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CASE REPORT

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Clear cell variant of calcifying epithelial odontogenic tumor: an unusual case report

Abstract:

The calcifying epithelial odontogenic tumor (CEOT), also known as Pindborg tumor, is a rare odontogenic neoplasm originating from epithelial tissue. The presence of clear cells within CEOT is an unusual finding, indicating a variant with distinctive histopathological features and possible clinical implications. This study presents a case report of a clear cell variant of CEOT in a 36-year-old male patient with painless swelling in the anterior mandible. The occurrence of clear cells in CEOT is uncommon and may mimic other clear cell tumors. Therefore, the identification of amyloid-like deposits and calcifications is essential in confirming the diagnosis of clear cell variant of CEOT.

Keywords: Calcifying epithelial odontogenic tumor; Clear cell; Mandible; Pindborg tumor.

INTRODUCTION

Calcifying epithelial odontogenic tumor (CEOT) or Pindborg tumor is a rare benign odontogenic tumor first described by Pindborg in 1955[1]. CEOT accounts for less than 1% of all odontogenic tumors and typically arises in the posterior mandible. The lesion is frequently seen in patients in the third and fourth decades with no sex predilection[2]. The radiographic characteristics of CEOT range from unilocular and well-defined lesions to diffuse and multilocular. CEOT may also be associated with impacted or unerupted teeth[3].

Microscopically, CEOT comprises sheets, nests or cords of polyhedral epithelial cells with abundant eosinophilic cytoplasm and distinct intercellular bridges. Concentric ring of basophilic calcifications and deposits of amorphous lightly eosinophilic amyloid are often found. A rare clear cell variant of calcifying epithelial odontogenic tumor (CCCEOT) exhibits a significant number of epithelial cells appear clear, due to the accumulation of glycogen or other intracellular substances. These clear cells can be focal or scattered throughout the tumor[4].

Statement of Clinical Significance
Clear cell variant of calcifying epithelial odontogenic tumor (CCCEOT) demonstrates demographic features and behavior similar to conventional calcifying epithelial odontogenic tumor. CCCEOT should be differentiated from other clear cell tumors, such as clear cell odontogenic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, and metastatic renal cell carcinoma.

CCCEOT has variable clinical behavior and may present a higher recurrence rate and aggressiveness than conventional CEOT[4,5]. Additionally, CCCEOT is challenging to diagnose because it resembles other clear cell odontogenic tumors, salivary gland tumors, and metastatic tumors[3,6]. The etiology of CCCEOT remains unclear, with limited cases reported in the literature. We present an additional case of CCCEOT highlighting its clinical presentation, radiologic and histopathologic characteristics.

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CASE REPORT

A 36-year-old white male patient was referred to a private dental service complaining of an increase in the size of the mandible. Intraoral examination revealed an asymptomatic increase in the lingual surface of the anterior mandible, between teeth 32 and 33. The lesion was covered by normal-colored mucosa and presented a slight central ulceration (Figure 1A). In addition, the patient also had orthodontic retention between teeth 33 and 43. Pulp vitality tests were performed showing positive responses. A cold stimulus was applied to the teeth associated with the lesion to assess reaction time and intensity of sensation. The tomographic examination showed a mixed lesion, measuring 1.0 x 0.7 cm in size and causing slight divergence of the roots of the involved teeth (Figure 1B-C). The diagnostic hypotheses were cemento-osseous dysplasia and cemento-ossifying fibroma. An incisional biopsy was performed under local anesthesia and microscopic examination revealed a neoplasm of odontogenic origin characterized by the proliferation of nests, islands, and cords of polygonal and cubic epithelial cells, with relatively abundant and well-defined eosinophilic cytoplasm and prominent intercellular bridges. The nuclei of the tumor cells were central and round, exhibiting varying degrees of chromatin condensation, as well as mild pleomorphism. A common feature was the presence of the tumor cells exhibiting clear cytoplasm, resulting in a vacuolated appearance. Mitotic activity was inconspicuous. Multiple foci of dystrophic calcification, occasionally exhibiting concentric internal lamellae, were tangential to the neoplastic cells (Figure 2). Irregular deposits of amorphous eosinophilic material consistent with amyloid were confirmed after Congo red staining and apple-green birefringence under polarized microscopy (Figure 3). Matrix deposits of eosinophilic material consistent with dentinoid or dysplastic dentin were also identified. The histopathological diagnosis of CCCEOT was made.

The surgical procedure was performed under local anesthesia. A lingual incision was made from the lower left canine to the lower right central incisor and a mucoperiosteal flap was reflected. A rigorous curettage of the lesion was performed with surgical drills and curettes followed by saline irrigation. Initially, postoperative healing was uneventful, and the patient's pain symptoms were effectively controlled by analgesics and nonsteroidal anti-inflammatory drugs. Microscopic examination

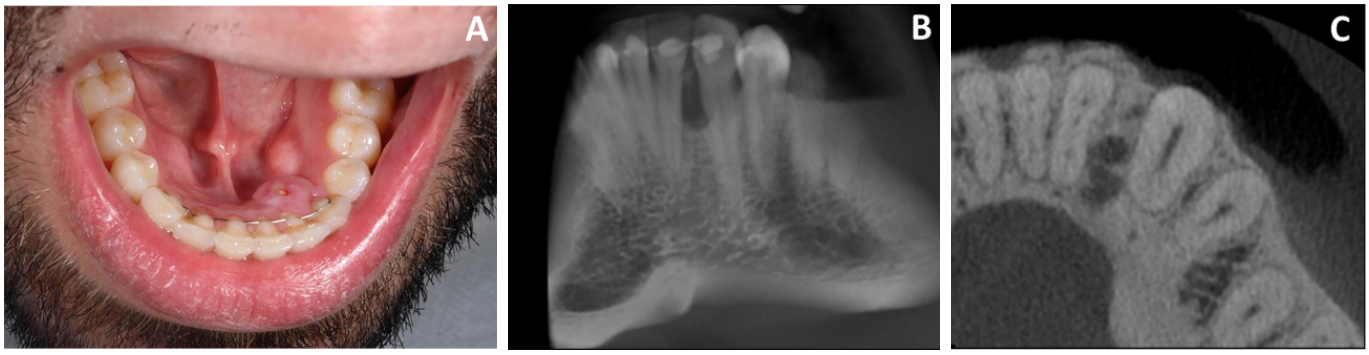

Figure 1. A: Clinical aspect of a sessile and normochromic nodule in the lingual surface of the anterior mandible with a slight central ulceration. B, C: Panoramic and axial CT sections showing a mixed lesion causing divergence of the roots of the involved teeth.

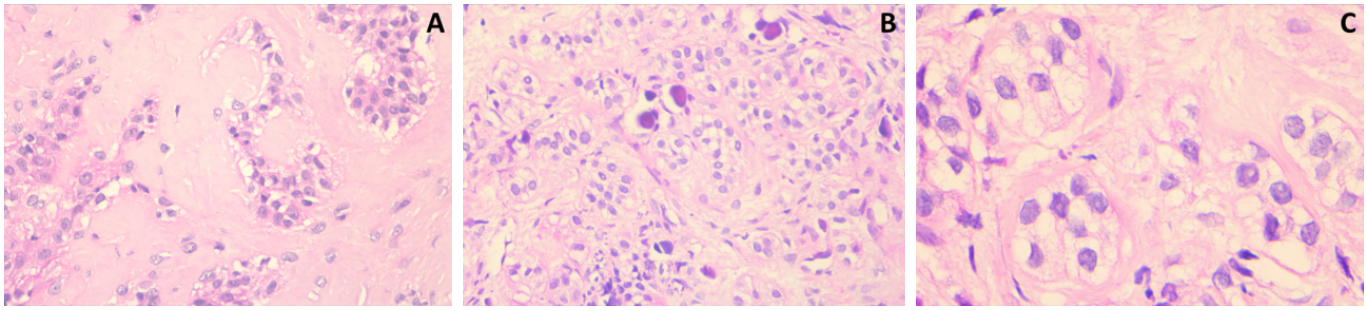

Figure 2. A: Microscopic examination showing nests and cords of polygonal and clear cells associated with foci of dystrophic calcification and matrix consistent with dentinoid or dysplastic dentin (hematoxylin and eosin, original magnification x400). B, C: Tumor cells revealing well-defined borders, prominent intercellular bridges, occasional vacuolated nucleoli, and nuclear pleomorphism (hematoxylin and eosin, original magnification x400 and x1000).

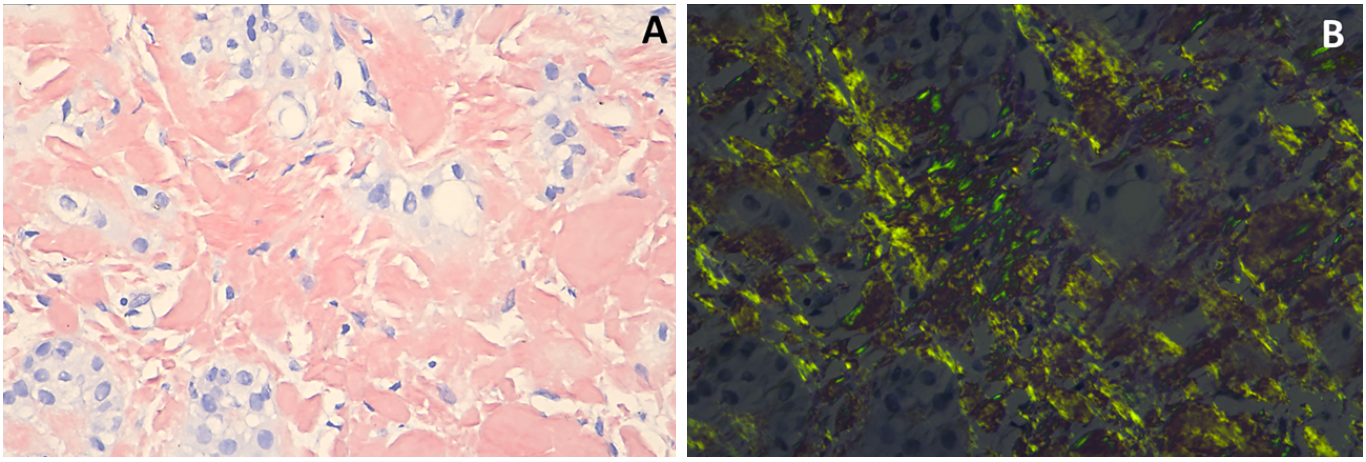

Figure 3. A, B: Irregular deposits of amorphous eosinophilic material compatible with amyloid were confirmed after Congo red staining and apple-green birefringence under polarized microscopy (Congo stain, original magnification x100).

of the specimen confirmed the diagnosis of CCCEOT. The patient has been monitored with semiannual clinical and radiographic examinations. After 18 months of follow-up, no evidence of recurrence was observed.

DISCUSSION

CCCEOT is rare and its pathogenesis remains controversial. It is presumed that CEOT develops from the remnants of the dental lamina, oral epithelium or the reduced enamel epithelium[7]. The expression of proteins such as cytokeratins and enamel proteins supports the tumor's odontogenic origin. Studies have identified multiple genetic alterations, including mutations in PTCH1, CDKN2A and PTEN genes, which are implicated in CEOT[8-10].

While a certain amount of clear cells is not unusual in various types of odontogenic and non-odontogenic tumors, Hicks et al.[11] proposed that the presence of clear cells in CEOT may be linked to more aggressive behavior and a higher recurrence rate than other variants of CEOT. However, another study[2] reported that CCCEOT shares demographic characteristics and behavior similar to those of CEOT, indicating that the presence of clear cells holds minimal clinical relevance and does not justify classifying this histological variant as a separate category.

The presence of both radiopaque and radiolucent areas is recognized as a classic pattern for CEOT, resembling "driven snow". CEOT can be unilocular or multilocular and is often associated with an impacted or unerupted tooth[3,6]. However, variations in radiodensity may occur depending on the amount of mineralized material[12]. Occasional opacities influence the radiographic presentation and, therefore, the diagnostic interpretation of the tumor. In the present case, the mixed radiographic appearance associated with the anatomical location favored a clinical suspicion of fibro-osseous lesion such as cemento-osseous dysplasia and cemento-ossifying fibroma. However, radiographically, cemento-ossifying fibroma is usually spherical to egg-shaped and equally expands the cortices[13], whereas cemento-osseous dysplasia demonstrates variable radiolucency and radiopacity depending on the stage of maturation of the lesion and rarely causes tooth displacement[14].

Histopathological criteria play a crucial role in the diagnosis of CEOT. Typical characteristics of CEOT include sheets and clusters of polyhedral epithelial cells with clear or eosinophilic cytoplasm. These cells display well-defined borders, prominent intercellular bridges, occasional vacuolated nucleoli, and nuclear pleomorphism. Additionally, minimal mitotic activity, concentric Liesegang ring calcifications, and deposits resembling amyloid material are observed[13,15,16]. The presence of Liesegang ring calcification and amyloid-like deposits are among the most distinguishing features of CEOT[17].

CCCEOT must be distinguished from other clear cell tumors such as clear-cell odontogenic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma and metastatic renal cell carcinoma[4,18]. Immunohistochemical reactions contribute to the differentiation of these tumors. Clear-cell odontogenic carcinoma mainly expresses CK-7, 8, 14, 18 and 19[19]. Regarding mucoepidermoid carcinoma, immunoreactivity is positive for CK-6, 7, 8, 14, 18 and 19[3]. Acinic cell carcinoma generally shows strong expression for DOG1 and SOX-10[20]. Metastatic

renal cell carcinoma expresses CD10 and PAX-8[21]. However, in our case, the distinctive histological characteristics, including amyloid presence and dysplastic dentin formation, allowed for the exclusion of these other tumors. Amyloid is detected by the increased optical anisotropy after Congo red binding displaying a birefringent apple-green color under polarized light microscopy. This method is commonly used in histopathology laboratories because it is simple and cost-effective[3,6].

CEOT may present a locally aggressive behavior. Management and treatment of CEOT generally involve surgical excision as the primary approach. The specific type of surgery and post-surgical care vary depending on factors such as the tumor's location, size and growth pattern[2]. Curettage has been associated with a higher recurrence[22]. CEOTs may require a marginal or segmental resection mainly for lesions located in the posterior region of the maxilla. For CCCEOT, establishing definitive treatment guidelines is challenging due to the limited number of reported cases. The present case was treated with conservative excision and the patient has remained under clinical and radiographic follow-up for 18 months without evidence of recurrence.

CONCLUSION

The presence of clear cells in CEOT is relatively rare and can make diagnosis challenging, as it may resemble other clear cell neoplasms. However, the combination of clear cells with amyloid-like deposits and calcifications helps confirm the diagnosis of CCCEOT. Continued documentation of cases and molecular studies are essential to improve our understanding of this entity and guide treatment protocols.

AUTHORS' CONTRIBUTIONS

KMF: data curation, investigation, visualization, writing – original draft. HS: visualization, clinical management. TPC: data curation, writing – original draft. NCTB: investigation, writing –review & editing. ERCR: writing –review & editing. RLCAJ: investigation, writing – review & editing. RG: conceptualization, investigation, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose..

Ethics approval: The Research Ethics Committee of the Federal University of Santa Catarina approved this study (#42095715.1.0000.0121).

REFERENCES

1. Pindborg JJ. Calcifying epithelial odontogenic tumour. Acta Pathol Microbiol Scand 1955;111:71.
2. Chrcanovic BR, Gomez RS. Calcifying epithelial odontogenic tumor: an updated analysis of 339 cases reported in the literature. J Craniomaxillofac Surg. 2017;45(8):1117-23. https://doi.org/10.1016/j.jcms.2017.05.007
3. Arruda JAA, Arantes DAC, Schuch LF, Mosconi C, Abreu LG, Andrade BAB, et al. A rare case of an aggressive clear cell variant of calcifying epithelial odontogenic tumor in the posterior maxilla. Int J Surg Pathol. 2020;28(5):526-35. https://doi.org/10.1177/1066896920901755
4. Anavi Y, Kaplan I, Citir M, Calderon S. Clear-cell variant of calcifying epithelial odontogenic tumor: clinical and radiographic characteristics. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(3):332-9. https://doi.org/10.1067/moe.2003.8
5. Cheng YSL, Wright JM, Walstad WR, Finn MD. Calcifying epithelial odontogenic tumour showing microscopic features of potential malignant behavior. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(3):287-95. https://doi.org/10.1067/moe.2002.121991
6. Siriwardena BSMS, Speight PM, Franklin CD, Abdelkarim R, Khurram SA, Hunter KD. CEOT variants or entities: time for a rethink? A case series with review of the literature. Head Neck Pathol. 2021;15(1):186-201. https://doi.org/10.1007/s12105-020-01200-9
7. Morais HGF, Silva WR, Andrade ACM, Silva NS, Xerez MC, Santos JWM, et al. Pindborg tumor associated with a supernumerary tooth: a case report. Autops Case Rep. 2022;12:e2021358. https://doi.org/10.4322/acr.2021.358
8. Peacock ZS, Cox D, Schmidt BL. Involvement of PTCH1 mutations in the calcifying epithelial odontogenic tumor. Oral Oncol. 2010;46(5):387-92. https://doi.org/10.1016/j.oraloncology.2010.02.023
9. Shimura M, Nakashiro KI, Sawatani Y, Hasegawa T, Kamimura R, Izumi S, et al. Whole exome sequencing of SMO, BRAF, PTCH1 and GNAS in odontogenic diseases. In Vivo. 2020;34(6):3233-40. https://doi.org/10.21873/invivo.12159
10. Sousa SF, Diniz MG, França JA, Pereira TSF, Moreira RG, Santos JN, et al. Cancer genes mutation profiling in calcifying epithelial odontogenic tumour. J Clin Pathol. 2018;71(3):279-83. https://doi.org/10.1136/jclinpath-2017-204813
11. Hicks MJ, Flaitz CM, Wong ME, McDaniel RK, Cagle PT. Clear cell variant of calcifying epithelial odontogenic tumor: case report and review of the literature. Head Neck. 1994;16(3):272-7. https://doi.org/10.1002/hed.2880160311
12. Li Y, Wan K, Wang M, Cui G, Chen B, Yu L, et al. Giant calcifying epithelial odontogenic tumor after I-125 seed implantation: a case report. Heliyon. 2023;9(7):e17087. https://doi.org/10.1016/j.heliyon.2023.e17087

13. Kaur T, Dhawan A, Bhullar RS, Gupta S. Cemento-ossifying fibroma in maxillofacial region: a series of 16 cases. J Maxillofac Oral Surg. 2021;20(2):240-5. https://doi.org/10.1007/s12663-019-01304-y
14. Salvi AS, Patankar S, Desai K, Wankhedkar D. Focal cemento-osseous dysplasia: a case report with a review of literature. J Oral Maxillofac Pathol. 2020;24(Suppl 1):S15-S18. https://doi.org/10.4103/jomfp.JOMFP_349_19
15. Germanier Y, Bornstein MM, Stauffer E, Buser D. Calcifying epithelial odontogenic (pindborg) tumor of the mandible with clear cell component treated by conservative surgery: report of a case. J Oral Maxillofac Surg. 2005;63(9):1377-82. https://doi.org/10.1016/j.joms.2005.05.298
16. Turatti E, Brasil J, Andrade BAB, Romañach MJ, Almeida OP. Clear cell variant of calcifying epithelial odontogenic tumor: case report with immunohistochemical findings. J Clin Exp Dent. 2015;7(1):e163-6. https://doi.org/10.4317/jced.51995
17. Patankar S, Choudhari S, Sharma S, Dhumal S. Noncalcifying clear-cell variant of calcifying epithelial odontogenic tumor: a case report and review. J Oral Maxillofac Pathol. 2021;25(1):204. https://doi.org/10.4103/jomfp.JOMFP_212_20
18. Jain A, Shetty DC, Juneja S, Narwal N. Molecular characterization of clear cell lesions of head and neck. J Clin Diagn Res. 2016;10(5):ZE18-23. https://doi.org/10.7860/JCDR/2016/14394.7867
19. Loyola AM, Cardoso SV, Faria PR, Servato JPS, Paulo LFB, Eisenberg ALA, et al. Clear cell odontogenic carcinoma: report of 7 new cases and systematic review of the current knowledge. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(4):483-96. https://doi.org/10.1016/j.oooo.2015.06.005
20. Rammal R, Batson B, Spector ME, Chiosea, SI, Seethala RR. Acinic cell carcinoma with high-grade squamoglandular and chondrosarcomatous transformation mimicking 'carcinosarcoma ex-pleomorphic adenoma': a wrinkle in the proposed nomenclature revision for sarcomatoid salivary gland neoplasms. Head Neck Pathol. 2024;18(1):44. https://doi.org/10.1007/s12105-024-01650-5
21. Kudva R, Nayal B, Kantipudi S, Ray S. Metastatic renal cell carcinoma of the buccal mucosa masquerading as a salivary gland neoplasm. J Oral Maxillofac Pathol. 2016;20(3):547. https://doi.org/10.4103/0973-029X.190967
22. Goode RK. Calcifying epithelial odontogenic tumor. Oral Maxillofac Surg Clin North Am. 2004;16(3):323-31. https://doi.org/10.1016/j.coms.2004.03.002