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An Immunohistochemical Diagnostic Approach of Clear Cell Calcifying Epithelial Odontogenic Tumor of Anterior Mandible

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ABSTRACT:

The calcifying epithelial odontogenic tumor (CEOT) is a rare benign neoplasm reported to be less than 1% of all odontogenic tumors. Dr. J J Pindborg in the year 1958 first described this lesion after which Shafer *et al* termed it as Pindborg tumor. This tumor is a locally aggressive benign neoplasm of odontogenic epithelial origin. The clear cell variant of CEOT (CCEOT) is more aggressive with highest recurrence rate of about 22%. Howell and Abrams reported the first case of CCEOT in the year 1967. Hence it is crucial to consider clear cell variant in histopathological diagnosis. Such a rare case of CCEOT is reported in our institution and its clinical, radiographical and histopathological features are discussed in this article. This rare case report gives an overview of a clear cell variant of CEOT in the anterior mandible of a 62-year-old female patient.

Keywords: Clear cell variant, Benign neoplasm, Pindborg tumor.

INTRODUCTION

Calcifying epithelial odontogenic tumors are classified under benign epithelial odontogenic tumors by recent classification of World Health Organization (WHO) in the year 2022 (1). CEOT is a rare, benign, painless, slow-growing and locally aggressive tumor (2),(3). The lower jaw is more commonly affected than the maxilla and it may cause mobility of adjacent tooth with tipping, migration and rotation movements (3). It has been reported that clear cell variant

shows more aggressiveness with higher recurrence rate (22%) (4). It may cause cortical plate expansion and infiltration into the overlying soft tissue (3).

Radiographically, this tumor exhibits either unilocular or multilocular radiolucency, with interspersed radiopaque masses of varying sizes exhibiting combined radiopaque and radiolucent areas (65%) owing to dispersed calcific deposits, thereby giving the typical "driven-snow" appearance (3) (5) .

CASE PRESENTATION

A 62 year old female reported to our OPD (Outpatient department) with a complaint of swelling in mandibular anterior teeth region for the past 3 years [Figure 1]. Patient's medical history revealed that she was a known diabetic and hypertensive for the past 4 years and she is under medication for the same. Past dental history revealed previous extraction of 18,26,28,46 and 48. On clinical examination, intraorally a diffuse swelling with normal color and smooth overlying mucosa and smooth surface measuring about 2x2x3 cms seen. The swelling is non tender, immovable, hard in consistency extending anteriorly from the distal aspect of 31, posteriorly to the mesial aspect of 33, inferiorly till the vestibule was noticed involving the gingival and alveolar regions.

Orthopantomogram (OPG) revealed a mixed radiolucency surrounded by well defined radiopacity in the anterior mandible with obliteration of the periodontal ligament space of 32 and 33. The radiolucent area was interspersed with multiple flecks of radiopacities [Figure 2].

After performing incisional biopsy, the specimen was submitted for histopathological examination. The received specimen was grossed, sectioned and stained for histopathology reporting.

Histopathologically, the H&E stained sections revealed fibrocellular connective tissue areas with dispersed nests, islands, cords and strands of cells showing predominantly a clear vacuolated cytoplasm similar to clear cells. In some areas, polyhedral tumor cells with hyperchromatic nuclei in the centre and eosinophilic cytoplasm with prominent intercellular bridges are seen. The tumour cells show nuclear and cellular pleomorphism in many areas. The entire section seems to be interspersed with focal areas of irregularly shaped and spherical acellular eosinophilic to basophilic calcifications. The connective tissue areas show moderate vascularity, areas of hemorrhage and focal areas of lamellar /concentric lighter and darker areas resembling Liesegang rings [Figure 3-A,B,C,D]. To confirm our provisional diagnosis the sections were subjected to immunohistochemistry (IHC) (CK 14 & CK 19) and special staining procedures (Congo red). Immunohistochemical markers CK 14 was negative and CK 19 was positive, confirming odontogenic epithelium [Figure 3-E]. Congo red staining showed no birefringence under polarized light.

After considering all the microscopic features, a definitive final diagnosis of clear cell variant of calcifying epithelial odontogenic tumor was given. The tumor was surgically excised and submitted for histopathology reporting with regular follow-up of the patient.

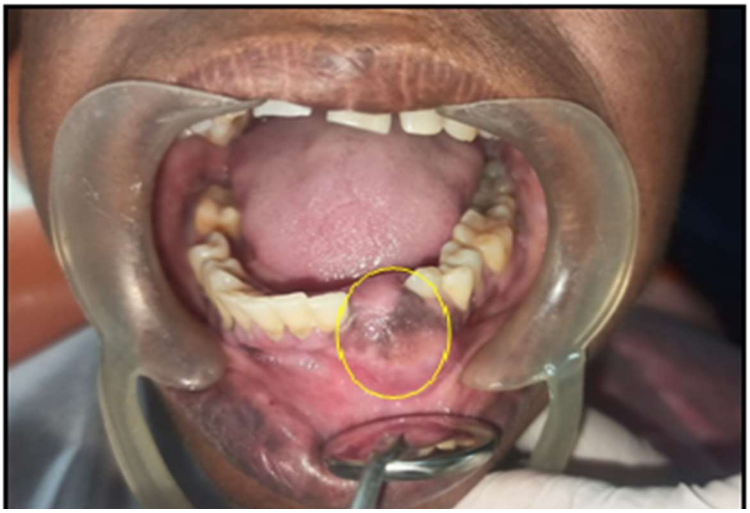


Figure 1: Unilateral diffuse swelling involving the gingiva and alveolar mucosa between 32 and 33

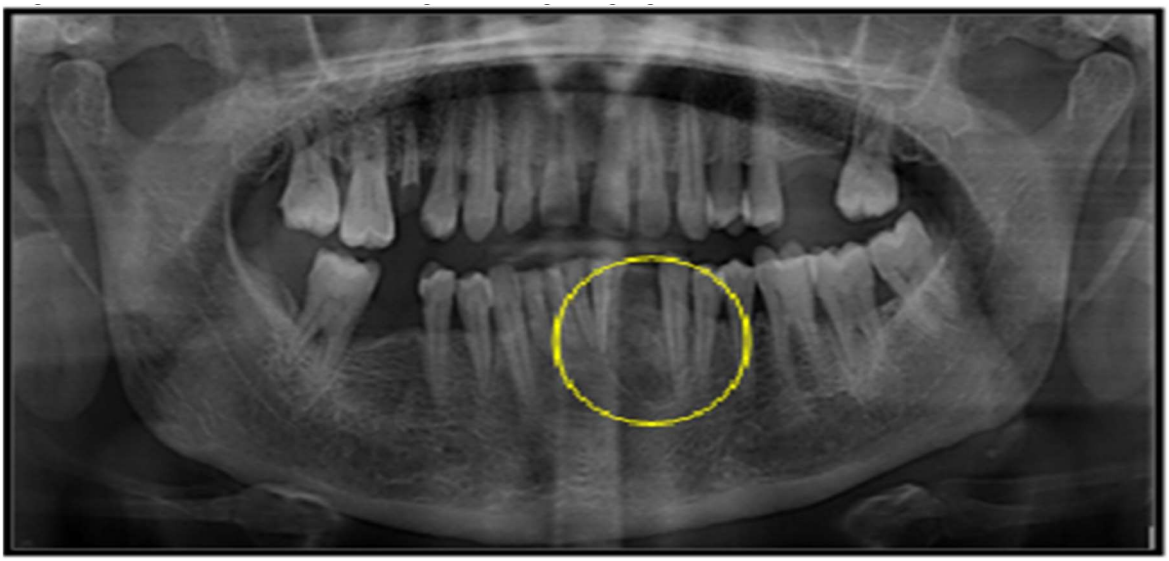
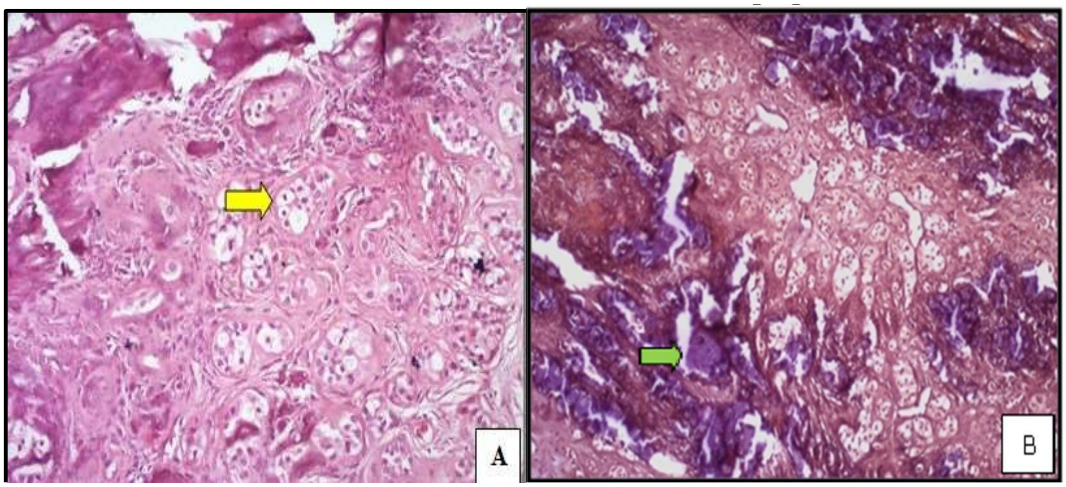


Figure 2: OPG revealing well defined radiolucency of 3x2 cms interspersed with flecks of radiopacities between 32 and 33 with thin radiopaque border



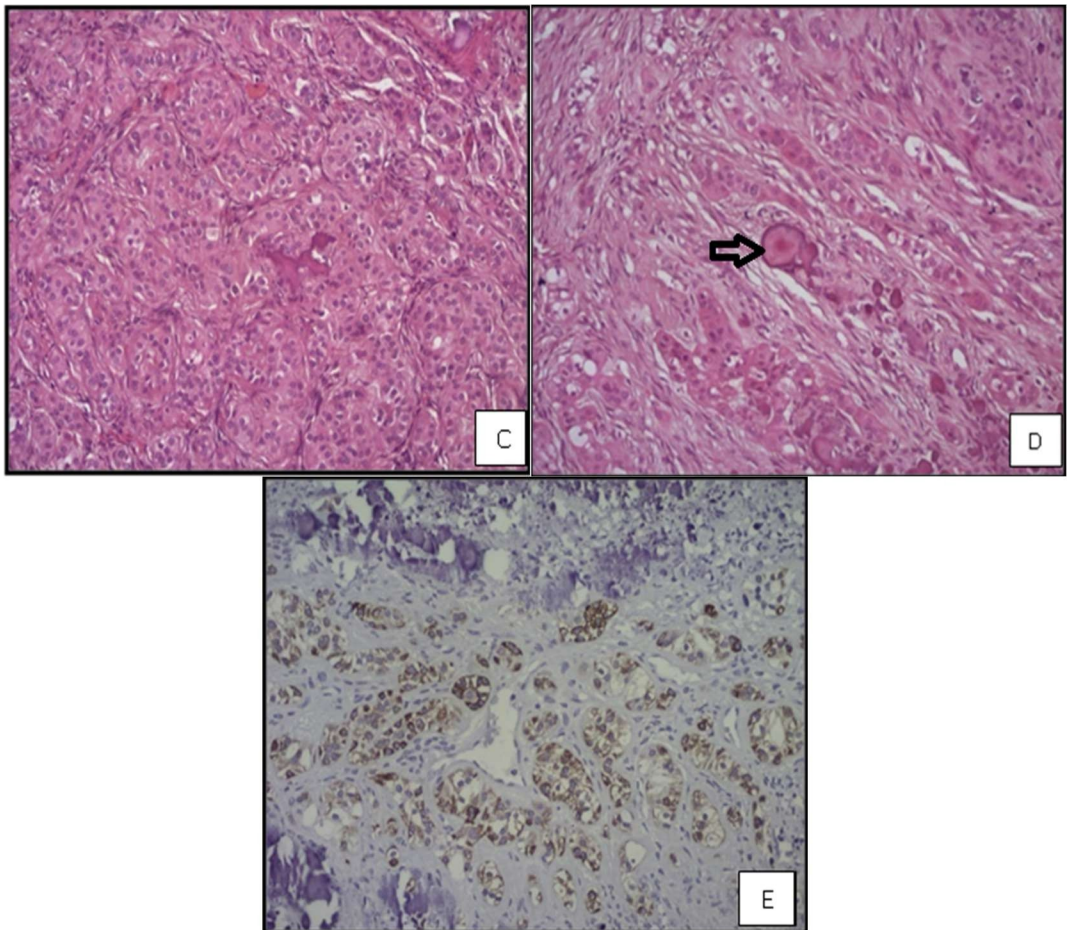


Figure 3: Photograph showing A. clear cells in CEOT (yellow arrow) (40X), B. calcification seen in CEOT (green arrow) (20X), C. nests and islands of polyhedral tumor cells with central nucleus (40X), D. concentric calcified lighter and darker areas resembling Liesegang rings (20X), E. CK19 positive odontogenic epithelial cells (40X)

DISCUSSION:

Dr. Pindborg in the year 1955 first described calcifying epithelial odontogenic tumor (CEOT) as an uncommon, benign odontogenic neoplasm. In 1992, the WHO classified it as a benign odontogenic tumor of epithelial tissue origin (6). The tumor characteristically contains numerous calcifying masses and homogeneous, eosinophilic amyloid-like material seen within the tumor epithelium and also in the connective tissue stroma. The CEOT has been reported previously in the names of calcifying ameloblastoma, malignant odontoma, adenoid ameloblastoma and cystic complex odontoma (3) (5).

CEOT is a slow-growing, locally aggressive tumor, reported frequently between 8–90 years with the average age of about 40 years. There is no gender predilection and it involves predominantly the mandible than the maxilla in a ratio of 2:1 (7). In our case the lesion presented in the anterior mandible, an unusual site which made it more special for reporting. The two clinicotopographic types are intraosseous (central) and extraosseous (peripheral) forms (8).

The etiology of Pindborg's tumor has been reported to originate from the stratum basale of the oral epithelium, REE (reduced enamel epithelium) or from the epithelial remnants of dental lamina (cell rests of Serrez) (3) (8). The intraosseous form seems to arise from the stratum

intermedium of the enamel organ and the extraosseous type is from the cell rests of Serrez or from the stratum basale of the gingival epithelium. CEOT arising from within the jaw bones are reported to be more aggressive with an elevated recurrence rate of approximately 14% compared to its extraosseous counterpart (9)

The molecular biology of CEOT remains unclear, but mutations in the AMBN (ameloblastin) gene which plays a major role in the process of cytodifferentiation of dental tissue and is highly expressed during the differentiation of the inner enamel epithelium, have been identified in CEOT and also in other odontogenic epithelial tumors such as ameloblastoma, squamous odontogenic tumor, and adenomatoid odontogenic tumor. This suggests a possible role in the tumorigenesis of these odontogenic tumors. Additionally, mutations in the PATCH1 gene has also been found in both calcifying epithelial odontogenic tumors and Odontogenic keratocysts though the significance of such mutations remain unclear. Mutations of p53 gene has been reported by Demian et al (2010) with evidence of his case showing malignant transformation and distant metastasis. Henceforth, the gene could serve as a potential biomarker (10) (11) (12) (13).

Radiographically, displacement of tooth within the tumor or at the periphery was a common finding (41%) (14). The radiographic presentation of the tumor can vary depending on its stage. In the early stage, it presents as a unilocular or multilocular radiolucent (soap-bubble) lesion, but in later stage, as the lesion progresses, areas of radiopacities increases. Radiological appearance of the lesion mimics complex odontoma, calcifying odontogenic cyst, ameloblastic fibro-odontoma, fibro-osseous lesion, odontogenic myxoma and osteoblastoma (13).

The five histological variations exhibited by CEOT includes, a) sheets or strands or islands of odontogenic epithelial cells with prominent intercellular bridges, b) A cribriform pattern with numerous spaces showing deposition of amyloid like substance which appears homogenous, eosinophilic with concentric calcified areas referred to as “liesegang-rings” c) densely packed tumour cells interspersed with MGC (Multinucleated Giant Cells) d) nests of epithelial cells resembling neoplastic glandular epithelium and e) prominent clear cells arranged in pseudoglandular manner interspersed with islands of polyhedral tumor cells (3) (15). The histopathological findings in this case is also similar showing numerous clear cells arranged in cords and small nests and also eosinophilic cells with pleomorphic nuclei and prominent intercellular bridges. The appearance of clear cells is because of intracytoplasmic glycogen (16). Hicks et al (1994) hypothesised that the clear cells present in CEOT could be linked with its aggressive behaviour (4).

Along with the typical microscopic features of CEOT, the deposition of eosinophilic substance resembling amyloid serves as an additional distinctive feature. The origin of this homogeneous material has been a debate. Yamaguchi et al (1980) reported the beta protein configuration in amyloid, which is similar to enamel matrix (8). Page (1975) has reported similarly that amyloid is the protein product of enamel organ in contrast to endocrine-associated or systemic amyloids. This homogenous amyloid-like material in CEOT when stained using congo red and viewed under polarizing microscope shows apple green birefringence. However, in the present case, the eosinophilic homogeneous material tested negative for Congo red birefringence. Due to the affinity of this amyloid-like material for mineral salts, this can undergo calcification leading to the formation of concentric lamellar bodies or Liesegang rings, which was observed in our case (13).

Immunohistochemically, positive immunoreactivity of tumor epithelial cells to AE1/AE3, CK5, CK6, Cam52 and p63 was found by Lee W et al in CEOT (17). Kumamoto et al found the positive immunohistochemical expression of tumor cells for CK 8, 19, and 13 (18) and similarly the tumor cells seen in this case also expressed CK19.

Treatment options for calcifying epithelial odontogenic tumor includes simple enucleation along with involved tooth to hemi-mandibulectomy in mandibular lesions and maxillectomy in case of maxillary lesions (19). Initially, due to the similar clinical appearances between CEOT and solid ameloblastoma, many experts have suggested aggressive treatment. However, recent evidences suggests that CEOT do not invade intertrabecular bony spaces, supporting conservative surgery as a treatment option for intrabony lesions. Additionally, mandibular tumors generally grow slower than maxillary tumors and tend to stay well-confined, requiring a wide surgical excision. The evidence of clear cells may denote increased tumor aggressiveness, which might require a more radical surgical intervention (20). Tumor-free surgical margins should be given in order to reduce the possibility of local recurrences (19). Hicks et al reported recurrence percentages of 14% for CEOT and 22% for clear cell variant associated with more aggressive behavior and malignant transformation of CEOT and so far only 7 cases are reported in the literature (4) (21).

CONCLUSION:

The clear cell variant of calcifying epithelial odontogenic tumor are less common, benign odontogenic tumors that predominantly affect the mandible than the maxilla and their origin remains a topic of ongoing debate. They can be locally aggressive and exhibit unpredictable clinical behavior. Although the radiographic features of CEOT appear distinctive, a biopsy is essential to confirm the histopathological variant of CEOT and treatment plan. Future research should focus on exploring the molecular and genetic concept of the clear cell variant of CEOT, and also for developing targeted drug therapies that could improve prognosis. This rare case report is one among the few cases available in the literature on clear cell variant of CEOT.

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