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Case Report

CLEAR CELL ODONTOGENIC CARCINOMA OF THE MANDIBLE: CLINICOPATHOLOGICAL FEATURES IN A RARE CASE

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Abstract

Clear cell odontogenic carcinoma (CCOC) is a rare malignant odontogenic neoplasm with aggressive biological behavior and considerable diagnostic complexity due to its overlapping features with other clear cell tumors of the jaws. This report describes a case of CCOC arising in the anterior mandible of a 39-year-old woman presenting with progressive, painless swelling. Radiographic and computed tomography examinations demonstrated an expansive intraosseous lesion with predominantly radiolucent characteristics and focal hyperdense areas. Histopathological analysis revealed nests and islands of polygonal epithelial cells with abundant clear cytoplasm embedded in a densely hyalinized stroma, associated with focal eosinophilic differentiation and infiltrative growth. Immunohistochemical evaluation showed strong positivity for p40, p63, and CK7, supporting odontogenic epithelial differentiation, while SOX10 negativity contributed to the exclusion of salivary gland clear cell neoplasms. Based on the integrated clinicopathological and immunohistochemical findings, a definitive diagnosis of CCOC was established. The patient underwent surgical resection with tumor-free margins and remained free of recurrence or metastasis after one year of follow-up. This case highlights the importance of a multidisciplinary diagnostic approach for distinguishing CCOC from other odontogenic and metastatic clear cell lesions, thereby enabling appropriate surgical management and long-term oncologic surveillance.

Keywords: Clear Cell Odontogenic Carcinoma; Odontogenic Tumors; Mandible; Immunohistochemistry; Differential Diagnosis.

Statement of Clinical Significance: Clear cell odontogenic carcinoma may mimic benign intraosseous jaw lesions, creating significant diagnostic challenges. Integration of clinicopathological and immunohistochemical findings is critical for accurate diagnosis, appropriate surgical treatment, and long-term oncologic surveillance.

INTRODUCTION

Clear cell odontogenic carcinoma (CCOC) is a rare malignant epithelial neoplasm of odontogenic origin characterized by a prominent clear-cell phenotype and infiltrative growth. Initially described as a clear cell odontogenic tumor by Hansen et al. in 1985, CCOC is currently classified as a malignant odontogenic tumor in the 5th edition of the World Health Organization (WHO) Classification of Head and Neck Tumours.[1–3]

CCOC most often affects middle-aged and older adults, with a female predominance. The mandible is the most frequently involved site, particularly the

mandibular body and anterior region, although maxillary lesions have also been reported. Clinically, patients most commonly present with swelling, which may be accompanied by pain, tooth mobility, or sensory disturbances. [4,5]

Radiographically, CCOC most commonly presents as a radiolucent or osteolytic intraosseous lesion, often with ill-defined margins and variable cortical expansion or destruction.[4,5] Because these findings are nonspecific, CCOC may mimic other odontogenic cysts and tumors, emphasizing the need for histopathologic evaluation. According to the 5th edition of the WHO Classification of Head and Neck Tumours, essential diagnostic features include a lesion arising in the jaws, typically presenting as an ill-defined radiolucency, a prominent clear-cell phenotype, an infiltrative tumor margin, and exclusion of metastatic disease.[2,3]

Histologically, CCOC is characterized by nests, cords, or sheets of epithelial cells with clear to faintly eosinophilic cytoplasm embedded within a hyalinized fibrous stroma.[6,14] The tumor cells are generally polygonal, with variably positioned nuclei, and may exhibit a biphasic pattern composed of clear and eosinophilic cells. Cytoplasmic clearing is commonly associated with glycogen accumulation and may result in periodic acid–Schiff positivity that is sensitive to diastase digestion.[6]

Immunohistochemically, CCOC typically exhibits epithelial differentiation, with expression of cytokeratins, epithelial membrane antigen, and p63 or p40, although the staining profile may vary among cases.[7,8] Markers associated with myoepithelial differentiation, including S100 protein, smooth muscle actin, and calponin, are generally absent or only focally expressed. Because of the substantial morphologic and immunophenotypic overlap with other clear-cell neoplasms, immunohistochemical findings should be interpreted in conjunction with the clinical, radiographic, and histopathologic features.[7,8]

Molecular studies have identified recurrent rearrangements involving the EWSR1 gene in CCOC, most commonly EWSR1–ATF1 and, less frequently, alternative fusion partners such as CREB1 and CREM.[8–11] These alterations may provide additional diagnostic support in challenging cases, although EWSR1 rearrangement should not be interpreted in isolation because similar alterations may occur in other clear-cell neoplasms.[7,9]

Despite its rarity, CCOC has important clinical implications because of its potential for local recurrence and metastatic dissemination.[4,5,8] Surgical resection is the

mainstay of treatment, and long-term follow-up is recommended because recurrence and metastasis may occur even after definitive treatment.[4,5]

In this context, the present report describes a case of clear cell odontogenic carcinoma arising in the anterior mandible of a 39-year-old woman and discusses the clinicoradiographic, histopathologic, and immunohistochemical findings relevant to its diagnosis.

CASE REPORT

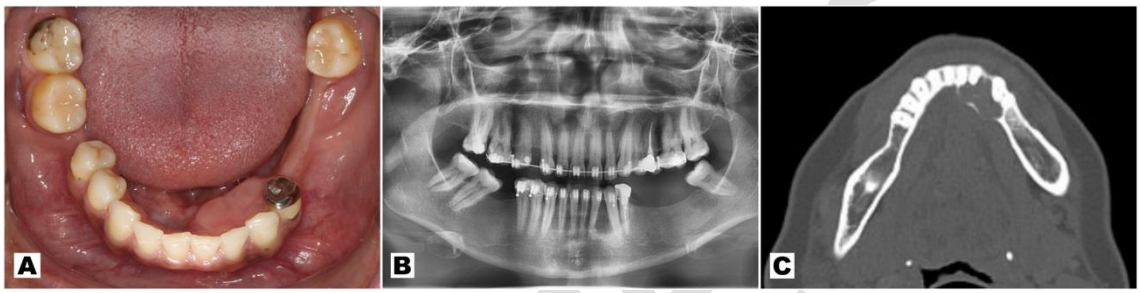

Figure 1. (A) Clinical image showing a firm, sessile nodule located on the lingual aspect of the mandible, extending from the mandibular left central incisor (tooth 31) to the mandibular left first premolar (tooth 34). (B) Panoramic radiograph showing a well-circumscribed radiolucent lesion in the anterior mandible. (C) Predominantly hypodense lesion with focal hyperdense areas on computed tomography, axial view.

A 39-year-old woman was referred to the oral and maxillofacial surgery service with a three-month history of swelling in the lingual region of the mandible. The lesion had progressively increased in size but was not associated with pain or other symptoms. The patient's medical history was unremarkable.

Extraoral examination showed no facial asymmetry or cervical lymphadenopathy. Intraoral examination revealed a firm, sessile nodular lesion located on the lingual aspect of the mandible, extending from the left central incisor to the first premolar. The overlying mucosa was intact and non-ulcerated (Figure 1A).

Panoramic radiography and computed tomography demonstrated a well-defined intraosseous lesion in the anterior mandible with an expansive growth pattern (Figures

1B and 1C). The lesion appeared predominantly radiolucent with focal hyperdense areas and mild cortical expansion.

An incisional biopsy was performed. Histopathological examination revealed a malignant epithelial neoplasm composed of nests and islands of tumor cells embedded in a densely hyalinized fibrous stroma (Figure 2). The tumor cells were predominantly polygonal with round to ovoid nuclei and abundant clear cytoplasm. Focally, clear cells were admixed with cells showing eosinophilic cytoplasm, producing a biphasic pattern. The lesion demonstrated infiltrative growth, with close association with the oral mucosal epithelium, mandibular bone, and vascular structures.

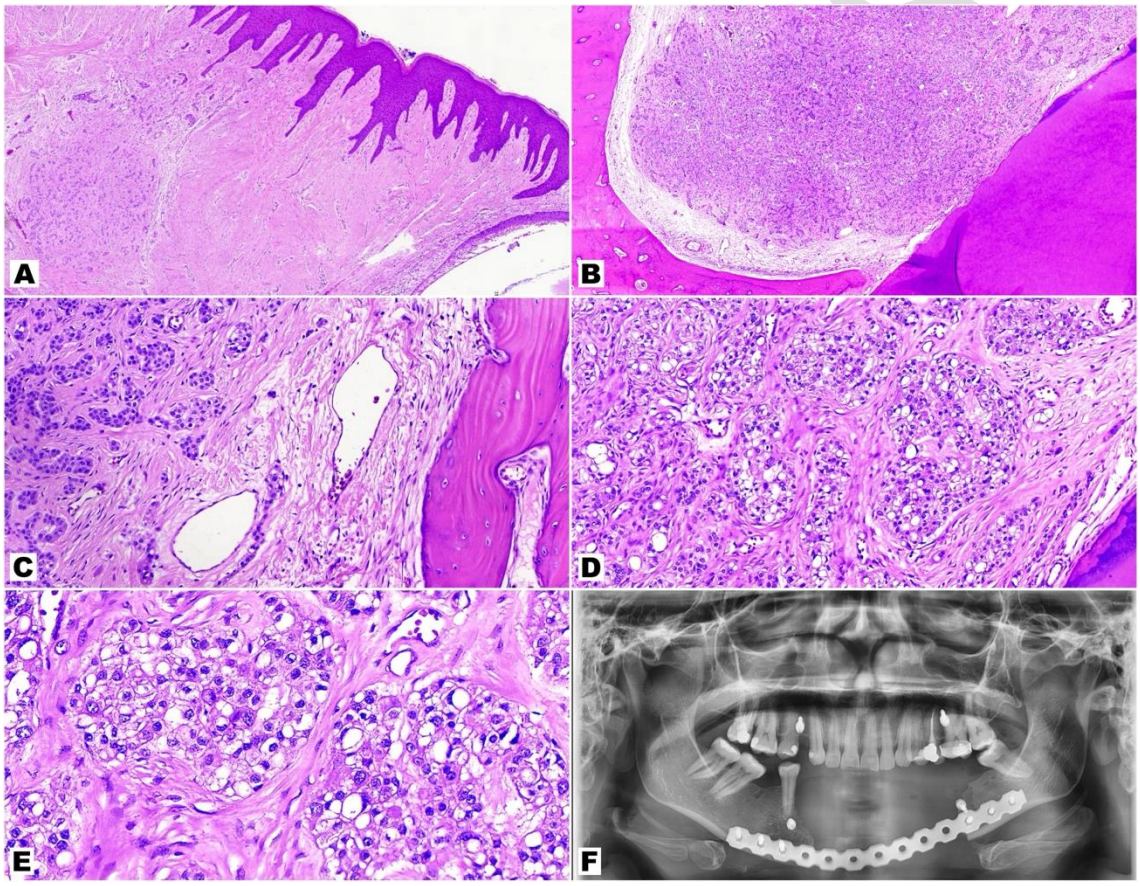

Figure 2. Clear cell odontogenic carcinoma showing proliferation of neoplastic epithelial cells with predominantly clear cytoplasm embedded in a hyalinized stroma. (A, B) Low-power views showing neoplastic cells in close association with the oral mucosal epithelium and mandibular bone (hematoxylin and eosin, ×40). (C) Nests of tumor cells showing light eosinophilic cytoplasm and perivascular invasion (hematoxylin and eosin, ×100). (D) Tumor cells exhibiting clear cytoplasm (hematoxylin and eosin, ×100). (E)

High-power view showing polygonal clear cells with round to ovoid nuclei (hematoxylin and eosin, ×400). (F) Panoramic radiograph obtained after surgical resection of the tumor.

Immunohistochemical analysis showed strong nuclear positivity for p40 and p63 and cytoplasmic positivity for CK7. Focal S100 reactivity was observed, while SOX10 expression was absent. These findings supported the diagnosis of CCOC when interpreted in conjunction with the clinicoradiographic and histopathologic findings.

Based on the clinicopathologic and immunohistochemical findings, a diagnosis of clear cell odontogenic carcinoma was established. The patient subsequently underwent segmental mandibulectomy with reconstruction plate placement, and histopathologic examination confirmed tumor-free surgical margins. At one year of follow-up, no evidence of local recurrence was observed.

DISCUSSION

The diagnosis of clear cell odontogenic carcinoma (CCOC) can be challenging because clear-cell morphology is shared by several primary and metastatic neoplasms involving the jaws. In the present case, the tumor presented as a painless mandibular swelling associated with an expansile intraosseous lesion, a presentation within the recognized clinical and radiographic spectrum of CCOC. In a review of 107 reported cases, swelling was the most common clinical presentation, while the posterior mandible, anterior mandible, and maxilla were the most frequently affected sites.[4] The more recent systematic review of 117 cases similarly identified swelling as the predominant clinical presentation and the mandibular body as the most common location, followed by the anterior mandible.[5]

The anterior mandibular location observed in the present case is less frequent than involvement of the mandibular body but remains within the recognized anatomic distribution of CCOC.[5] Radiographically, CCOC most commonly presents as an expansive radiolucent or osteolytic lesion, frequently with poorly defined margins, although well-defined radiolucent and mixed radiographic patterns have also been reported.[4,5] These findings are nonspecific and may overlap with those of other odontogenic lesions; therefore, radiographic characteristics alone are insufficient to establish the diagnosis.

Histopathologic examination remains central to the diagnosis. In the present case, the tumor was composed of nests and islands of epithelial cells with predominantly clear cytoplasm embedded in a densely hyalinized stroma, with focal eosinophilic differentiation and an infiltrative growth pattern. These findings are consistent with the characteristic morphologic spectrum of CCOC.[6,14] The coexistence of clear and eosinophilic cells has also been described as part of the morphologic spectrum of CCOC.[6]

Immunohistochemistry provides important ancillary information in diagnostically challenging cases. In the present case, strong nuclear expression of p40 and p63 and cytoplasmic CK7 positivity supported epithelial differentiation and, when interpreted together with the intraosseous location and characteristic morphology, favored an odontogenic origin. However, the immunophenotype of CCOC overlaps substantially with that of other clear-cell neoplasms, particularly hyalinizing clear cell carcinoma (HCCC). Comparative studies and recent reviews have demonstrated substantial overlap in the expression of epithelial and squamous/basal markers, including CK7, p63, and p40, emphasizing that individual immunohistochemical markers should not be interpreted in isolation.[7,12] Focal S100 reactivity and absence of SOX10 expression in the present case were therefore interpreted as ancillary findings within the overall clinicopathologic assessment.

HCCC of salivary gland origin represents one of the most important differential diagnoses because of its close morphologic resemblance to CCOC. Both tumors may exhibit nests, cords, or trabeculae of clear to eosinophilic epithelial cells within a hyalinized stromal background.[7,12] HCCC may also express p63, p40, and cytokeratins and may harbor EWSR1–ATF1 rearrangements, further increasing the diagnostic overlap.[7,8,12] Accordingly, the intraosseous location and integration of the clinical, radiographic, histopathologic, and immunohistochemical findings are critical for distinguishing CCOC from HCCC.

Metastatic clear cell renal cell carcinoma (ccRCC) should also be considered when a clear-cell neoplasm is identified in the jaws. Histologically, ccRCC typically exhibits nests or alveolar groups of clear cells associated with a prominent vascular network. Immunohistochemical assessment with renal-lineage markers, including PAX8, PAX2, RCC marker, and CD10, may provide evidence of renal origin.[13] Clinical correlation and appropriate investigation for a primary renal neoplasm are therefore essential. The exclusion of metastatic disease is also an essential diagnostic feature of

CCOC in the 5th edition of the World Health Organization Classification of Head and Neck Tumours.[2,3]

Other primary clear-cell neoplasms may also enter the differential diagnosis. The clear cell variant of calcifying epithelial odontogenic tumor may mimic CCOC but is favored by the presence of amyloid deposition and characteristic calcifications, whereas clear cell variants of central mucoepidermoid carcinoma may be distinguished by mucous differentiation.[14]

Molecular studies have further contributed to the characterization of CCOC. Recurrent rearrangements involving the EWSR1 gene have been identified in a substantial proportion of cases, most commonly involving EWSR1–ATF1 and, less frequently, alternative fusion partners such as CREB1 and CREM.[8–11,14] Although these alterations may provide valuable diagnostic support in challenging cases, EWSR1 rearrangement is not specific to CCOC, particularly because EWSR1–ATF1 may also occur in HCCC.[7,8,12] Therefore, molecular findings should be interpreted in conjunction with morphologic, immunohistochemical, and clinical data rather than used as an isolated diagnostic criterion.

From a clinical perspective, CCOC demonstrates clinically relevant malignant behavior, with local recurrence and metastatic disease documented in the literature. Guastaldi et al. reported recurrence in 38 of 88 cases for which recurrence data were available among 107 reported cases.[4] A subsequent systematic review of 117 cases reported recurrence in 52.4% of cases in its summary data, while detailed analysis identified recurrence information for 84 cases and documented metastatic disease in 30 cases, most commonly involving the lungs (14.5%) and cervical region (8.5%).[5] These findings support definitive surgical management and long-term oncologic surveillance. In the present case, the patient underwent segmental mandibulectomy with histopathologically tumor-free margins and remained free of local recurrence at one year of follow-up.

This case highlights the importance of considering CCOC in the differential diagnosis of intraosseous jaw lesions exhibiting prominent clear-cell morphology. Recognition of the substantial clinicopathologic overlap among clear-cell neoplasms is essential to avoid diagnostic misclassification and to guide appropriate surgical management and long-term surveillance.

CONCLUSION

Clear cell odontogenic carcinoma is a rare malignant odontogenic neoplasm that may clinically and radiographically mimic other intraosseous lesions of the jaws. This case highlights the importance of integrating clinicoradiographic, histopathological, and immunohistochemical findings to establish an accurate diagnosis. The patient underwent surgical resection with tumor-free margins and remained free of local recurrence after one year of follow-up. Given the potential for local recurrence and distant metastasis, long-term oncologic surveillance is essential for appropriate patient management.

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AUTHORS CONTRIBUTION

Laís Inês Silva Cardoso: Conceptualization of ideas; formulation or evolution of overarching research goals and aims; development or design of methodology.
Ingrid Araújo Oliveira Consolaro: Conceptualization of ideas; formulation or evolution of overarching research goals and aims; development or design of methodology.
Alberto Consolaro: Methodology by development or design of methodology; Oral Pathology.
Carlos Gabriel Valério da Silva: Preparation and writing the initial draft.
Palena Araujo Pinto: Writing - Review & Editing; Preparation, and revision – including pre-publication stages.
Thalita Santana: Supervision; Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. Formal analysis - application formal techniques to analyze or synthesize study data.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest related to this manuscript.

ETHICS APPROVAL:

As a single-case report with the patient's signed consent, no other ethical review was required.

PATIENT CONSENT

The patient reported in this manuscript provided written informed consent for the publication of the case details.

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PATIENT CONSENT

The patient reported in this manuscript provided written informed consent for the publication of the case details.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.