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Review Paper
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Clear cell odontogenic carcinoma: a rare jaw tumor. A summary of 107 reported cases

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Abstract. The purpose of this study was to summarize the currently published cases of clear cell odontogenic carcinoma (CCOC). The PubMed and Springer databases were used to collect available reports, searching for 'clear cell odontogenic carcinoma', 'CCOC', or 'clear cell ameloblastoma'. The search resulted in 75 reports detailing 107 cases between 1985 and 2018. Clinically the tumor manifests as a swelling in the posterior mandible ($n = 46$), anterior mandible ($n = 33$), and maxilla ($n = 28$). Radiological analysis of 85 cases typically showed a poorly defined expansive radiolucency ($n = 83$). Of the 70 patients with symptoms reported, 44 specified a swelling, 11 tooth mobility, seven gingival/periodontal issues, five numbness, and three decreased jaw opening. One patient presented with a neck mass. The duration of symptoms prior to seeking care was specified for 52 patients: 2 months to 1 year for 34 patients, 1–2 years for seven, 2–4 years for two, 4–7 years for six, and 7–12 years for three. The incidence of recurrence appeared to be 38 of the 88 cases where recurrence was reported. CCOC can be distinguished from other oral cancers by its distinctive histology and immunohistochemical characteristics and less aggressive behavior. Currently, treatment should be early and aggressive resection with clear surgical margins and long-term follow-up. The overall goal is to collect a cohort of patients.

Key words: clear cell odontogenic carcinoma; odontogenic tumors; carcinoma; jaw; immunohistochemistry.

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Clear cell odontogenic carcinoma (CCOC) is a rare intraosseous tumor of the jaws. Its biological behavior is distinct from that of other tumors, benign and malignant. To date, only 107 cases have been reported in the literature since its first description by Hansen et al. in 1985[1]. Given the limited number of cases reported, CCOC remains a largely uncharacterized tumor. CCOC was formerly known as clear cell odontogenic tumor (CCOT) or clear cell ameloblastoma (CCA)[2].

According to the World Health Organization (WHO) classification of odontogenic tumors in 1992, CCOC was classified as a benign neoplasm with capacity for local invasion. However, due to its locally destructive and aggressive behavior with local recurrence, regional lymph node metastasis, and rare distant metastasis, the WHO reclassified CCOC in 2005 as a 'malignant carcinoma' of odontogenic origin[2,3].

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Tumors containing the clear cell component in the head and neck region can originate from various sources and may originate in the odontogenic epithelium, salivary gland pathologies, or even as metastases from distant locations like the kidneys[4]. Odontogenic tumors, salivary gland tumors (primary or secondary), and metastatic renal carcinomas were previously considered as differential diagnoses of CCOC. Considering its morphological, immunohistochemical, and clinical characteristics, metastatic renal carcinomas were recently eliminated from the list[5]. Recent data indicate that CCOC may be the bony counterpart of hyalinizing clear cell carcinoma of the salivary gland and may be a low-grade sarcoma[6,7].

Gaining an understanding of the biological and prognostic behavior of CCOC is still challenging due to the rareness of the lesion, resulting in diverse treatment strategies[4]. As additional cases are described and longitudinal follow-up is reported, the biological behavior of CCOC continues to be elucidated.

The aim of this study was to review the literature, summarize what is currently known of this rare tumor, and create a library/cohort of cases for further evaluation.

Materials and methods

The PubMed and Springer databases were used to collect all reports of CCOC. Searches were performed by searching the terms 'clear cell odontogenic carcinoma', 'CCOC', or 'clear cell ameloblastoma'. References in the publications were screened and cross-referenced for more cases. Data extracted included demographic characteristics, presenting signs and symptoms, radiographic findings, histological and immunohistochemical features, treatment, recurrence, and follow-up.

Results

Search strategy and demographic characteristics

The PubMed searches for 'clear cell odontogenic carcinoma,' 'CCOC,' and 'clear cell ameloblastoma' returned 118, 57, and 79 results, respectively. The same search criteria used in the Springer database yielded 92, 302, and 14 results, respectively. The process resulted in 75 articles (by language: 73 in English, one in Arabic, and one in French) with 107 case reports, resulting in a total of 107 cases[3,6,8–78].

CCOC occurs most often in the fifth decade of life, with an average patient age of 52.8 years (range 14–89 years). Most cases have been reported from the USA ($n = 29$), India ($n = 14$), and China ($n = 11$), although cases have been documented in multiple countries. The ethnicity of patients has rarely been noted; 17 of 34 documented cases were Caucasian. There was a predominance of female patients among the 107 cases (67/107).

Clinical manifestations (presenting clinical symptoms) and radiology

The most frequent site of occurrence of CCOC was found to be the posterior mandible ($n = 46$), followed by the anterior mandible ($n = 33$) and maxilla/palate ($n = 28$).

Of the 70 patients for whom presenting clinical symptoms were reported, 44 specified a swelling. Swelling was often the only reported symptom, with or without pain. Other presenting symptoms included tooth mobility ($n = 11$), gingival/periodontal issues ($n = 7$), numbness ($n = 5$), and decreased opening ($n = 3$). One case presented as a neck mass, one with an uncontrolled tumor, one with systemic symptoms (loss of appetite and loss of weight), and one presented as a thyroid metastasis.

The duration of symptoms before seeking care was specified for 52 patients. Patients sought care in the case of a painless swelling that had started to increase in size, tooth mobility, or the development of pain. In one instance, the patient underwent periodontal care for 5 years prior to addressing the tumor. In another case, the patient had been aware of a gingival mass for 45 years and only sought care when new growth was observed over the course of 2 months. Positive regional lymph nodes were reported in 12 cases on initial presentation ($n = 6$ clinical; $n = 6$ imaging). Only seven were deemed positive on histological examination.

Radiological analysis ($n = 85$) of CCOC tumors typically showed a poorly defined expansive radiolucent lesion, irregular margins, and tooth resorption. This was unilocular ($n = 11$) or multilocular ($n = 7$), not described as either uni- or multilocular ($n = 65$), or was radiopaque ($n = 2$).

Treatment

Treatment was specified in 86 of the 107 cases: tumor removal described as curettage or excision ($n = 10$), usually repeated and followed by resection; resection (maxillectomy or mandibulectomy) ($n = 62$); marginal or segmental osteotomy ($n = 14$). In the most recent cases, it was found that resection with 'wide margins' was favored.

Only 24 cases had neck dissection. Of the 24 cases that had neck dissection (20 mandible and four maxilla), 12 were deemed positive at presentation either by clinical examination ($n = 6$) or imaging ($n = 6$; computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT)). Of the 12 'positive neck nodes' preoperatively, only seven were positive on histological examination.

Recurrence was reported for 88 cases. Four cases presented as a known recurrence (sometimes of multiple episodes). Of the other reported cases, 34 had recurred (some multiple times) at some point prior to publication. Thus, the incidence of recurrence appears to be 38/88 (over a mean 3.5 years, range 2 months to 15 years). Reported local recurrence was regional ($n = 13$) or metastasis ($n = 18$). Metastasis was seen in the regional lymph nodes ($n = 12$), lung ($n = 5$), pubic bone ($n = 2$), brain ($n = 1$), vertebrae ($n = 1$), and liver ($n = 1$). There was little long-term or follow-up data for the 107 reported cases.

Twelve of the 107 reported patients with CCOC had died prior to publication. Of these, eight cases were histologically defined as biphasic, one as ameloblastic, and one as monophasic; there was no histological data for two. Eight cases were in the mandible and four were in the maxilla. All 12 patients had a swelling as the presenting symptom. At least two of these patients had a long duration of symptoms prior to seeking initial care (1 year and 2 years). Six were treated by some form of tumor removal (ranging from curettage to resection) and five had tumor removal and adjuvant therapy: one had neck dissection, two had chemotherapy, one had radiotherapy, and one had chemotherapy and radiation. Eight patients appeared to have died as a result of the tumor; two others had multiple tumor recurrences and at the latest recurrence had not received care due to medical comorbidities. Another two appeared to have died from complications of surgery. An additional patient who was listed as 'palliated' at the time of publication had been aware of a gingival mass for 45 years and had only sought care when new growth occurred 2 months prior to presentation.

Histological and immunohistochemical features

Histological data were presented in 102 of the 107 case reports, and three histological variants of CCOC were identified. The

biphasic variant ($n = 86$) presents as islands and strands containing two populations of cells: clear cells with well-defined borders and a centrally placed nucleus, and hyperchromatic polygonal cells with eosinophilic cytoplasm and eccentrically placed nuclei, both embedded in a fibrous stroma. The monophasic variant ($n = 3$) is composed almost entirely of clear cells. The ameloblastomic variant ($n = 13$) is composed predominantly of columnar cells with ameloblast-like differentiation at the periphery of the tumor islands. Partially cellularized stroma was observed in eight of the 107 cases. Epithelial nests and chords often showed nuclear palisading along the stromal barrier.

Only 79 of the 107 cases reported immunohistochemical studies and tested positive for at least one type of cytokeratin. Cytokeratin 19 was reported in 39 of the 79 cases. Similarly, epithelial membrane antigen (EMA) was reported in 45 of the 79 cases (Table 1).

Genetics

Only four of the 75 articles ($n = 4$ cases) discussed genetics. In one case/manuscript, gene expression analysis was performed on tumor samples and showed multiple upregulated (ELKI, WBSCR14, PDE9A, CUL5, PCMT1, NT5B) and downregulated (NBL1, PPP2RI, NDUFV1, MT1H, SMPD1, ERCC1, RENT2) genes. In another three cases, a genetic rearrangement between Ewing sarcoma (EWS) was found and in two cases a fusion of EWS and activating transcription factor 1 (ATF1) was found (Table 2).

Discussion

This tumor was originally described by Hanson et al. in 1985 as a benign odontogenic tumor[1]. The behavior of the tumor led to its reclassification as malignant by the WHO in 2005. More recently obtained genetic data appear to indicate that it may be of the sarcoma family[6,7]. Any discussion of this tumor is limited by the lack of available data. The review of these cases concurs with the WHO 2005 classification of the tumor as a low-grade malignancy.

This study is a summary of a retrospective analysis of case reports. There are inconsistencies in the data reported and in the style of reporting. This combined with the rarity of cases, makes it difficult to draw conclusions.

Of the 107 patients with CCOC, only one had non-specific systemic systems (loss of appetite and loss of weight). Local symptoms are often restricted to swelling, with or without pain, tooth mobility, and gingival/periodontal issues. Less commonly reported symptoms include bleeding, delayed healing of ulcerations, expansion of the oral mucosa, and paresthesia. The duration of symptoms prior to seeking care is unusually long for a malignancy (a few months to many years). This tumor has an atypical behavior as a malignancy and appears indolent without treatment in 31% of cases (1–12 years). The duration prior to seeking care was reported for 52 patients: 2 months to 1 year ($n = 34$), 1–2 years ($n = 7$), 2–4 years ($n = 2$), 4–7 years ($n = 6$), and 7–12 years ($n = 3$). One additional patient reported noticing a gingival mass 45 years prior, with new growth occurring 2 months before seeking care. Another patient underwent 5 years of periodontal care prior to addressing the tumor. Of note, nine cases noted a swelling 4–12 years prior to seeking care[3,20,22,23,38,41,42,49,51]. Interestingly no metastatic disease was reported in these cases.

Genetics was only discussed in four of the 75 manuscripts ($n = 4$ cases) included in this review[40,58,67,73]. In one case, gene expression analysis of the tumor showed multiple upregulated and downregulated genes[40]. We cannot deduce anything from this information as we do not (yet) know what this up/down regulation means. The other three cases were positive for the characteristic rearrangement of EWS. Two of these three cases were positive for the rearrangement EWS–ATF1[58,73]. Three other papers that were not included in the present review, as they reported only genetics and not cases, showed positive EWS rearrangement in 15 cases, of which six tested positive for ATF1 rearrangement; one tested positive for CREB and eight were listed as 'unknown' or 'negative'[6,79,80]. With further genetic analysis, an understanding of the tumor may allow for more appropriate therapy (targeted immunotherapy).

In conclusion, the data compiled here represent a summary of previously published case reports. CCOC can be distinguished from other jaw malignancy by its distinctive histology and immunohistochemical makeup. The invasiveness of

Table 1. Common immunohistochemical markers in clear cell odontogenic carcinoma ($n = 79$ cases).

	AE1/AE3	Cytokeratin 19	EMA	S-100	Vimentin	SMA	PAS	Desmin
Positive	29	39	45	19	5	2	7	0
Negative	0	0	0	29	30	30	1	17
Not tested	78	68	62	59	72	75	99	90

EMA, epithelial membrane antigen; PAS, periodic acid-Schiff; SMA, smooth muscle actin.

Table 2. Common genetics expressed on tumor samples of the only four reported cases (4/107).

Authors	Number of cases	Gene expression analysis			
		Upregulated genes[a]	Downregulated genes[b]	Rearrangement EWS	Rearrangement EWS–ATF1
Carinci et al., 2003 [40]	1	X	X		
Yancoskie et al., 2014[58]	1				X
Harbhajanka et al., 2015 [67]	1			X	
Ginat et al., 2016 [73]	1				X

EWS, Ewing sarcoma; ATF1, activating transcription factor 1.
[a] ELKI, WBSCR14, PDE9A, CUL5, PCMT1, NT5B.
[b] NBL1, PPP2RI, NDUFV1, MT1H, SMPD1, ERCC1, RENT2.

the tumor coupled with its high rate of recurrence means that it should be treated early and aggressively, obtaining clear surgical margins with surgical resection. As they are low-grade tumors, it would be anticipated that chemotherapy or radiation therapy would not be effective.

As a very limited number of cases are reported in the literature and considering the need to further understand these cases, please contact the corresponding author if CCOC cases are available to add to the cohort of this rare jaw tumor.

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Competing interests

The authors declare no conflict of interest.

Ethical approval

Not required.

Patient consent

Not required.

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