

# International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 2, Issue – 6, November - December - 2019, Page No. : 471 - 477

# Clinicopathological Correlation of Clear Cell Variant of Calcifying Epithelial Odontogenic Tumor Involving the Mandible

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Type of Publication: Case Report

**Conflicts of Interest:** Nil

## Abstract

Calcifying epithelial odontogenic tumour (CEOT) is a rare, locally invasive, slow enlarging benign tumour of odontogenic epithelial origin, accounting for 0.4-3% of all odontogenic neoplasm of jaws. Radiographically, it is unilocular/multilocular with classical driven snow appearance. Histopathological features reveal polyhedral neoplastic odontogenic epithelial cells with amorphous eosinophilic material in the connective tissue showing apple-green birefringence under polarized microscope.

A 65 year-old female patient reported with a firm, diffuse, non-tender swelling in mandible since last 2 years. Incisional biopsy revealed the presence of odontogenic epithelial cells with sharply defined cell borders and amorphous eosinophilic material with concentric calcified masses in the connective tissue. The striking feature was the presence of multiple clear cells with foamy cytoplasm and pyknotic nuclei within the connective tissue stroma. A confirmatory diagnosis of clear cell variant of CEOT was made after special stain and cytokeratin assay.

She was referred to the Department of Oral Surgery for management of the lesion.

Among other histopathological variants, clear cell type of CEOT is more aggressive with a higher recurrence rate. So proper clinicopathological and histopathological evaluation is necessary to delineate the actual treatment guide line.

**Keywords:** Amyloid, Apple-green birefringence, Clear Cell, CEOT, Odontogenic Neoplasm, Pindborg Tumor.

#### Introduction

CEOT is a slowly growing, benign, non-encapsulated and locally invasive, epithelial, odontogenic neoplasm with a

singular histomorphological pattern characterized by irregular sheets and islands of eosinophilic, polyhedral, and often pleomorphic cells, that eventually disintegrate into an eosinophilic, amorphous substance, which stains with amyloid markers and tend to calcify [1,2,3]. It was first described by Prof. J.J.Pindborg in the year of 1955 [4,5,6].

Etiopathogenesis of this neoplasm is controversial. Initially, the source of epithelial cells as suggested by Pindborg was the reduced enamel epithelium but now a days, various researchers believe that cells of stratum intermedium are responsible for the development of this neoplasm [4,7,8,9].

The incidence of this rare tumor ranges from 0.4 percent to 3 percent of all odontogenic neoplasm of jaws [7]. It can arise in patients of any age (ranging between 8 to 92 years) with a mean of about 40 years [4,10]. Generally, the tumor is intraosseous in nature (94 percent), while the other 6 percent is of extra osseous or peripheral variety. Intra bony tumor affect mandible twice as that of maxilla (mandible: maxilla - 2:1), mainly involving molar and premolar region (82 percent) [4,8], whereas extra osseous variant predominantly occurs in the anterior portion of jaw along with gingiva [11].

Clinically, CEOT is a slow enlarging, asymptomatic locally invasive swelling associated with expansion of the cortical plates [8]. Pain or paresthesia may develop based on tumor size, growth pattern, anatomical position and vicinity to neurovascular structure [11]. CEOT of maxilla may cause epistaxis, nasal obstruction and proptosis [1,12].

Radiographically, the tumor appear as an irregular, unilocular / sometimes multilocular (soap bubble in appearance) lesion with well-defined or diffused (1/5th cases) borders. One third of the lesion, seemed radiolucent as they are relatively shorter in duration and other two third showed mixed pattern due to the varying degree of calcifications and produce classical 'driven snow' type of appearance [4,8,10]. In those cases where tumor is associated with the impacted tooth, increased radiopacity close to the occlusal surface of impacted tooth may be noted, and described as 'coronal clustering 'by Pindborg [1].

Franklin and Pindborg enlisted the histological criteria for the diagnosis of classical CEOT [11,12], which comprises of sheets or islands or strands of polyhedral epithelial cells with sharply defined cell borders, and distinct intercellular bridges. Some of these neoplastic cells may appear as spindle shaped [5]. Nuclei are often pleomorphic but the number differs from one tumor to another. Nuclear atypia like binucleation, hyperchromatism and giant nuclei are also noted [5,13]. Mitotic figures are rarely spotted, but in case of malignant transformation, increased numbers of mitotic figures are found.

Within the tumoral stroma and in between the sheets of neoplastic odontogenic epithelial cells, various amount of extra cellular (either finely fibrillary material or small round to irregular homogeneous substance), hyalinized, acellular, amorphous substances are present [14,15], resemble amyloid like (pseudo amyloid) material. Calcifications, which are a distinctive feature of this neoplasm may develop within the amyloid like material and form 'concentric ring like' pattern (Lisegang Ring Calcification). These calcified areas tend to fuse and form large complex masses [1]. Several other histopathological varieties like Non-Calcifying CEOT, Clear cell variant CEOT, CEOT with Langerhans / Myoepithelial Cell differentiation, CEOT with cementum like substances [11], CEOT associated with giant cell [7], Cystic variant and Malignant CEOT [16] are also noted.

Innumerable treatment modalities has been applied to treat this tumor depending on several aspects such as tumor size, location, adjacent vital structures, patient's age – health status and operator's skill to reconstruct after surgery [11].

For mandible small, intra bony lesion with well-defined margins; can be treated by simple enucleation or vigorous curettage. But, the lesion with more advanced bone infiltration, resection of tumor or hemimandibulectomy should be the surgical approach followed by reconstruction procedures [17].

Maxillary neoplasm should be treated more aggressively, as it can expand more rapidly and invade within the vital structures. Recurrence of CEOT mainly occurs due to inadequate treatment, so 5 years follow up is mandatory to cure this benign neoplasm [4].

### 2. Case Report

A 65 years old female patient reported to the Department of Oral & Maxillofacial Pathology of Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata, India with the chief complaint of swelling involving the lower front teeth region since last 2 years. The patient gave a history of a small swelling involving the lower anterior teeth region associated with mobility of regional teeth which exfoliated on its own. She also noticed another swelling at the same region which increased gradually to attain the present size. No history of discomfort or paresthesia at the lower lip area was reported. Extra orally, there was a firm, diffuse, nontender swelling involving the mid portion of mandible. Overlying skin appeared normal without any regional lymphadenopathy. Intraoral examination revealed the presence of a well-defined lobulated firm, non-tender, non-compressible swelling involving the anterior region of partially edentulous mandible with marked expansion of buccal and lingual cortical plates along with destruction of alveolar ridge, extending from left premolar to right premolar region with obliteration of labial vestibule and presence of prominent vascular markings (Figure 1).



Figure 1: Extra oral clinical photograph (a) showing a diffuse swelling involving the mid portion of mandible. Intra oral photograph (b) showing the presence of well-defined lobulated swelling involving anterior portion of partially edentulous lower jaw with vestibular obliteration and vascular prominence.



Figure 2: Panoramic radiograph (OPG) (a) revealed the presence of round to ovoid, large, well defined unilocular radiolucent area involving symphysial region which crosses the midline. Standard occlusal radiograph (b) revealed multiple radio opaque foci of calcification with in the radiolucent area, mimicking 'driven snow' appearance, involving mandibular anterior region.

Orthopantomogram and standard occlusal radiograph revealed the presence of a large, irregular, ovoid radiolucent area crossing the midline of partially edentulous lower jaw in extending from left lower premolar (34) to right lower premolar (44). Multiple areas of radio opaque foci were also noted within the radiolucent area along with deviation of 35 and 36. A patient was otherwise healthy and all routine investigations were within normal limits (Figure 2).

Based on the above clinical and radiological findings the provisional diagnosis of benign locally aggressive odontogenic neoplasms and fibro osseous lesions were made.

Ethical clearance was obtained along with informed consent from the patient. An incisional biopsy was performed from the representative site of the lesion and specimen was sent for histopathological evaluation.

Light microscopic features revealed the presence of sheets of polyhedral neoplastic pleomorphic odontogenic epithelial cells with abundant eosinophilic cytoplasm and sharply defined cell borders along with well-developed intercellular bridges. Conspicuous homogenous eosinophilic amorphous materials were present in between cells and within connective tissue stroma. Irregular and concentric 'Liesegang ring' like calcified masses were also present within the connective tissue stroma. One of the most striking feature is the presence of multiple clear cells with foamy cytoplasm and pyknotic nuclei within the connective tissue stroma which stains positively with Periodic Acid Sciff (PAS) stain. A provisional diagnosis of clear cell variant of odontogenic tumor was made and to confirm this



Figure 3: High power photomicrographs (40x, H & E) (a,b,c) showing sheets of polyhedral, pleomorphic epithelial cells with abundant eosinophilic cytoplasm with sharply defined cell borders and well developed intercellular bridges along with multiple clear cells, areas

of irregular and concentric calcifications (blue arrow, ) © 2019 IJDSIR, All Rights Reserved and amyloid like amorphous eosinophilic material (orange arrow, ). High power photomicrographs (40x, PAS) (d) showing PAS positive clear cells. High power photomicrographs (40x, IHC) (e,f) showing CK 14 & CK 19 positive epithelial cells.

diagnosis, immunohistochemical (IHC) evaluation was performed. IHC markers such as cytokeratin 14 and 19 confirmed the presence of odontogenic epithelium within the neoplasm (Figure 3). Congo Red staining of homogenous amorphous amyloid like material revealed typical apple-green birefringence under confocal microscope with polarized light (Figure 4).

Keeping all the microscopic features in mind, the diagnosis of 'Clear Cell Variant of CEOT' was made and the patient was referred to the Department of Oral Surgery for further surgical treatment and management.



Figure 4: Low power (a) (10x, Congo red) & High power (b) (40x, Congo red) photomicrograph showing apple green birefringence of amyloid like material, under polarised microscope.

#### Discussion

CEOT is a locally aggressive, benign neoplasm of odontogenic epithelial origin which rarely arises in the dento-alveolar complex in comparison to other odontogenic tumors. Though the tumor is termed by Shafer *et al.* as 'Pindborg Tumor' [18], but Thoma and Goldman reported the first case as an 'Adenoid Adamantoblastoma' in 1946 [14,19]. In the year of 1971, WHO accepted and adopted the term CEOT and in 1992 categorized it as benign odontogenic tumor with entirely epithelial origin [5].

Clinically, according to various literature, the tumor presents as a slow growing painless mass, mostly affecting the mandibular premolar-molar region associated with expansion and destruction of cortical plates [4,9]. The patient under discussion was a senior citizen, aged 65 years presented with a well-defined swelling in anterior portion of lower jaw, causing expansion of buccal and lingual cortical plates and destruction of alveolar ridge. These clinical findings are similar to the observations reported by the authors of different studies [1,8,11,12]. In 52 percent of cases the tumor is concomitant with an impacted tooth [11]. Though it is not present in our case.

The conventional radiological features of CEOT usually exhibit a unilocular or multilocular radiolucencies with radio opaque flakes of calcifications which appears as 'driven snow' type [4,8,10]. The panoramic and occlusal radiological view of the present case also revealed the same imaging features.

Under light microscope, histopathological sections of CEOT revealed the presence of polyhedral neoplastic odontogenic epithelial cells having distinct border and inter cellular bridges with nuclear pleomorphism and granular cytoplasm [11,18]. Within the tumoral stroma there is presence of eosinophilic amorphous amyloid like material and areas of concentric calcification suggestive of 'Liesegang rings' which coalesce together and form irregular calcified masses [1]. Several histopathological variant of CEOT have been reported, among them clear cell type is very rare and consisting of cells with pyknotic nucleus and clear foamy cytoplasm which is PAS positive, due to presence of intercellular glycogen [8,19]. According to one hypothesis, clear cells are formed due to aberrant degeneration of the odontogenic epithelial cells [16]. Another hypothesis, stated by Yamaguchi et al., at 1980 suggested that these clear cells are the features of cytodifferentiation rather than a simple degenerative process [4,8]. Other researchers suggested that the amorphous material of the tumor appear eosinophilic in H and E staining and took mahogany brown color in Iodine staining [20]. These amyloid like materials also stain positively with Congo Red stain (C33H22N6Na2O6S2) and produce apple green birefringence under polarized light. Under fluorescent microscope above mentioned substance emitted yellow intense light and apple green light after staining with Thioflavin T and Thioflavin S stain respectively [1]. Immunohistochemically, various types of Cytokeratin (CK) expression is noted in the tumor cells. Consistent positive reaction, especially in strongly eosinophilic cells, is given by CK "cocktail" antibodies like KL-1, AE1/AE3, and TK [21,22,23]. Kumamoto et al., in 1999 [24] along with other researchers [25,26] detected certain high molecular weight CKs like CK-1, CK-5, and CK-14 in his study whereas, later in 2017, R. P. Chatterjee et al observed CK-8 positivity too [8]. The low molecular weight CK-19 was also detected in several studies, but not in all tumors [22,26].

In the present case, neoplastic cells revealed similar tissue morphology, cellular architecture and staining characteristics of CEOT after proper histopathological and immunohistchemical staining. These histopathological and immunohistochemical features help to differentiate it from other clear cell neoplasms like Metastatic Renal Cell Clear Cell Odontogenic Carcinoma. Carcinoma. Peripheral Ameloblastoma with Clear Cell differentiation, Mucoepidermoid Carcinoma, Acinic Cell Carcinoma, Clear Cell Carcinoma of the salivary gland, Clear Cell variant of Oncocytoma, Hyalinizing Clear Cell Carcinoma of the salivary gland (HCCC) and Glycogen-rich Adenocarcinoma [4].

The method of treatment varies from simple enucleation or curettage to hemi-mandibulectomy or hemimaxilectomy. This histopathological variant is more aggressive than other types with recurrence rate of 22 percent [11]. Periodic follow up is mandatory, to detect recurrence and initiate early treatment.

#### Conclusion

Though CEOT is exclusively benign in nature, some variants are characterized by high propensity to invade in the adjacent structures. So proper clinicopathological evaluation is necessary which delineates the actual treatment guideline.

Acknowledgements- Our deepest gratitude to Prof. (Dr.) R.R. Paul for his continuous support. I would like to thank Prof. (Dr.) Amit Roy and Prof. (Dr.) Kousik Dutta for their immense help. I am highly grateful to Mr. Samir Bose, laboratory technician, to make histological preparation of the specimen possible. I am thankful to all other faculty members of my department like, Prof. (Dr.) Sk. A. Mahmud, Dr. R. P. Chatterjee, Dr. Neha Shah, Dr. Swagata Gayen, for their encouragement. There is no conflict of interest related to this study.

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