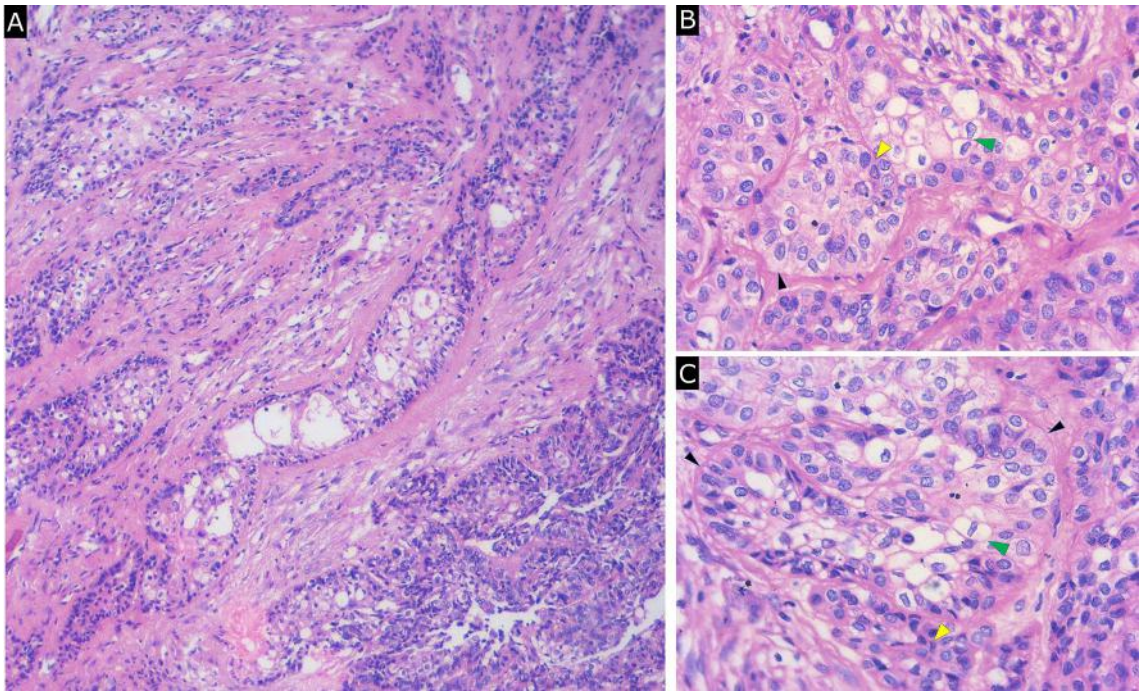

Fig. 2 **A** Lobulated sheets of epithelial cells exhibiting nuclear palisading in the peripheral cells (H and E, 10×); **B** and **C** Clear cells (green arrowheads), basaloid cells with eosinophilic cytoplasm (yellow arrowheads) and tall columnar ameloblast-like cells (black arrowheads) (H and E, 40×)

Palisading of nuclei was noted in the peripheral cells of epithelial nests and strands, along the stromal barrier. The pattern was reminiscent of ameloblastoma in some strands or islands wherein the peripheral cells were low-to-tall columnar cells exhibiting reversal of nuclear polarity and subnuclear vacuolization was present peripherally (Fig. 2). Nuclear atypia could be noted in both cell populations. Occasional mitoses were noted, although abnormal mitotic figures were absent.

Although the histopathological picture was distinctive of CCOC, the features were not pathognomonic as they may also be seen in various other neoplasms. Therefore, the exclusion of other clear cell-rich neoplasms, including salivary gland neoplasms (clear cell carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma), amelanotic melanoma, metastatic renal cell carcinoma (RCC), and the clear cell variant of the calcifying epithelial odontogenic tumor was warranted before imparting a final diagnosis.

A panel of IHC markers and special stains was employed for ruling out the histopathological differential diagnosis which is delineated in Fig. 3. The clear cells exhibited diastase-labile positivity on staining with Periodic Acid-Schiff stain. They stained negative for mucin when stained by mucicarmine and negative for amyloid on staining with Congo red. Strong Cytokeratin AE1/AE3 positivity was noted diffusely in the cytokeratin of epithelial cells. The epithelial cells exhibited focal moderate positive immunoexpression of CK19 and Calretinin (Fig. 4). The immunoexpression of Calponin, HMB-45 and Pax8 was negative. On the basis of findings from IHC and special stains, a final diagnosis of CCOC was imparted. The patient refused to undergo any treatment because of certain socioeconomic issues.

Discussion

CCOC is a rare malignant odontogenic neoplasm that tends to occur in relatively older individuals, particularly in patients older than 40 years (about 81% cases), as compared to other odontogenic tumors such as ameloblastoma or adenomatoid odontogenic tumor which tend to occur at an earlier age [1, 5]. CCOC exhibits a female predilection with a male:female ratio of 1:1.8 [4]. Clinically, CCOC has a propensity to occur in the mandible, particularly in the posterior body and ramus region [1, 4, 5].

CCOC classically occurs as a painless swelling of the jawbones. Although infrequently, symptoms such as pain and paresthesia may be present owing to the impingement of nerve fibers by the tumor. In corroboration with the existing clinicodemographic data, the present case occurred as a painless swelling in a 45-year-old female [1, 4, 5].

Radiographically, CCOC often appears as a poorly defined, uni- or multi-locular radiolucency, often with resorption of the roots of adjacent teeth [1]. Given the locally

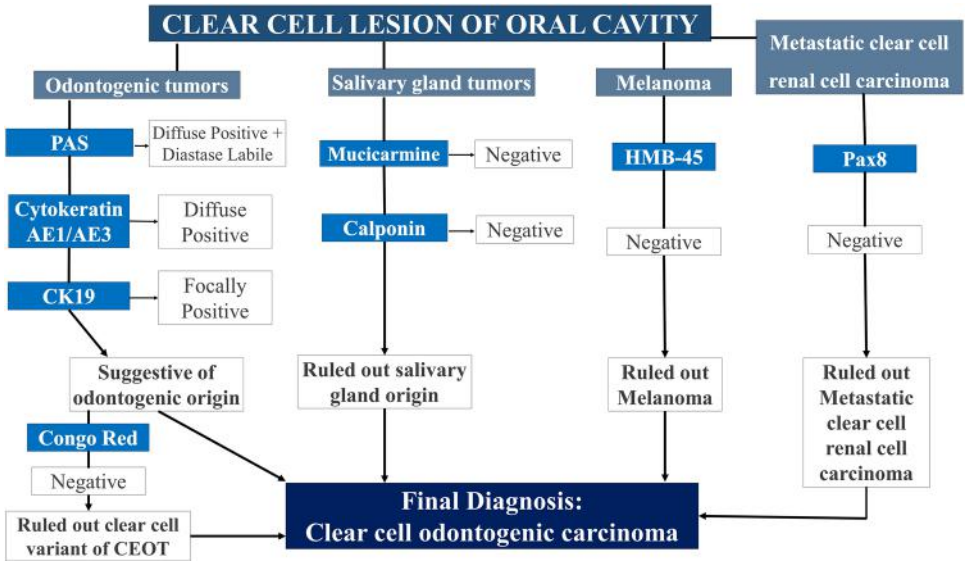

Fig. 3 Outline of IHC panel and special stains followed to exclude the differential diagnosis in the present case

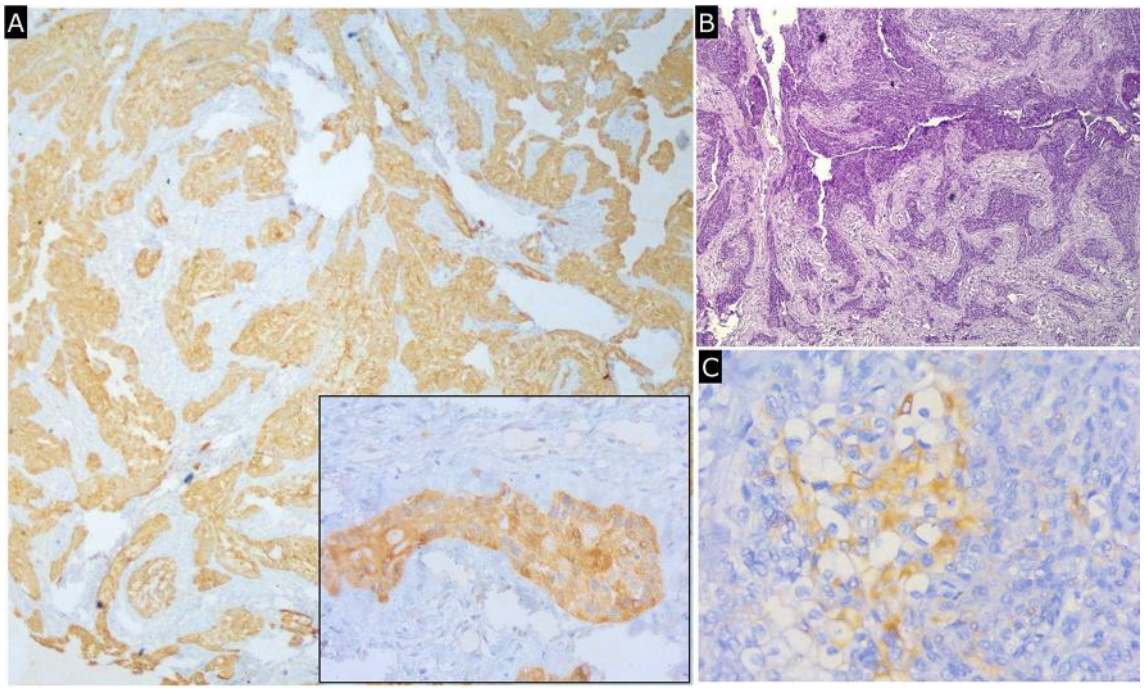

Fig. 4 **A** Diffuse cytoplasmic immunostaining in the epithelial cells for Cytokeratin AE1/AE3 (10×, inset: 40×); **B** Positive staining in the epithelial cells with Periodic acid-Schiff stain (10×); **C** Focal cytoplasmic immunostaining in the epithelial cells for CK 19 (40×)

aggressive nature of the tumor, advancing the destruction of bone could be well appreciated in the present OPG. The resorption of roots of all three mandibular left molars noted in the present case would account for their slight mobility that could be elicited clinically.

Histopathologically, CCOC demonstrates three types of patterns: (i) A monophasic pattern that is composed almost entirely of polygonal clear cells, (ii) A biphasic pattern, comprising of clear cell and basaloid cell population and (iii) Ameloblastoma-like pattern in which ameloblast-like columnar cells are noted at the periphery of epithelial nests or strands. The biphasic pattern is noted most commonly (85%) while the other two variants are uncommon [1, 6].

In the present case, the ameloblastoma-like cells suggested the odontogenic origin of the tumor, thereby, aiding in the diagnosis. Even so, other clear-cell-rich lesions from other origins need to be excluded for a confirmatory diagnosis of CCOC. The absence of such ameloblast-like cells

in the monophasic or biphasic variants makes differentiation of CCOC from other clear cell tumors more difficult and warrants a careful histochemistry and IHC-based approach for diagnosis.

About 90% of the clear cell neoplasms in the head and neck region are either of odontogenic or salivary gland origin, while only a small percentage comprises melanoma or metastatic tumors from other sites such as kidneys, thyroid or prostate [7]. In CCOC, the clear cells are generally glycogen-rich and negative for mucin, although glycogen may be lost during fixation or decalcification. CK14, CK19, and pancytokeratin AE1/AE3 have been inferred as the most reliable diagnostic markers for CCOC although the clear cells may show positive expression of various other cytokeratins [1].

Negative immunoexpression for vimentin, S100 protein, Calponin, HMB45, alpha- 1-antichymotrypsin, and CD10 can help in the exclusion of other clear cell-rich entities [1]. Pax8 is a more sensitive marker for RCC as compared to the commonly employed CD10 [8]. Therefore, Pax8 was included in the IHC panel instead of CD10 to rule out metastatic RCC for the present case. The Ki-67 proliferative index is highly variable and thus, not reliable for CCOC.

Recently, the rearrangement of the EWSR1 gene has been implicated in the pathogenesis of CCOC with ATF1 as its translocation partner. The same translocation has been found in clear cell carcinoma of salivary glands. Coupled with the histopathological similarity between the two lesions, it has been theorized that the tumors may be related [9].

Approximately 12% of the reported cases of CCOC had metastasis to cervical lymph nodes or lungs, and less frequently to the bone. The high recurrence and metastasis rates of the lesion warrant surgical resection with wide margins for the treatment of CCOC. Adjuvant radiotherapy may be implicated in cases showing soft tissue extension or incomplete surgical margins [10]. The outcome has been death in 15% of cases, with a median survival of 14 years [1, 10].

Conclusion

Diagnosis of CCOC can be extremely challenging, particularly, in the absence of an ameloblastoma-like pattern. The present case report would aid pathologists in differentiating CCOC from other clear cell-rich tumors. Given the rarity of lesions, reporting additional cases of CCOC would elucidate the biological and prognostic behavior of CCOC.

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Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

Human or Animals Rights The research does not involve animals. We report only a single human case of clear cell odontogenic carcinoma.

Informed Consent Informed consent of the patient was not obtained because the patient's identity was not revealed in any form.

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