Invited Review

Int J Oral Biol 44:77-80, 2019
pISSN: 1226-7155 • eISSN: 2287-6618
https://doi.org/10.11620/IJOB.2019.44.3.77

International Journal of Oral Biology
IJOB
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Clear cell odontogenic carcinoma: a mini review

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Clear cell odontogenic carcinoma (CCOC), a very rare neoplasm located mostly in the mandible, has been regarded as a benign tumor. However, due to the accumulation of case reports, CCOC has been reclassified as a malignant entity by the World Health Organization. Patients with CCOC present with regional swelling and periodontal indications with variable pain, often remaining misdiagnosed for a long period. CCOC has slow growth but aggressive behavior, requiring radical resection. Histologic analysis revealed the monophasic, biphasic, and ameloblastic types of CCOC with clear cells and a mixed combination of polygonal and palisading cells. At the molecular level, CCOC shows the expression of cytokeratin and epithelial membrane antigen, along with markers that assign CCOC to the sarcoma family. At the genetic level, Ewing sarcoma breakpoint region 1-activating transcription factor 1 fusion is regarded as the key feature for identification. Nevertheless, the scarcity of cases and dependence on histological data delay the development of an efficient therapy. Regarding the high recurrence rate and the potential of distant metastasis, further characterization of CCOC is necessary for an early and accurate diagnosis.

Keywords: Odontogenic tumor, Carcinoma, Clear cell

Clear cell odontogenic carcinoma (CCOC) is an erratic intraosseous lesion in the jaw. CCOC was first reported by Hansen in 1985, and only 107 cases have been reported in the literature until 2018 according to PubMed and Springer databases [1,2]. CCOC is hard to diagnose and does not present distinctive clinical and radiological characteristics [3]. CCOC manifests symptoms of swelling, tooth mobility and inconstant pain [4]. The World Health Organization (WHO) classified CCOC as "a benign but locally invasive neoplasm originating from odontogenic epithelium and characterized by sheets of islands of uniform, vacuolated and clear cells" until 1992 [5]. However, further examination revealed the regional aggressiveness and destructiveness with local recurrence and metastatic potential, which led the WHO redefine CCOC as a malignant carcinoma in 2005 [6].

The aggressive nature of CCOC is revealed radiologically with ill-defined limits of osteolytic lesions and dental root resorption [7]. Tumors harboring clear cell phenotypes may have origins from the odontogenic epithelium, the salivary gland or the distant metastatic cells from the kidney [8]. Salivary gland tumors and metastatic renal carcinomas were regarded as differential diagnoses of CCOC. However, these two were removed from the list due to the immunohistochemical, morphological, and clinical differences [9,10]. Histology exhibits three types of CCOC [10,11]. The monophasic type is comprised of almost completely of clear cells. The biphasic type, which takes the most significant portion of the reported cases (80%), displays clear cells and hyperchromatic polygonal cells surrounded by a fibrous stroma. The ameloblastic type is constituted by columnar cells with ameloblast-like morphology at the periphery [12].

Received September 10, 2019; **Revised** September 15, 2019; **Accepted** September 18, 2019
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The morphological features and the arrangement of CCOC cells, including the focal palisading and the inductive hyalinization of the nearby fibrous tissues, have suggested the odontogenic origin, but the precise etiology of CCOC has remain elusive [13-16].

CCOC occurs mostly in the mandibular region with the complex diagnosis and in the fifth decade with a predominance of female patients [2]. The occurrence sites include the posterior and the anterior mandible, the maxilla and the palate [17,18]. The rarity of CCOC contributes to the misdiagnosis. Regional complains are easily limited to swelling inconstantly accompanied by pain, tooth movement and gingival or periodontal symptoms [19]. A delay in the healing of oral ulcerations, bleeding, paresthesia or expansion of oral mucosa is less frequently reported [20]. The long duration, months to years, up to 45 years, is often observed prior to receiving the matching diagnosis. As an incomplete or a partial resection may lead to a relapse, the radical surgery is recommended for the treatment. Chemotherapy or radiation therapy would not be expected to eradicate CCOC due to the low-grade characteristics. The invasiveness of tumor with the high rate of recurrence requires the understating of CCOC at the cellular and molecular level for the development of an effective therapy after the surgery.

Immunohistochemical analysis, according to the WHO description and in the case reports, reveals the positivity for cytokeratin, among which cytokeratin 19 was expressed in 39 of 79 CCOC cases [3]. Epithelial membrane antigen is another key antigen, whose expression is reported in 45 of 79 CCOC cases [2]. The expressions of p53 and Ki-67 are low, and the expression of CD31, CD45, vimentin or S-100 protein is not detected [21,22]. Gene expression analysis showed the upregulation of ELK1 transcription activator and WBSCR14 transcription repressor [23]. Tumor suppressors such as NBL1 and PPP2RIA are downregulated, but p53 or pRb is not. The genetic rearrangement of Ewing sarcoma breakpoint region 1 (*EWSR1*) gene is frequently observed with the fission and the fusion with activating transcription factor 1 (*ATF1*) [24]. Recent genetic data analysis points out that CCOC may belong to the sarcoma family, but the paucity of available data hinders drawing the definitive conclusion [25].

The presence of clear cells in the odontogenic tumors indicates their origin from the dental lamina [26]. Clear cell ameloblastoma (CCAM), another variant of clear cell tumor, bears the undistinguishable similarity with CCOC, thus suggesting the possibility that CCOC is a malignant continuum of CCAM [4]. These clear cells exhibit a clear halo around the nuclei, an absence of staining by hematoxylin and eosin, probably resulting from the fixation artifacts, the accumulation of glycogen, water, intermediate filaments and immature zymogen granules or the scarcity of organelles [27]. In the maxillofacial region, clear cell tumors arise from odontogenic, salivary or metastatic origin [11]. Clear cell carcinoma of salivary gland, together with CCOC, is diagnostically confirmed by the presence of the *EWSR1* gene fission [10]. Regarding the inductive potential of embryonic epithelium, the developmental remnant or the persisting embryonic epithelium, including dental lamina, may contribute to the etiology of maxillofacial neoplasia including CCOC [28]. Pathologic activation of the remaining lamina or even a reprogramming to the embryonic epithelial status by a gene fission or fusion can be speculated, but the current accumulation of data limits the understanding of the developmental origin.

Conclusions

In summary, CCOC is a malignant tumor with a low occurrence rate, which issues a challenge in a timely diagnosis. Misdiagnosis due to the slow progression and the rarity often delays the initiation of the effective treatment. The high rates of relapse and the distant metastatic potential raises a concern for the current lack of understanding in developmental, cellular and molecular etiology of CCOC. As clear cell tumors in the maxillofacial region present a conundrum in differential diagnosis, establishing *in vitro* model by cell culture [29] or organoid generation and *in vivo* model by xenograft [29] or genetic modifications will provide the essential platforms for identifying the pathogenic mechanisms of CCOC, discovering markers for differential diagnosis and developing novel therapeutics in the pursuit of achieving a completion in the cure.

Acknowledgements

This work was supported by Pusan National University Research Grant, 2016.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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