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Revisiting Pindborg Tumor: A Rare Odontogenic Enigma

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ABSTRACT:

Pindborg tumor, also known as Calcifying Epithelial Odontogenic Tumor (CEOT), is a rare odontogenic neoplasm first identified by J.J. Pindborg. This tumor is exclusively epithelial in origin and accounts for less than 1% of all oral tumors. CEOT typically presents as a painless swelling, often associated with unerupted teeth, with both intraosseous and extraosseous variants. Radiographically, it may exhibit a distinctive "honeycomb" or "driven snow" appearance due to calcifications. Histologically, the presence of amyloid-like material and Liesegang rings serves as a key diagnostic feature. Although generally benign, the tumor may exhibit aggressive behavior in rare cases, especially in its clear cell variant. This review aims to provide a comprehensive overview of the tumor's epidemiology, clinical features, radiographic characteristics, histologic patterns, and management strategies to aid in accurate diagnosis and treatment planning.

Keywords: Pindborg tumor, Calcifying Epithelial Odontogenic Tumor, CEOT, odontogenic tumors, amyloid-like material, Liesegang rings, oral neoplasms, clear cell variant, odontogenic epithelium.

INTRODUCTION:

Odontogenic tumors are rare tumor variants that most commonly occur in the tooth and occasionally occur the in jaws. They usually arise from abnormal proliferation of odontogenic epithelium and odontogenic mesenchymal cells[1]. Classifying these odontogenic tumors has made our understanding towards them better and is crucial to make an accurate diagnosis and to identify its distinguishing features of each odontogenic neoplasm. Additionally it helps us predict the prognosis and potential recurrence of neoplasm. WHO 2022 (fig 1) has classified odontogenic tumors into four, it includes tumors that are benign epithelial odontogenic tumors, benign mixed epithelial and mesenchymal odontogenic tumors, benign mesenchymal odontogenic tumors and malignant odontogenic tumors[2].

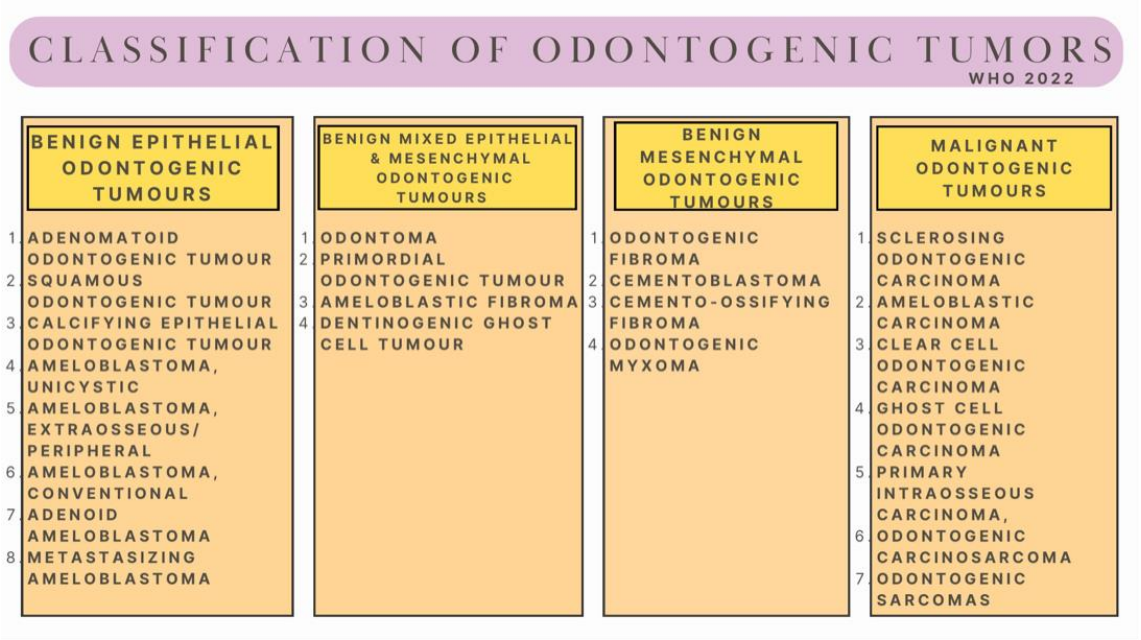

Fig 1. Classification of odontogenic tumor

The WHO classifies odontogenic tumors as rare tumor variant, as they regard for less than 1% of all oral tumors.[3,4] An interesting tumor variant which was was first introduced more than 50 years ago by J.J Pindborg exclusively occurs only in epithelial component[5].In 1856, Pindborg mapped the tumor as a separate entity and named it " calcifying epithelial odontogenic tumor" [6,7]. Many authors suggested that this interesting tumor was first described by Homa and Goldman ten years before Pindborg himself and they named this tumor as adenoid-type adamantoblastoma[8,9].This tumor goes by a bewildering array of names such as adenoid type adamantioblastoma[8,9], adamantioblastoma[8,10], ameloblastoma of unusual type with calcifications[8,11], malignant odontoma[8,12], and cystic complex odontoma[8,13].It is said that Pindborg first described four cases of these unusual tumors which later was coined as "Pindborg tumor" by Shafers *et al*[5]. *T*his review of the literature aims to provide insight into every aspect of Pindborg's tumor and provide more insights and a more concise learning experience.

EPIDEMICS:

Epidemiological studies conducted for the occurrence of odontogenic tumor has shown a great variance in their incidence and distributional pattern. It has been reported more than 350 times in literature[14]. The incidence of odontogenic tumor was found to be around 2.17% with males being more commonly affected than females[15]. The favorite location for these tumor is commonly noted in the posterior mandibular region which accounts for almost two-thirds of its occurrence[1]. Out of the occurrence of odontogenic tumor, ameloblastoma occurs more frequently.

PATHOBIOLOGY:

Several authors have various explanation to demonstrate the formation of CEOT. Pindborg originally suggested that CEOT arises from reduced enamel epithelium of unerupted teeth[6,16]. other researchers suggest it could arise from stratum intermedium cells because of the morphological resemblance of the cell. Other researchers suggest that primitive dental lamina could be the source of cells for CEOT, however this does not explain the occurrence of CEOT without the involvement of an unerupted tooth or tumors occurring in the jaws. The exact pathogenesis of this tumor is relatively unknown[17]. (Fig 2)

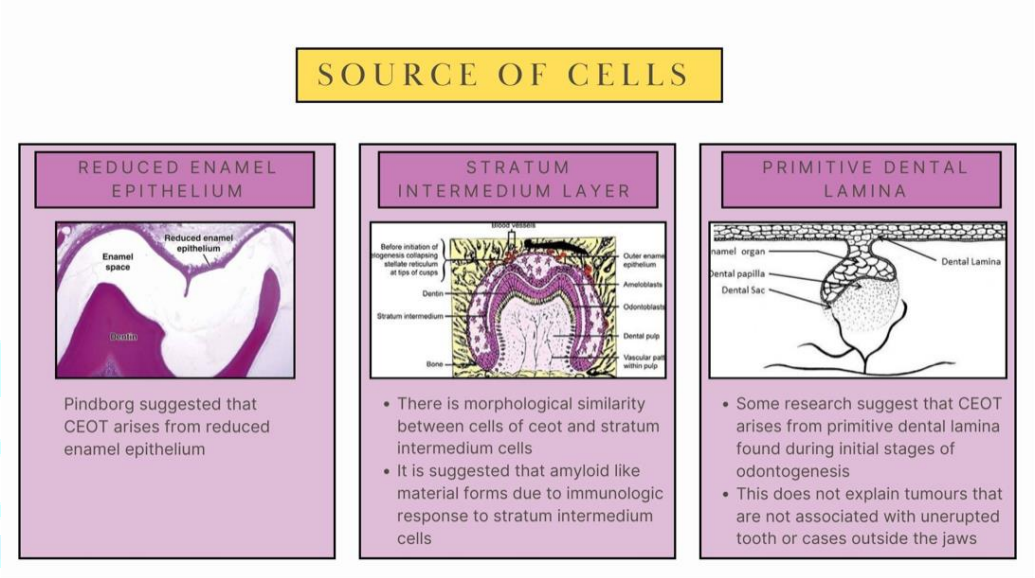

Fig 2. Source of cell for pathogenesis of Pindborg tumor

The pathogenesis is described by Z.S Peacock[18] as PTCH1 gene undergoing the sonic hedgehog pathway which influences embryonic development and regulates odontogenesis through epithelial-mesenchymal interaction. Hence, he suggested that dysregulation in the PTCH1 gene results in the formation of CEOT.

CLINICAL PRESENTATION:

With the least frequency ranking on the “hit list” of odontogenic tumors, it commonly occurs in middle age with a mean age distribution of 40 years[17]. According to Neville[6,21], Regezi[6,20], Everson[6,22] it shows no gender predilection. According to Shafers[17] there is an occurrence of CEOT in 49% of males and 51% of women. It clinically presents as a painless swelling with slow growth. Only a few cases have been reported where aggressive tumor is seen invading other surrounding structures and very rarely malignant transformation is also observed[23]. It is 52% of the time associated with an unerupted or impacted tooth. CEOT can cause tipping, rotation, mobility or migration of the tooth which is later followed by root resorption[5].

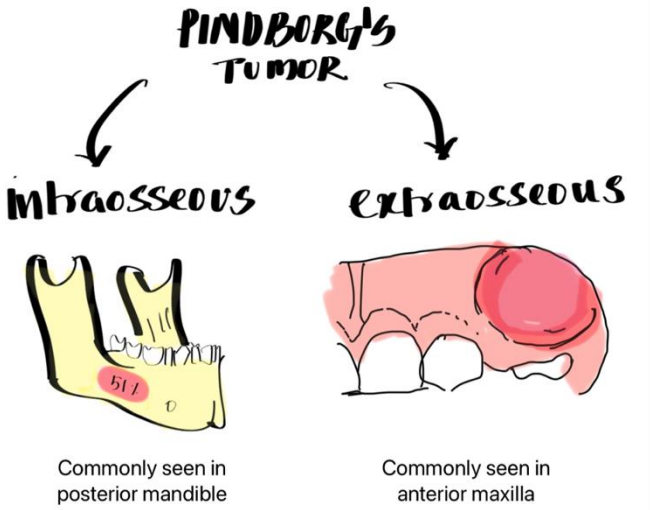

Fig 3. Variants of CEOT

There are primarily two variants of CEOT which are intraosseous and extraosseous, (fig 3) the latter being very rare in occurrence is seen commonly in anterior gingiva except for one case that was reported in upper lips[17]. The Extraosseous variants were first observed by pindborg[6] which are non-specific, sessile gingival masses[24] and are less infiltration than the intraosseous variant . The intraosseous variant occurs more commonly in the mandible than the maxilla with a 71% chance of prevalence. It has 51% more chances of manifesting in mandibular molar regions than cuspids. In very few cases where the maxilla is affected, the patient complains of nasal blockage, headache and nasal bleeding[25]. The intraosseous variant varies from 1 to 4 cm in diameter. The tumor exhibits a spectrum of colors including grayish white, pink or yellow[6].

RADIOGRAPHIC PRESENTATION:

Shafers[17] described that initially, it appears as radiolucent which mimics a dentigerous cyst as it is often associated with unerupted or impacted teeth. In its second phase of development, small intramural calcifications are observed with osseous destruction, in the final phase of CEOT, it gives rise a to honey comb appearance. (Fig 4)

The radiograph above reveals a honeycomb pattern where both of the cases are associated with an impacted tooth. 58% of the time CEOTs are unilocular whereas 27% of the time it is multilocular, the remaining 15% of the time it is nonloculated[26].

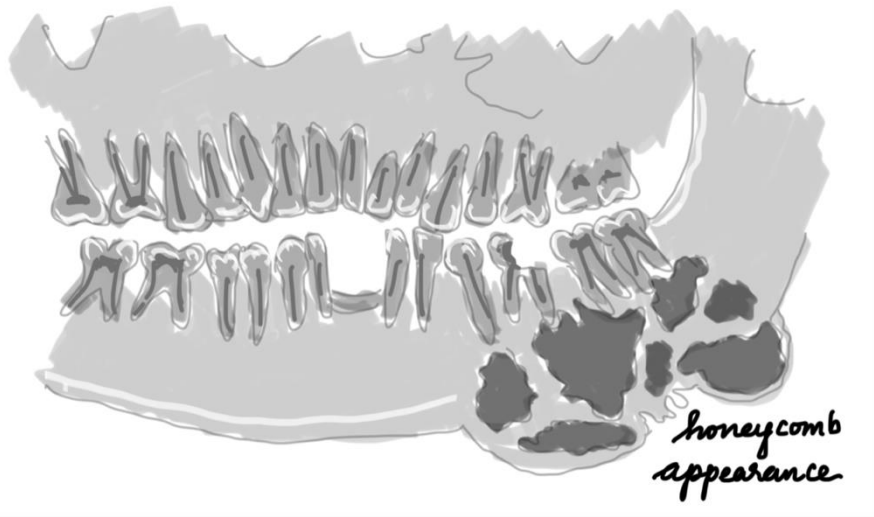

Fig 4. Honeycomb Radiographic appearance

The characteristic feature of CEOT observed in a radiograph is 'driven snow appearance'[17], where scattered flecks of calcification is seen throughout the radiolucency. (Fig 5)

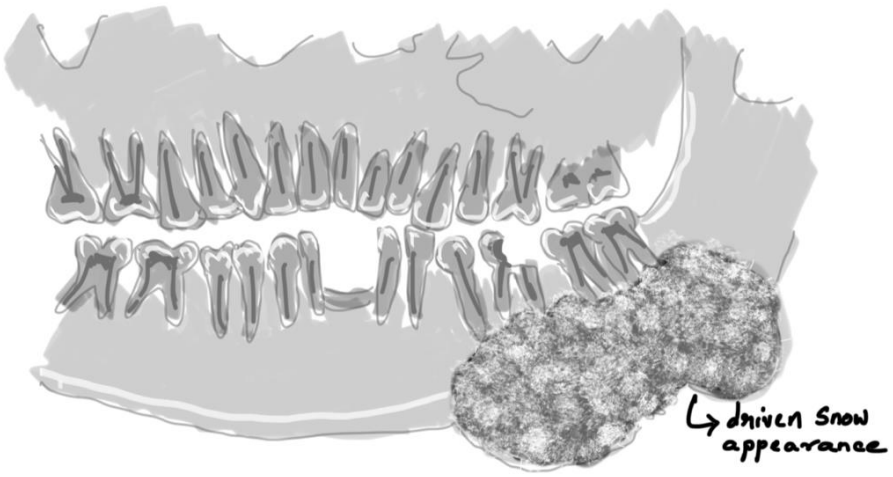

Fig 5. Driven snow appearance seen in CEOT

To analyze the extent of facial bones, jaw and skull involvement, advanced imaging techniques can be used. A CT of CEOT usually reveals scattered radiopaque foci with thinning of cortical plates and a well defined mass. MRI imaging shows hyperintense T2 weighted and hypointense weighted images[13].

HISTOLOGIC ARCHITECTURE:

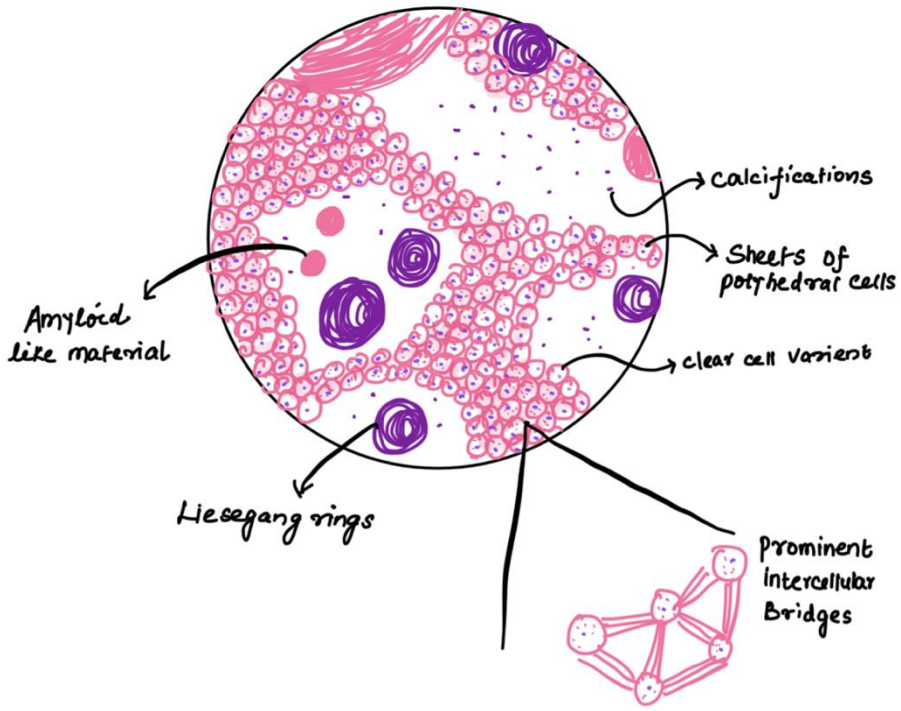

Fig 6. Histologic pattern of Pindborg's tumor

WHO defined Pindborg's tumor as "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 th cells break down" [27].

CEOT has a unique histological pattern which could be bizarre[6] (Fig 6). It is unencapsulated, infiltrating tumor. The distinctive feature of CEOT is the presence of calcifications and amyloid like material. Absence of mineralization can lead to misdiagnosing the case as squamous cell carcinoma which has a very disastrous consequence during its management[28].

EPITHELIAL CELLS:

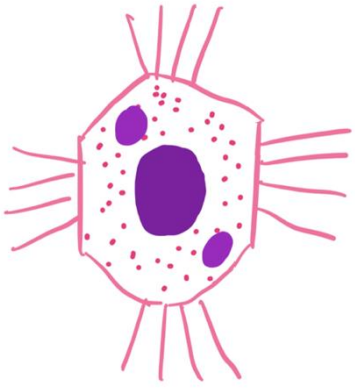

Fig 7. Epithelial cell of Pindborg's tumor

The cells are arranged into broad, branching and interconnecting sheet like masses with minimal intervention of stroma[26].Epithelial cells of this tumor appear polyhedral with well outlined cell border and finely granulated eosinophillic cytoplasm with prominent intercellular ridges (fig 7). The nucleus appears pleomorphic, giant or multiple nucleation is seen. Mitotic figures rarely appear in the cells[17]. There is no major difference observed in the histology of intraossous and extraosseous variants of CEOT except for minimal or absence of calcification seen in extraosseous types[6].

CLEAR CELL VARIANT:

Abrams and Howell were the first to describe CEOT with clear cell components. It is most commonly seen in the mandible[29] and is intraossous in nature with mean age of occurrence ranging around 44 years[8]. The cells of this variant ships clear vacuolated cytoplasm without any eosinophilic granules. The nucleus appears round or oval or flattened against the cell membrane[17].

The clear cell variant stains positive for PAS which is diastase labile and doesn't stain with Alcian blue[8,29]. most of these cells are mucicarmine negative. These cells may form the bulk of tumor or may be scattered[6]. Clear cell neoplasms are mostly malignant in nature and proper care must be taken before arriving at diagnosis.

AMYLOID LIKE MATERIAL:

It is suggested that an enclosed mass of hyaline material gives CEOT its cribriform appearance[21]. This material stains homogeneously with eosin and can be interpreted as amyloid, comparable glycoprotein, basal lamina, keratin or enamel matrix[17]. They can be either in small amounts or in large quantities. Almost in most cases, this material has a tendency to stain metachromatically with crystal violet, shows positive staining with congo red due to its beta pleated sheets that rotates the plane of polarised light , hence it shows apple green dichroism with congo red staining[28] , fluorescence under ultraviolet light with thioflavin T, similar to that of amyloid. The exact nature of this amyloid like material is not known, although some researchers believe it is due to the immunological response of stratum intermedium cells.

LIESEGANG RINGS:

Generalised calcification is noticed in CEOT whereas sometimes these calcifications can be seen in large amounts which appear arranged as concentric circles called as liesegang rings. This mineralization is centered on the epithelium which appears like fossilizing cells[28]. Many authors believe that these calcifications are derived from the calcification of amyloid like material, whereas Shafers[17] suggests that there is no correlation between these calcifications and amyloid like material. This cementum like material stains nagative PAS unlike the amyloid material which stains positive[6]. Some researchers believe that the amyloid like material acts as an inductive stimulus for these calcifications, which causes the stromal cells to differentiate into producing collagen matrix which undergoes mineralization to resemble cementum[6].

LANGERHAN CELLS AND MYOEPITHELIAL CELLS:

It is noted that, almost eight intraosseous cases and two extraosseous cases of non calcified CEOT are reported[8,31,32]. Langerhan cells are reported in two cases where the cells were observed ultra structurally. These cells showed racket shaped Birbeck granules[6].The langerhan cells when present in abundance in CEOT, appear histologically as clear cells and cases reported so far shows no calcification reported with such cases except a case where it was reported shows the presence of langerhan rich case with calcification, this proves as a challenge for the existing assumption of all langerhan rich variant being non calcified[8]. Myoepithelial cells were also observed which was not demonstrated before in any odontogenic tumors and it is not seen in any other electron microscope studies of CEOT[19].

CYSTIC/MICRO CYSTIC VARIANT :

A pseudoglandular appearance is seen in this type of CEOT with conventional CEOT features . Many similar cases have been reported hence this was established as a variant of CEOT. The pathogenesis and occurrence of these tumors are unknown. No recurrence has been seen so far[5].

DIAGNOSTIC CRITERIA FOR CEOT:

The diagnosis for CEOT is done with proper correlation of clinical, Radiographic and histologic findings. The amyloid like material and calcification seen help us navigate towards diagnosing Pindborg tumor.

MANAGEMENT STRATEGIES:

To efficiently manage and treat a case of CEOT, a long term follow up is needed. Shafers[17] suggests that for small intrabony tumors, enucleation or current age can be done along with judicious removal of the surrounding thin layer of bone. But for persistent and recurrent tumors, segmental resection can be done. CEOT is noted to be similar to solid or multicystic ameloblastoma, although the progression is slower for CEOT, some authors believe that these two tumors should be treated the same with an identical approach[6]. The treatment depends mainly on its location, marginal clearance and presence of recurrence. The treatment approach hence depends on each tumor with careful studying of the tumor characteristics and quality imaging.

POST TREATMENT RELAPSES:

It has been noted that the recurrence rate of CEOT post conservative treatment is around 10-20%. The patient who underwent hemimandibulectomy has shown no recurrence on 6 month follow up[5]. Waldron and Hansen have suggested that a radical line of treatment approach is needed for clear cell variant since it is very aggressive in nature and has recurrence[6].

CONCLUSION:

The development of diagnostic criteria for tumors is an ongoing process, often hindered by the lack of molecular tools to accurately classify tumor variants.In conclusion, CEOT typically appears as a radiolucent image in younger patients and as a mixed radiopaque-radiolucent image in older individuals. The pathologic profile and variants are defined by the distribution of three key elements: epithelium, amyloid, and calcification. Younger patients tend to have epithelium-rich cases, while older patients have amyloid- or

calcification-rich cases. Early diagnosis can help the patient treat these tumors and cause less debilating conditions. Hence learning thoroughly about CEOT's clinical, radiographic and histologic profile helps us arrive at a better and faster conclusion.

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