Clear cell odontogenic carcinoma: case report with immunohistochemical findings adding support to the challenging diagnosis

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Clear cell odontogenic carcinoma (CCOC) is a rare odontogenic tumor associated with aggressive clinical behavior, metastasis, and low survival. We report a case of CCOC affecting the mandible of a 39-year-old man. The tumor presented a biphasic pattern composed of clear cell nests intermingled with eosinophilic cells and separated by collagenous stroma. Immunoreactivity to cytokeratin (CK), specifically AE1/AE3 and CK 8, 14, 18, and 19 was found, as well as to epithelial membrane antigen (EMA). The tumor cells were negative for S100 protein, CK 13, vimentin, smooth muscle actin, laminin and type IV collagen. Low labeling indices for the proliferation markers Ki-67 and proliferating cell nuclear antigen and to p53 protein might predict a favorable prognosis for the lesion. A surgical resection was performed, followed by adjuvant radiotherapy. A 2-year follow-up has shown no signs of recurrence. The significance of histochemical and immunohistochemical resources in the correct diagnosis of CCOC is analyzed.
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Clear cell odontogenic carcinoma (CCOC) is an extremely uncommon entity that was originally described in 1985 by Hansen et al.[1] as a benign but locally invasive tumor. However, owing to its behavior as an infiltrative neoplasm with a marked tendency for local recurrence, regional lymph node and possible distant, mainly pulmonary, metastasis,[2,3] the World Health Organization (WHO) reclassified it in 2005 as a malignant tumor of odontogenic origin.[4] This tumor tends to occur in the mandible of older adults, with a predilection for women.[5-15] A prominent histopathologic feature is the presence of islands composed of clear cells with well defined outlines and centrally placed nuclei.[16] Various differential diagnoses are considered, including squamous cell carcinoma, mucoepidermoid carcinoma, clear cell ameloblastoma, hyalinizing squamous cell carcinoma,[16] calcifying epithelial odontogenic tumor, and metastatic clear cell carcinoma of renal origin and metastatic melanoma.[13]

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Complete understanding of the behavior of CCOC remains unclear, because only 54 cases have been described since 1985. Despite the increased awareness and improved recognition of these tumors, reported treatment strategies remain diverse. Therefore, additional cases and long-term follow-up could help to elucidate the tumor biology. We report a case of CCOC of the mandible, presenting the clinical and radiologic aspects, and focusing on the importance of histopathologic and immunohistochemical features in properly establishing its diagnosis.

CASE REPORT

A 39-year-old man presented for evaluation with a painful swelling of 2 months' duration on the right side of his mandible, noticed after a tooth extraction. However, the pain had started only recently. Local physical examination showed a firm irregular lump that appeared to arise from the right mandible. Intraorally, the tumor could be seen as a 4 cm reddish, bulging, fleshy mass presenting areas of ulceration (Fig. 1, *A*). The remainder of the physical examination was not contributory, and lymph nodes were nonpalpable. Orthopantomogram of the mandible showed a well delineated radiolucent multilocular lesion in the lower right molar area extending to the ramus, centered in and destroying a portion of the right mandibular body without cortical bone expansion (Fig. 1, *B*). A clinical diagnosis of malignant neoplasm of odontogenic origin was given.

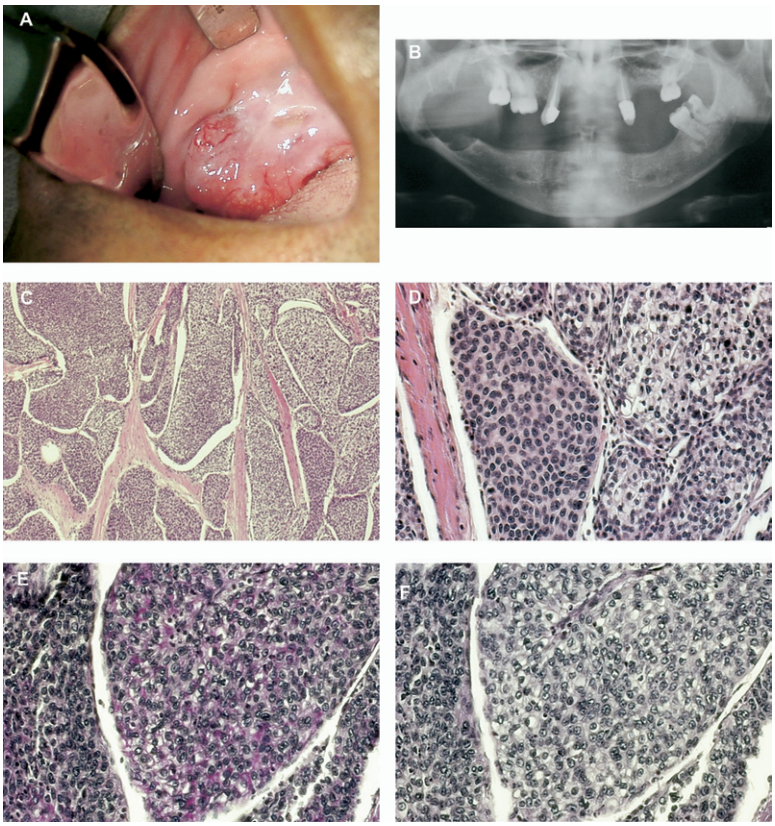

Fig. 1. Clinicopathologic features of clear cell odontogenic carcinoma. **A,** Intraoral photograph showing reddish and bulging mass with areas of ulceration in the right mandible. **B,** Panoramic radiograph revealing a well defined radiolucent multilocular lesion in lower right molar area extending to the ramus. **C, D,** Islands of clear cells admixed with polygonal cells with abundant cytoplasm eosinophilia, separated by dense fibrous septa. Clear cells with intracytoplasmic periodic acid–Schiff (PAS) positivity (**E**) and diastase sensitivity (**F**). Original magnifications: hematoxylin and eosin, ×25 (*C*), ×100 (*D*); PAS, ×100 (*E, F*).

After incisional biopsy of a representative portion of the lesion, microscopic examination showed an odontogenic tumor presenting biphasic pattern characterized by nests of large clear cells and polygonal cells with eosinophilic cytoplasm lying on a richly cellular, collagenous stroma (Figs. 1, *C* and *D*). Some neoplastic clusters entirely composed of clear cells, showing only a peripheral rim of cells with abundant eosinophilic cytoplasm, were also seen (Figs. 1, *C* and *D*). Occasionally, the neoplastic nests showed central duct-like structures lined by flattened cells with eosinophilic cytoplasm. Nuclear pleomorphism and mitotic activity were generally unremarkable. Evidence of ameloblastic differentiation, such as presence of tall columnar cells showing nuclear polarization, peripheral palisading, cystic degeneration, or squamous differentiation, also was not observed. The abundant clear cytoplasm of the cells was strongly positive for periodic acid–Schiff (PAS) (Fig. 1, *E*). This PAS positivity was diastase sensitive indicating intracytoplasmic glycogen (Fig. 1, *F*).

The tumoral cells were immunoreactive for wide-spectrum cytokeratins (CKs) AE1/AE3 (M3515, 1:100; DakoCytomation, Carpinteria, CA), CK 8 (M0631, 1:50; DakoCytomation), CK 14 (MS-115-P, 1:1000; NeoMarkers, Fremont, CA), CK 18 (M7010, 1:50; DakoCytomation), CK 19 (M0888, 1:50; DakoCytomation), and epithelial membrane antigen (EMA; M0613, 1:75; DakoCytomation). The tumor cell type and the immunostaining pattern varied for each protein (Table I and Fig. 2). Immunostaining pattern was considered to be homogeneous when uniformity of the staining intensity and the cell type involved could be observed, although heterogeneous pattern referred to the variability of the above-mentioned parameters.

Negativity to CK 7 (M7018, 1:50; DakoCytomation), CK 13 (MS-947-S, 1:50; NeoMarkers), vimentin (M0725, 1:800; DakoCytomation), laminin (Z0097, 1:3000; DakoCytomation), S-100 (Z311, 1:700, DakoCytomation), smooth muscle actin (SMA; M0851, 1:200; DakoCytomation), enolase (M0873, 1:400, DakoCytomation), chromogranin