Synchronous Calcifying Epithelial Odontogenic Tumor: Case Report and Analysis of the 5 Cases in the Literature

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Abstract

Calcifying epithelial odontogenic tumor (CEOT), or Pindborg tumor, is infrequent and accounts for less than 1% of all odontogenic tumors. It is benign and usually asymptomatic but displays locally infiltrative and expansile behavior. Synchronous lesions affecting the jaws are exceedingly rare. We present a case of synchronous CEOTs affecting the maxilla and mandible and describe the clinical, radiographic, histologic, and immunohistochemical features. We further review five cases previously described in the literature.

Keywords Calcifying epithelial odontogenic tumor · Pindborg tumor · Synchronous · Odontogenic tumor

Introduction

The calcifying epithelial odontogenic tumor (CEOT), a rare tumor of the jaws, was first described by the Danish pathologist Jens Pindborg in 1955. For this reason, it has been known by the eponym of Pindborg tumor for more than 30 years [1]. CEOT is a benign tumor of odontogenic epithelium without an ectomesenchymal component [2]. It usually affects individuals between the 3rd and 4th decades of life (mean 38.1 years) without gender predilection. It presents clinically as a slow growing, expansile neoplasm with locally invasive and aggressive behavior [3]. There are both intraosseous (central) and extraosseous (peripheral) variants, and the posterior mandible is the most commonly affected site [3]. CEOT is associated with a tooth, erupted or unerupted, in 48% of cases [4]. Radiographically, a mixed radiolucent and radiopaque lesion, unilocular or multilocular, is most characteristic [4].

The clinical and radiographic aspects of CEOT overlap with several other odontogenic and non-odontogenic

conditions that may be considered in the differential diagnosis. Correct diagnosis and treatment requires careful assessment of the clinical, radiographic, and histopathologic findings [5].

A recent review showed that there are nearly 350 cases of CEOT reported in the literature [4]. There are only five reports of synchronous CEOTs, however, and only three of them are intraosseous (Table 1) [5–9]. In this article, we present a new case of synchronous, intraosseous CEOTs with clinical, radiographic, histologic, and immunohistochemical findings. We discuss the differential diagnosis and likely etiology of synchronous odontogenic lesions and review the outcomes of the five cases previously described in the literature.

Case Report

A 33-year-old Caucasian woman was referred to the Stomatology Department of Dental Public Service by a general dentist for evaluation of suspected pathology of the jaw bones. The clinical and radiographic examinations revealed two intraosseous lesions: one located in the mandible and the other in the maxilla. The mandibular lesion comprised an asymptomatic mass localized to the buccal alveolar ridge of the right premolar area. It was expansile and firm to palpation with intact overlying mucosa of normal coloration (Fig. 1a). Radiographically, a well-circumscribed

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Table 1 Literature review of clinical and radiographic features of the five cases of synchronous calcifying epithelial odontogenic tumor

Authors	Age/sex	Variant	Location	Radiographic	Treatment	Follow up
Sedghizadeh et al. [5]	51/M	Intraosseous	4 lesions in maxilla and 1 in mandible	Well circumscribed, unilocular, and varying amounts of radiopaque material within the radiolucent areas.	Enucleation	NA
Tarsitano et al. [6]	55/M	Intraosseous	Maxilla and mandible	Large multi-lobate radiolucent lesions.	Enucleation	NED after 42 months
Chomette et al. [7]	40/F	Intraosseous	Maxilla and mandible	Maxilla: radiolucent Mandible: radiolucent with numerous microopacities	Enucleation	NA
de Oliveira et al. [8]	43/F	Extraosseous	Maxilla and mandible	Cupping, with no signs of bone involvement.	Enucleation	NED after 12 months
Abrahão et al. [9]	40/F	Extraosseous	Mandibular (bilateral)	Bilateral displacement of premolars.	Enucleation	NED after 42 months

M male, *F* female, *NA* not available, *NED* no evidence of disease

Fig. 1 **a, b** Intraoral views of both lesions. The mandibular lesion is nodular and sessile and associated with buccal surface bone expansion. Normal oral mucosa overlies the lesion. In the maxilla, the lesion is expansile and also covered by normal oral mucosa

radiolucency with an internal radiopaque focus was identified mesial to the right mandibular second molar. It measured 1 cm in largest dimension (Fig. 2a, b).

In the maxilla, an asymptomatic, expansile mass was situated at the edentulous alveolar ridge in right premolar

area. It was firm and displayed a rough surface texture with normally colored overlying mucosa (Fig. 1b). The radiographic features were similar to those of the mandibular lesion, showing a well-defined radiolucency with an internal radiopaque focus (Fig. 2a–c).

The differential diagnosis of CEOT includes a number of entities and may vary depending on the case-specific clinical, demographic, and radiographic features. Due to the mixed radiolucent and radiopaque presentation of this case, primary bone lesions such as a fibro-osseous lesion and osteoma were considered in the differential diagnosis. Odontoma and adenomatoid odontogenic tumor associated with an odontoma were also possibilities due to the prominent radiopaque foci, especially of the inferior lesion. Excisional biopsy was performed at two different surgical appointments (Fig. 3). Both lesions were enucleated, and tissues at the margins were macroscopically normal.

Histologic sections revealed sheets and islands of odontogenic epithelial cells with polygonal shape, homogenous eosinophilic cytoplasm, and large ovoid nuclei (Figs. 4a and b, 5a and b). Discrete intercellular bridges between the epithelial cells and minimal nuclear pleomorphism were detected. The tumor islands were surrounded by a fibrocollagenous stroma containing variable amounts of an eosinophilic to a basophilic amorphous, amyloid-like material (Figs. 4a and b, 5a and b). With Congo red staining under polarized light, the focus of amyloid-like material demonstrated an apple-green birefringence (Figs. 3c, 4c). The epithelial tumor cells exhibited an intense positivity with cytokeratin AE1/AE3 (Figs. 4d, 5d).

Total bone repair with no evidence of recurrence was observed in both surgical sites after 2 years of follow up (Fig. 6a–c).

Fig. 2 **a** Panoramic radiograph shows a radiolucent area with a radiopaque focus and well-defined margins in both the maxillary (**b**) and mandibular (**c**) lesions

Discussion

According to the World Health Organization, CEOT is an extremely rare, benign tumor of the gnathic bones that arises from odontogenic epithelium [2]. A recent retrospective study in Brazil observed that CEOT comprised only 1% of all OTs included in their study [17]. Histopathologic examination is decisive at establishing the final diagnosis. To date, only five cases of synchronous CEOTs have been reported [5–9]. Three cases of synchronous lesions were intraosseous and two were extraosseous (Table 1). Here, we present a new case of exceedingly rare, synchronous, intraosseous CEOTs with similar characteristics to the other cases described in the literature.

Similar to this case, most intraosseous CEOTs present as asymptomatic, slow-growing masses which may cause cortical expansion [10]. Radiographic findings are variable and correlate to the tumor size, location, and amount of mineralized product. CEOTs may be unilocular, multilocular, or without loculations. Most cases are unilocular and become mixed radiolucent-radiopaque with maturation and expansion [11, 12]. This case exhibited a usual radiographic presentation of radiolucent lesions with internal radiopaque foci and well-defined margins [11].

Even though the present case showed several clinical and radiographic findings characteristic of CEOT, other lesions were considered in the differential diagnosis due to their similar features and higher prevalence. The mixed radiolucent-radiopaque appearance increased our suspicion for a benign fibro-osseous lesion (BFOL) or primary bone lesion. Amongst entities within the BFOL category are cemento-ossifying fibroma (COF), cemento-osseous dysplasia

Fig. 3 Intraoperative view of the maxillary lesion. **a** Intraoperative view before surgical enucleation. **b** Intraoperative view after surgical enucleation

Fig. 4 Microscopic appearance of maxilla lesion. **a, b** Strands of polyhedral odontogenic epithelial cells (arrows) supported by fibrocollagenous stroma (arrow heads). Area with mineralized eosinophilic to basophilic amorphous substance (asterisks) is observed with surrounding epithelial cells (H&E staining; X200 and X400). **c** Irregular nests and cords of polyhedral epithelial cells (arrows) supported by fibrocollagenous stroma (H&E staining; X400). **d** Sheets of

polyhedral tumor cells with pleomorphic and hyperchromatic nuclei (arrows). Cell outlines are distinct but intercellular bridges are not prominent (H&E staining; X1000). **e** Focus of amyloid-like material with an apple-green birefringence (Congo red staining; X200). **f** Island of epithelial tumor cells positive for cytokeratin (SABC staining; X100)

(COD), and fibrous dysplasia (FD). Histologically, the entities within this group share a fibrous stroma containing mineralized tissue such as bone or cementum-like calcifications. The radiographic appearance depends on the maturity of the lesion with increasing internal radiopacity over time [13].

Among the BFOLs, COD was most likely due to its overlapping characteristics including demographics, clinical presentation, and radiographic features. COD is the most common BFOL of the jaws and multi-site involvement is characteristic of the florid variant. It has a female

Fig. 5 Microscopic appearance of the mandibular lesion. **a** Islands of tumoral odontogenic epithelial cells (arrows) surrounded by fibrocollagenous vascularized stroma (arrow heads) (H&E staining; X200). **b** Calcification (arrow heads) associated with sheets of epithelial cells (arrows) (H&E staining; X400). **c** Tumor islands, nests, and cords (arrows) supported by fibrocollagenous stroma (H&E stain-

ing; X400). **d** Polyhedral cells in sheets with some prominent desmosomes (arrow heads), eosinophilic cytoplasm, and pleomorphic and hyperchromatic nuclei (H&E staining; X1000). **e** Stroma of the tumor shows extracellular amyloid-like material (Congo red staining; X200). **f** Island of epithelial tumor cells positive to cytokeratin (SABC staining; X200)

predilection and occurs around middle-age [14, 15]. COD usually presents as an asymptomatic, slow-growing, non-expansile lesion identified incidentally on routine dental radiographs. The florid variant of COD, however, may cause osseous expansion [13]. The radiographic appearance is radiolucent, radiopaque, or mixed depending on

lesional maturity. The margins are well-defined with a thin radiolucent periphery [13].

Of the odontogenic entities, odontoma topped the differential diagnosis. Odontoma is the most frequent OT and comprises dental hard and soft tissues. It is usually asymptomatic and exhibits slow growth [16]. Radiographically, it

Fig. 6 a–c Radiographic images show no evidence of recurrence and total bone repair after 2 years of follow-up

appears as a radiopaque mass surrounded by a radiolucent rim [16]. Even though this case had many features of an odontoma, they mostly occur as a single lesion and few cases of multiple odontomas are reported [16].

Another diagnostic consideration was an osteoma, a similarly benign tumor with slow-growing and asymptomatic behavior. Radiographically, a well-circumscribed radiopaque mass is observed [18]. Usually, these lesions are solitary unless associated with Gardner's syndrome of which multiple osteomas is characteristic [18]. The radiographic and clinical aspects of the present case are quite different from the usual presentation of osteomas, making this diagnosis less likely.

The diagnostic histologic features of CEOT are unique and consist of sheets and nests of polyhedral neoplastic odontogenic epithelial cells. The cells exhibit abundant eosinophilic cytoplasm, prominent intercellular bridges, and pleomorphism is characteristic [3]. Some tumors have increased mitotic activity; however, in the present case, there was no evidence of mitotic activity or pleomorphism. Accumulation of eosinophilic material, described as “amyloid-like,” and concentric calcifications, or *Liesegang rings*, are considered pathognomonic microscopic features [3]. Both were present in this case. Occurrence in combination with other benign tumors, such as adenomatoid odontogenic tumor or squamous odontogenic tumor, is reported [3, 6, 19].

The treatment for CEOT is individualized to each case due to the clinical, radiographic, and histologic variation amongst tumors [10]. Surgical procedures may involve conservative enucleation, marginal (segmental) resection, or partial resection for extensive or aggressive features [4,

5]. One review showed that the recurrence rates of CEOT ranged around 15% and could be higher if treated conservatively. Patients that were treated with resection had fewer recurrences [3]. Of the synchronous cases reviewed here, all were treated with enucleation without recurrence in the follow-up period (Table 1). Similarly, in our case, no evidence of recurrence was observed in either surgical site 2 years after enucleation. Due to the slow growth of this tumor, a follow-up period from 5 to 10 years is recommended [20]. In our case, we recognize that longer follow-up is necessary in order to guarantee that this patient is cured from this pathology.

Sedghizadeh et al. pointed out that the synchronous variant of CEOT could be the result of genetic alterations [5]. In 2010, a study identified specific genetic mutations in the pathogenesis of CEOT [21]. This research made considerable improvements on the understanding of this tumor's etiology by investigating the Sonic hedgehog pathway (SHH) and *PTCH1*. SHH is responsible for regulating epithelial proliferation at tooth development and *PTCH1* is a tumor suppressor gene. Mutations in the *PTCH1* gene had already been identified in patients with nevoid basal cell carcinoma syndrome and occasional neoplasms such as keratocystic odontogenic tumor, basal cell carcinoma, and medulloblastoma. Peacock et al. discovered that this mutation was also present in CEOT after DNA extraction and sequencing of seven cases [21]. In this case, no DNA extraction or sequencing was performed. Further research to include genetic analysis on rare tumors is necessary to understand the pathogenesis and behavior of these diseases.

Conclusion

The present report describes an uncommon case of synchronous CEOTs affecting the maxilla and mandible with similar clinical and radiographic characteristics and behavior to the other five cases previously described. An accurate final diagnosis can be established through a combination of clinical, radiographic, and histopathologic analysis. Diagnostic accuracy is essential to provide adequate treatment.

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