

Review article

Calcifying Epithelial Odontogenic Tumor (Ceot)

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ABSTRACT

Calcifying epithelial odontogenic tumor is a rare benign epithelial odontogenic lesion that comprises from 0.2% to 1.1 of all odontogenic tumors. In the past a number of different names have been given to this lesion, such as calcifying ameloblastoma, cystic complex odontoma, uncommon ameloblastoma with calcifications and others. There is a need to study and explore various aspects of this tumour, this article gives a broad idea of the various aspects of this tumor and which aspect of this tumour needs more investigation

Key words: Tumour, Calcifying epithelial odontogenic tumour (CEOT).

DOI: <http://dx.doi.org/10.3329/bjms.v13i1.17378>

Bangladesh Journal of Medical Science Vol. 13 No. 01 January '14 Page 14-19

introduction:

Tissue that contribute to the formation of teeth undergoes stages of differentiation concomitant with the period over which the entire dentition is developing and in mature form may persist in the jaws not only while the individual retains any teeth but also after they become edentulous. Any of the tissues participating in this process may be involved in the development of malformations (hamartomas) or neoplasm's, collectively often referred to conveniently as odontogenic tumors¹. CEOT is a rare benign epithelial odontogenic lesion that comprises from 0.2% to 1.1 of all odontogenic tumors. In the past a number of different names have been given to this lesion, such as calcifying ameloblastoma, cystic complex odontoma, uncommon ameloblastoma with calcifications and others.

In 1856, Pindborg delineated this lesion as a distinct entity and named it the calcifying epithelial odonto-

genic tumor². In 1963, along with a comprehensive review of the literature, Shafer et al.³ suggested the eponym "pindborg tumor". Some authors suggested that the epithelial cells of the pindborgs tumor are reminiscent of the enamel organ in the tooth development some hypothesize that pindborg tumor arises from remnants of the primitive dental lamina found in the initial stages of odontogenic and these epithelial rests are the more likely true progenitor cell. The definitive etiology of this neoplasm still remains enigmatic^{3,4}.

Over the years, there have been a lot of articles published regarding CEOT, but none of them have a concised description regarding all the aspects of this particular tumor, and there have been over lap of description regarding this tumor from different authors and this is one of the big difficulties in understanding the exact nature of this lesion. This article is an attempt to describe all the aspect of this

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tumor for the purpose of understanding this tumor better.

CEOT as a benign tumor under the heading neoplasms and other tumors related to odontogenic apparatus⁵. Histologic classification, they consider CEOT to be a benign neoplasm or tumor related to the odontogenic apparatus with odontogenic epithelium without odontogenic ectomesenchyme. Latest histologic classification there is no difference and they consider CEOT to be a benign neoplasm or tumor line lesion arising from the odontogenic apparatus, with odontogenic epithelium with mature, fibrous stroma and without odontogenic ectomesenchyme⁶.

Incidence & prevalence and relative frequency

The CEOT has one of the lowest frequency ranking on a "hit list" of odontogenic tumors. The peripheral or extra osseous variant constitutes about 6% of the total number of CEOTs.

Age

According to Neville⁷ and Shafer³ the mean age of occurrence is 40 years. According to Regezi⁸ and Everson⁹ it occurs more in young & middle aged persons in between 30 & 50 years and according to Riechart¹⁰ it occurs in young & middle aged adults 8-92 years at the time of diagnosis with mean 36.9 years. Intra osseous type = 8 to 92 years, Extra osseous type = 12 to 64 years

Sex

According to Neville⁷, Regezi⁸ and Everson⁹ CEOT does not show sex predilection. According to Shafer³ CEOT show no significant difference in gender with men = 49% and women = 51%, and according to Riechart¹⁰ male: Female, for intraosseous = 80:81 and Male: Female, for extra osseous = 6.5, peak incidence for men = 3rd decade, peak incidence for female = 4th decade.

Site

CEOT commonly occurs in molar premolar region with 2:1 of mandibular & maxilla ratio and undoubtedly the associated with an unerupted or embedded tooth^{7,8,10-13}. CEOT in the maxillary sinus have been reported, Gon¹³ and Cameron¹⁴. CEOT with intracranial extension have been reported¹⁵.

Pathogenesis

Pindborg was initially of the opinion that the CEOT was of odontogenic origin and developed from, the reduced enamel organ of the unerupted tooth¹¹. The

cells from which these tumors are derived are unknown, although the dental lamina remnant and the stratum intermedium of the enamel organ have been suggested^{3,8}, tumor cells also bear close morphologic resemblance to cells of the stratum intermedium of enamel organ⁸. The appearance of report of cases of intra osseous CEOTs without an associated unerupted tooth and particular case of the peripheral variant – it became evident that other sources than reduced enamel epithelium should be considered when discussing the histogenesis of CEOTs, the peripheral location strongly suggests the possibility that the tumor arises from rests of the dental lamina or from the basal cells of oral epithelium¹⁰.

Macroscopic

The intraosseous located CEOT is often easily enucleated, and the tumor size varies from 1 to 4cm in diameter. The mass varies in color from grayish white or yellow to tan pink. Bisecting the specimen usually reveals calcified particles that make a crumbling sound during cutting. The tumor may be solid or contain minute cystic spaces. If associated with an unerupted tooth, the crown (or hard dental structures of an odontoma) can be found embedded in the tumor mass.

Microscopy Histologic definitions:

According to the WHO classification¹⁶ a CEOT is "a locally invasive epithelial neoplasm characterized by the development of intra epithelial structure, probably of an amyloid like nature, which may become calcified and which may be liberated as the cells break down".

Histology

The CEOT has a unique and sometimes bizarre microscopic pattern⁸. It has discrete islands, strands or sheets or polyhedral epithelial cells in fibrous stroma⁷. Occasionally, the cells are arranged in cords or results, mimicking adenocarcinoma, the nuclei are frequently pleomorphic, with giant nuclei and multinucleation being quite common but mitotic figures rare. The tumor cells in some lesions are characterized by extreme morphologic variation with severe cellular abnormalities, minimizing those often seen in some highly malignant neoplasm, while other cases of the CEOT are composed of very monomorphic, innocuous appearing tumor cells; yet, the biologic behavior does not differ between the two³.

There is no fundamental difference in histomorphol-

ogy between the intraosseous and extra osseous variants of CEOT except for the minimal amount or total lack of calcified material in the later¹⁰.

Occurrence of amyloid

In the CEOT the tumor island frequently enclose masses of hyaline (amyloid – like) material. This results in cribriform appearance⁷. This eosinophilic substance has been variously interpreted as amyloid comparable glycoprotein, basal lamina, keratin of enamel matrix. In most cases, it stains metachromatically with crystal violet, positively with Congo red, and fluorescence under ultraviolet light with thioflavin T, all in a fashion similar to amyloid.

Though there have been several views about this amyloid like (Pseudoamyloid) materials, like its origin from light chain fragment of immunoglobulin molecule¹⁷, origin from immune amyloid or amyloid of unknown origin¹⁸ and its similarity to enamel matrix¹⁹ and few stain & technique which proved the similarity of this material to amyloid, there has been no proof by any technique that it is amyloid. So there has to be more research done on two with never & promising technique.

Occurrence of cementum like components of CEOT stroma

These calcifications are sometimes in large amounts and often in the form of liesegang rings. The calcification actually appears and occur in some instances in globules of amyloid like material, many of which have coalesced and are transformed from being PAS (periodic acid – Schiff)- Negative to PAS – Positive during this calcification process³. It has been suggested that the amyloid- like material is an inductive stimulus for the stromal cells to differentiate towards production of a collagenous matrix that is destined to mineralize and resembles cementum. It should, however, be remembered that the majority of calcified homogenous matter of CEOT stroma is thought to be dystrophic calcification¹⁰.

The future

Study should be done as to whether the globules of amyloid like material from which calcification occur resembles or have any of the properties of cells of dental follicle

Occurrence of clear cells:

In this type, the tumor cells exhibit a clear vacuolated cytoplasm rather than on eosinophilic cytoplasm. The nucleus may remain round or oval in the center of the cells or be flattened against the cell mem-

brane. Most of the clear cells are mucicarmine negative, the clear cells may comprise the bulk of the tumor cells while, in others, they consists of only a few scattered foci³. It is believed that clear tumor cells represent a simple degenerative phenomenon⁶. In a case of clear cell variant showed positive Immunohistochemical staining for wide spectrum cks, ck8, 13 and 19 indicating an odontogenic origin²⁰.

The future

If the clear cell are considered to be a degenerative phenomenon why does it have a specific age range of 45.9 years and if the IHC indicates it to be odontogenic origin why is it less related to unerupted tooth needs to be ascertained in future studies.

Occurrence of Langerhans cells

In two cases reported the tumor chiefly consisted of scattered small islands of epithelial cells. In some nests there were few, occasionally several, clear cells positive for S-100 protein, lysozyme, MT1 LN- 3, and OMT 6 antibodies, but not for keratin antibody. Almost no calcification of homogenous eosinophilic material was observed. Ultra structurally the S-100 positive cells were identified as Langerhans cells based on the finding of rod and tennis, racket shaped Birbeck granules^{21,22}.

It has been clearly ascertained that Langerhans cells function as antigen presenting cells and as allogenic stimulator cells to primed T lymphocytes in the epithelium^{23,24}. Langerhans cells – rich variant of CEOT may have distinct predilection for occurrence in the anterior and premolar region of maxilla, compared to clinical CEOTs occurring usually in the molar and ascending ramus area of the mandible.

Occurrence of myoepithelial cells

In a study, one population constituted the classic polyhedral epithelial cells, and the others comprised cells arranged peripherally with elongated profiles and juxtaposed to the tumor epithelial cells. The later cells exhibited a large number of cytoplasmic fine filaments with occasional electron dense areas similar to those seen in the smooth muscle type cell. These cells found to extend basally around the tumor epithelium in most of the epithelial islands examined. They showed a lamina densa continuous with that of the neighboring epithelial cells and demonstrated a large number of hemidesmosomes. However desmosomes between these cell and tumor epithelial cells were not present. The ultra structural char-

acteristics of these cells were interpreted to those of myoepithelial cells. This cell type, although found in tumors of glandular origin, has not been described previously in any of the odontogenic tumors and its occurrence in CEOT has so far not been confined in other electron microscopic studies of this tumor¹⁰.

Combined epithelial odontogenic tumors

First case of presence of CEOT like areas within two cases of adenomatoid odontogenic tumors was reported in 1983 & later which was named as combined epithelial odontogenic tumors²⁵. A total of 24 cases of histologic CEOT /AOT variant have been reported²⁶.

Recommendation and Conclusions

There is nothing to indicate that a CEOT/AOT lesion reflect a true combination of two distinct and separate odontogenic tumor entities and there are no reported cases of AOT in which CEOT – like areas predominate lastly, all published cases of the CEOT/AOT variant show a biological behavior identical to that of an AOT; that is, truly benign (harmartomatous) odontogenic lesions. Apart from histologically combined appearance of this lesion, the radiographic pattern can also help in analyzing & to differentiate this lesion to a minimal level.

Extra osseous type

Extra osseous type of CEOT was first observed by Pindborg². The lesion is less infiltrative in character than their central counter part¹⁰. The opinion that tumor arises from the reduced enamel epithelium or possibly that the oral epithelium may be site of origin needs greater amplification²⁷. The peripheral location further suggests the possibly that it arises from rests of dental lamina which are located in the gingival, or from the basal cells of the surface epithelium. In a case, connection between the tumor and mucosal epithelium was noted^{28,29}. The mean age for occurrence is 34.4 years and mostly shows female predilection^{30,31}, why there is predominance of clear cells in most extra osseous types should be prodded and the level of aggressiveness in extra osseous CEOT with increased clear cells should be compared.

IHC (Immunohistochemistry)

In a study examination of CEOT immunohistochemically for localization of intermediate filament proteins, the tumor epithelium cells were slightly positive or negative for (monoclonal keratin bodies) PKKI detectable keratins, but slightly to strong pos-

itive for KLI (monoclonal keratin bodies) and TK (polyclonal anti- keratin antibodies), tumor epithelium was slightly positive for vimentin but negative for desmin³². Two enamel proteins, amelogenin and enamelin were located in small foci in a case of CEOT when detected immunohistochemically³³. Localization of fibroblast growth factor FGR -1 and FGF – 2 and receptor FGFR2 and FGFR3 in the epithelium of human odontogenic tumors was done immunohistochemically, CEOT showed positivity for FGF 2 and receptor FGFR – 2 while FGF and the receptor FGFR3 were absent or weakly detected³⁴ one case demonstrated reactivity for hepatocyte growth factor (HGF); transforming growth factor ? (TGF-?) and their receptor by neoplastic cells of CEOT immunohistochemically²⁰. P63, CK 5/6, calponin low molecular weight cytokeratin (CK7) and glial fibrillary acidic protein in one case were positive³⁵.

Recommendations

Though CEOT shows positivity for many tissue specific lineage markers, its importance in immediate and precise identification & in prediction of prognosis and response therapy should be seriously considered.

Ultra structural study:

Studies have been conducted on ultra structural localization of alkaline phosphatase in calcifying epithelial odontogenic tumor³⁵. The majority of enzyme activity was associated with the adjacent stromal tissue. The reaction product of alkaline phosphatase was also detected in same membrane bound vacuoles (lysosomes) and the Golgi apparatus of tumor cells. It suggested that the appearance of enzyme activity associated mostly with epithelial cells membranes may be related to transport function of cell membranes. Is alkaline phosphate related to calcification process in case of CEOT still needs to be studied in future with greater interest.

J. Treatment & recurrence

It is evident that long term follow up information is required for the CEOT in order to choose the best treatment modality and assess the incidence of recurrence. Some authors have seen recurrences even after several decades and recommend a radical line of treatment others consider conservative surgery as the treatment of choice. In its ability to recur if treatment is not adequate, the CEOT is similar to the solid/ multicystic ameloblastoma, and although its growth pattern may be slower, some believe that the

two should be treated with an identical approach. As reported by Waldron³⁶ and Hansen³⁷, the occurrence of clear cells may prove to be sign of increased tumor aggressiveness indicating the need for more radical surgical approach.

k. Recommendations and conclusions

Correlation between the prognosis of CEOT and occurrence of Langerhans cells also needs further investigation. In view of the biological behavior of the CEOT destructive procedures such as a wide resection or hemi resection of mandible seen unwarranted. Enucleation with a margin of macroscopic normal tissue is therefore the recommended treatment for lesions involving the mandible. CEOT of maxilla however, should be treated more aggressively, as maxillary tumors generally tend to grow more rapidly than their mandibular counterparts and not usually remain well confined. Treatment should be

individualized for each because the radiographic and histologic features may differ from one lesion to another. Although it has not been established in the literature, 5 years should be absolute minimum follow-up necessary to assess the care for CEOT. Although many more cases are needed to evaluate the prognosis for the extra osseous or peripheral variant of the CEOT, none of the 11 cases published so far has shown signs of recurrence after conservative Enucleation. Treatment should also include the awareness of the people of their responsibilities regarding their own health, it is important that people should be encouraged to immediately report to a doctor whenever they see any unusual swelling any discomfort and not wait for the swelling to grow and cause great discomfort & jeopardy to themselves in future. The rapid growth of the mass usually imposes additional challenges to the treating team as it will compromise airway and feeding³⁸.

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