CASE REPORT

A Combined Epithelial Odontogenic Tumor? A 7-Year Follow-Up Case

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Received: 16 August 2016 / Accepted: 31 October 2016 / Published online: 5 November 2016
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Abstract Adenomatoid odontogenic tumor (AOT) is a benign epithelial odontogenic tumor characterized by slow and progressive growth. When central lesions are associated with an unerupted permanent tooth, they are also known as the follicular type. Histological variants of AOT may complicate diagnosis with possible adverse effects on treatment and prognosis. The aim of this study is to report a case of a follicular AOT with extensive calcifying epithelial odontogenic tumor (CEOT)—like histopathological areas in the anterior region of the mandible that was treated by enucleation. The teeth displaced by the tumor were repositioned with orthodontic treatment, and after 7 years of follow-up, the bone trabeculae were normal with no evidence of recurrence. The clinical, radiographic and histopathologic aspects of these tumors are discussed and the debate surrounding whether these cases are true combined lesions or histologic variants of the primary tumor is raised.

Keywords Adenomatoid odontogenic tumor · Calcifying epithelial odontogenic tumor · Congo red staining · Odontogenic epithelium · Odontogenic tumors · Orthodontic treatment

Introduction

Adenomatoid odontogenic tumor (AOT) is a benign epithelial odontogenic tumor, first reported by Stafne in 1948 [1]. It accounts for 2–7% of all odontogenic tumors and is characterized by its association with impacted teeth, slow and progressive growth, affecting patients from young age groups and low recurrence rates after treatment [2, 3]. AOT is predominantly asymptomatic and intraosseous, with a preference for the maxilla over the mandible. Intraosseous AOTs associated with an unerupted permanent tooth characterize the follicular type of the tumor.

Calcifying epithelial odontogenic tumor (CEOT) is a benign epithelial odontogenic tumor first described by Pindborg in 1955 [4] and also referred to as *Pindborg tumor* [5]. CEOTs account for approximately 1% of all odontogenic tumors and their clinical behavior is different from AOTs. They occur in patients aged around 40 years [6] and have no gender predilection. When intraosseous, they affect the mandible more than the maxilla with a preference for premolar/molar regions, although any site may be affected, with lesions being locally aggressive [7].

An association between AOTs and CEOTs has been previously described by some authors [8–14], although others consider that CEOT-like areas in AOTs are a histologic variant [15–17].

Therefore, there is a lack of agreement in the literature. Moreover, histologic variants of AOTs presenting similar features to other odontogenic tumors or cysts may have

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unspecific clinical and radiographic features that overlap with those of other odontogenic tumors. These characteristics reinforce the fundamental role of microscopic examination in diagnosis, to ensure appropriate treatment.

The aim of this report is to describe a case of follicular AOT in an unusual location, presenting extensive calcifying epithelial odontogenic tumor (CEOT)-like areas, successfully treated by surgical excision, extraction of the associated canine, curettage of healthy bone margins and repositioning of displaced teeth using a fixed orthodontic appliance. Clinical, radiographic and histopathologic aspects of the lesion are discussed based on a seven-year follow-up period.

Case Report

The patient gave informed consent for inclusion in this study. The authors have followed the Helsinki Declaration guidelines of 1975, as revised in 1983.

A 17-year-old white female was referred with an asymptomatic facial swelling in the anterior region of the mandible causing a discrete asymmetry on the left side of her chin. The lesion had been incidentally detected in a panoramic radiograph taken for orthodontic purposes. Intraorally, there was cortical expansion of the mandible covered by normal mucosa associated with a missing canine tooth and displacement of the crowns of adjacent incisors and premolars. A panoramic radiograph showed a well-defined unilocular radiolucent lesion containing fine calcifications and the missing canine, all partially circumscribed by a radiopaque halo and displacement of the roots of the neighboring teeth with no evidence of root resorption (Fig. 1a). Needle aspiration of the contents of the lesion yielded a clear fluid, which was compatible with a provisional clinical diagnosis of dentigerous cyst (despite the “snowflake” appearance of the fine radiopaque dots). An

incisional biopsy was carried out, which revealed the presence of a cystic space surrounded by a whitish fibro-elastic capsule and smooth surface appearance containing a transparent liquid material. A sample of the cystic wall was removed and sent for microscopic examination.

Histopathological analysis showed a benign neoplasm of odontogenic epithelium. At low magnification, the lesion showed a thick fibrous capsule partially lined by a thin epithelium. The capsule contained proliferating spindle, cuboidal and columnar cells toward the lumen arranged as nodules. There were rosette-like and rarely duct-like structures lined by a single row of cuboidal and columnar epithelial cells with the nuclei polarized to the basal side, away from the luminal surface. Foci of eosinophilic amorphous material and calcifications were present in between epithelial cells. Mainly at the periphery, strands of epithelium in a cribriform pattern were also observed. (Fig. 2a–f). In a large part of the tumor, next to the nodules located close to the capsule, there were polyhedral, eosinophilic epithelial cells with a squamous appearance, with distinct cell boundaries, prominent intercellular bridges and occasional pleomorphic nuclei. Amyloid-like material and calcifications were observed in between cells (Fig. 2a–d and g). Congo red staining showed green birefringence when subjected to polarized light in the cytoplasm of these eosinophilic cells, in the amorphous hyaline material between these cells and in the adjacent stroma (Fig. 2h). Histopathological evaluation led to the diagnosis of an AOT with CEOT-like areas.

The tumor was treated by surgical excision under local anesthesia, including exodontia of the canine tooth and vigorous curettage of bone margins. Clinical and radiographic follow-up was performed periodically. Two years later, the newly formed healthy bone trabeculae permitted repositioning of the displaced teeth using orthodontic treatment. The most recent follow-up record 7 years post-operatively indicated no evidence of recurrence (Fig. 1b).

Fig. 1 a Conventional diagnostic panoramic radiography showing an expansive, unilocular, radiolucent and well-delimited lesion in the mandible, with radiopaque foci and peripheral bone condensation, extending from the elements 41–36, involving the tooth 33 (arrow).

b Digital preservative panoramic radiography after 7 years of follow-up, presenting the alignment of the teeth after orthodontic treatment, normal trabecular bone formation and regional residual mandible expansion

Fig. 2 Histological sections. **a** and **b** AOT with extensive CEOT-like areas. Note a *thick* fibrous capsule adjacent to AOT *solid* cell nodules and CEOT-like areas located on the site opposite to the capsule (HE, $\times 40$ and HE, $\times 100$, respectively). **c** and **d** CEOT-like areas close to AOT cell nodules (HE, $\times 100$ and HE, $\times 200$, respectively). **e** and **f** Common AOT area with cubic or columnar

cells in *solid* arrangement forming rosette-like structures (HE, $\times 200$ and HE, $\times 400$, respectively). **g** Common CEOT-like area formed by eosinophilic polyhedral cells with defined limits and calcifications (HE, $\times 400$). **h** Congo *red* staining under polarized light showing the amyloid-like material in CEOT-like areas as a *green* birefringence ($\times 40$)

Discussion

The microscopic features observed in the present case were consistent with the diagnosis of an AOT with CEOT-like areas, or the so-called combined epithelial odontogenic tumor, an altogether unusual lesion. Authors elsewhere have described odontogenic tumors with combined characteristics of AOT and CEOT [8–14]. Such association between tumors is questionable, however, as other authors have considered them as usual histological variants of AOTs [15–17]. In the most recent WHO International Classification of Tumors, there is also a lack of consensus

regarding the grouping of this entity as an original combined tumor or a histopathologic variant of AOT since both have been described in the above-mentioned book [3, 7].

The histopathological analyses of the current case revealed a lesion with the classical features of an AOT with prominent CEOT-like areas, an unusual feature (Fig. 2a). There were few pleomorphic cells, corroborating the hypothesis that this is a variant type of AOT and not a true combined tumor, although it was positive for Congo red staining, a method admittedly used for the diagnosis of CEOTs (Fig. 2h). In a multicentric study that analyzed the largest series of AOT variants from a clinicopathological

viewpoint, only 10 of the 36 exceptional cases showed positivity for Congo red under polarized light, with seven cases limited to CEOT-like areas, as in this study [18].

Classically, AOTs are encapsulated tumors featuring cuboidal or columnar epithelial cells forming solid nodules of varying sizes in a scanty stroma of mature loose connective tissue. The cells may be arranged in rosette-like structures or in tubular structures that resemble ducts. The ductiform structures are formed of a layer of columnar cells with nuclei polarized to the side opposite to the lumen and may contain eosinophilic material, which may also be observed within the rosettes and between epithelial cells along with calcifications. The cells may also form interconnected strands giving a cribriform appearance. Dysplastic hyaline material or calcified osteodentine may also be present in varying amounts [3].

The variants that show CEOT-like areas are described as tumors containing eosinophilic epithelial polyhedral cells of squamous appearance, with evident intercellular bridges and occasionally pleomorphic nuclei, amorphous amyloid materials and globular masses of solid substances CEOT-like [3]. Those who consider that these CEOT-like areas are routine histopathologic findings of an AOT argue that,

in the microscopic areas compatible with the CEOT, the epithelial cells lack the typical pleomorphism of a true CEOT and tend to be confined to those areas of the AOT that produce mineralized tissue [13, 14].

Radiographically, intraosseous AOTs appear as well-defined unilocular radiolucent lesions around the crown or root of a permanent tooth mimicking a dentigerous cyst, which may also contain calcification foci [3]. Similarly, CEOTs tend to appear as unilocular or multilocular radiolucent lesions with radiopaque deposits [7], sometimes hindering a precise radiographic diagnosis between these lesions. In the current case, the radiographic findings were compatible with a classic follicular AOT with foci of calcification (Fig. 1a).

The clinical behavior observed in this case also corroborates the aforementioned hypothesis. The literature regarding follow-up of AOTs with CEOT-like areas shows that most such tumors exhibit the clinical features of a conventional AOT, including localization to the maxilla and a predilection for young females. Enucleation resolved most of the lesions and all of them had a good clinical outcome without recurrences (Table 1). Although these lesions have been previously documented, to the authors'

Table 1 Identified cases of hybrid AOT-CEOTs (combined epithelial tumors) or AOT variants including CEOT-like areas with clinical data and follow-ups in English literature

Case	Author	Entity as described	Location	Sex	Age (years)	Treatment	Follow-up
1	Damm et al. [8]	Hybrid AOT-CEOT	Mandible	M	18	Enucleation	5 y (NR)
2		Hybrid AOT-CEOT	Mandible	F	15	Excision	1 y (NR)
3	Bingham and Adrian [9]	Hybrid AOT-CEOT	Mandible	F	14	Curettage	2 y (NR)
4		Hybrid AOT-CEOT	Maxilla	F	17	Enucleation	1 y (NR)
5	Siar and Ng [10]	Hybrid AOT-CEOT	Maxilla	M	28	Enucleation	9 y (NR)
6	Siar and Ng [14]	Hybrid AOT-CEOT	Maxilla	M	13	Enucleation	11 m (NR)
7			Mandible	F	14	Enucleation	2 y (NR)
8			Maxilla	F	22	Enucleation	2 y (NR)
9			Mandible	F	28	Enucleation	1 y (NR)
10	Ledesma et al. [15]	AOT variant	Maxilla	F	17	Enucleation	11 y (NR)
11		AOT variant	Maxilla	F	14	Enucleation	8 y (NR)
12		AOT variant	Maxilla	F	21	Enucleation	5 y (NR)
13		AOT variant	Maxilla	F	20	Curettage	2 y (NR)
14		AOT variant	Mandible	M	10	Excision	2 y (NR)
15		AOT variant	Maxilla	F	21	Enucleation	1 y (NR)
16		AOT variant	Mandible	F	15	Enucleation	6 m (NR)
17		AOT variant	Maxilla	M	13	Enucleation	9 y (NR)
18		AOT variant	Maxilla	F	17	Enucleation	10 m (NR)
19		AOT variant	Maxilla	F	10	Enucleation	6 m (NR)
20		AOT variant	Mandible	F	17	Enucleation	1 y (NR)
21		AOT variant	Maxilla	F	15	Enucleation	2 y (NR)
22	Miyake et al. [12]	Hybrid AOT-CEOT	Maxilla	F	16	Enucleation and curettage	5 y (NR)
P		AOT variant	Mandible	F	17	Enucleation and curettage	7 y (NR)

F Female; M Male; y Year; m Month; NR No recurrence; P present case

knowledge, the present report shows the longest clinical follow-up of such variations occurring in the mandible. Furthermore, there are no former reports on the use of orthodontic appliances for dental repositioning after enucleation of these tumors, as in the current case.

Variant AOTs that show CEOT-like areas are uncommon odontogenic tumors and their incidence amongst classic AOTs is unclear. In a multicentric retrospective study, Leon et al. [18] found 36 AOTs with CEOT-like areas among 39 classic cases analyzed. A recent investigation demonstrated only four cases of AOTs with CEOT-like areas among 15 classic cases reviewed [19]. More evidence-based studies are needed to clarify the real occurrence of these variations among odontogenic tumors [18, 19].

It is easy to understand why some authors consider these lesions as combined epithelial tumors and not variations of a primary tumor. The literature data are divergent and show reports of different combinations of odontogenic tumors, such as AOT with calcifying odontogenic cyst (calcifying cystic odontogenic tumor) [20], AOT with dentigerous cyst [21], AOT with odontoma [22], AOT with ameloblastoma [23], ameloblastoma with odontogenic keratocyst and ameloblastic fibroma with calcifying odontogenic cyst [24].

Future knowledge on the molecular pathology and cell culture of odontogenic tumors could shed light on the development of these lesions. In a recent study, Amm et al. [25] established diverse primary CEOT epithelial-derived cell populations and showed the expression of ameloblastin (AMBN) in these cells. The *AMBN* gene expresses a protein that has an important role in the epithelium-mesenchyme signaling during odontogenesis. Mutations in this gene have been identified by capillary electrophoresis in AOTs and ameloblastomas [26]. Both AOT and CEOT cells are descended from epithelial odontogenic cell lineages and, if such neoplastic cells receive appropriate stimuli, they could perhaps give rise to similar “reprogrammed” neoplastic daughter cells in either lesion or even any odontogenic tumor of epithelial origin for that matter, as previously shown in other cells and tissues [27–29]. Such an assumption requires further investigation, as the inductive potential of the neoplastic epithelial odontogenic cell lines has not been explored [29].

In conclusion, the clinical data available on these neoplasms indicate that these lesions are more likely to be AOT variants than true hybrid tumors with diverse clinical behavior (Table 1). Future studies might make it possible to reach a consensus on nomenclature and classification criteria, as to whether one ought to classify lesions according to their biological behavior rather than their histological variants or to take their histological features as valid and ignore their biological behavior.

Acknowledgements The authors wish to thank Jeruza Pinheiro da Silveira Bossonaro and Nadir Severina de Freitas for their excellent technical expertise and assistance. This research did not receive any specific Grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

Conflicts of interest There are no conflicts of interest.

Ethical Approval The study has been approved by the institutional research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the participant included in the study.

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