Multiple Pathology in a Single Lesion: AOT Associated with Dentigerous Cyst

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Abstract Odontogenic cysts and tumors are quite common occurrences in jaw bones, although both of them occurring together are rare. The epithelial lining of odontogenic cyst has a potential to transform into neoplastic conditions like squamous cell carcinoma and mucoepidermoid carcinoma, and odontogenic tumors like ameloblastoma and adenomatoid odontogenic tumor. However, the frequency of such cases being encountered is very less. Here, we report a case of adenomatoid odontogenic tumor (AOT) associated with a dentigerous cyst around the crown of an unerupted lateral incisor (follicular variant), in a 14-year-old boy. We also attempt to unravel its mechanism of cytodifferentiation and tumor progression. The origin and nature of such kind of lesions (i.e., independent development of multiple pathologies as a single lesion in a single location, single pathology giving rise to another pathology or a distinct entity/new variant) cannot be explained with certainty at this point of time. The molecular mechanism of tumor development needs to be further elucidated in order to conclude that a different entity called ‘hybrid’ AOT exists.

Keywords Adenomatoid odontogenic tumor · Dentigerous cyst · Pathogenesis · Multiple pathology

Introduction

Adenomatoid odontogenic tumor (AOT), first described by Stafne in 1948, is a slow growing, benign odontogenic

lesion with few or no symptoms. Tumor growth may cause displacement of teeth rather than tooth resorption. Philipson et al. [1] subdivide this condition into three groups referred to as follicular, extra follicular, and peripheral. These variants have common histologic characteristics that indicate a common origin, as derived from the complex system of dental lamina or its remnant [1]. The central variants account for 97.2 %, of which 73 % are follicular. The peripheral variant is the rarest, with only 18 cases reported so far [2]. The follicular variant (M:F ratio 1:1.9) is three times as the extra follicular [1]. The central variants are more commonly found in the maxilla than in the mandible at a ratio of approximately 2:1 [3].

The follicular variant is associated with the crown and often part of the root of an impacted tooth. This is most commonly the maxillary canine (40 %) and rarely the permanent molars as well as the deciduous teeth. All four canines constitute about 59 % of AOT-associated embedded teeth [2]. Therefore, the follicular variant is often initially regarded as a dentigerous cyst based on clinical and radiographic evaluation. Indeed, as many as 77 % of follicular variants of AOT are clinically diagnosed as dentigerous cysts [4].

The extra follicular variant is not associated with the crown of an unerupted tooth. Instead, this variant presents as a well-defined, unilocular radiolucency between, above or superimposed upon the roots of erupted permanent teeth. Consequently, a clinical diagnosis of a residual, radicular, globulomaxillary or lateral periodontal cyst can be made according to the definite intraosseous location of the variant. The peripheral variant almost certainly always appears as a gingival fibroma or epulis in the anterior maxilla (88 %) [1, 2].

Very rarely, AOT is associated with an odontogenic cyst. Till date, only 11 existing cases of AOT associated

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Fig. 1 Buccal (a) and palatal aspects (b) of the swelling

with dentigerous cyst are reported. Here, we present an uncommon case of AOT associated with a dentigerous cyst around the crown of an unerupted lateral incisor displacing the maxillary canine in a 14-year-old boy.

Case Report

A 14-year-old boy presented with painless, slowly increasing swelling in the right side of middle third of face since 2 years. There was no history of trauma, discharge, pain or any altered sensation. The swelling presented as a mass in the lateral nasal region with obliteration of nasolabial groove. On intraoral examination, a firm, non-tender swelling with ill-defined borders was seen over the right upper buccal gingiva, vestibule, and palatal gingiva. Labially, it extended from the left upper central incisor to the right first premolar and palatally up to the midline and measured approximately $5 \times 4.5 \text{ cm}^2$ in size (Fig. 1a, b). No sinus opening or color change of overlying mucosa were noted. The upper right permanent lateral incisor and canine were missing and deciduous lateral incisor canine were retained. On palpation, the swelling was firm in consistency. Perforation of cortical bone was noted 1 cm above retained right upper deciduous canine. The retained upper right deciduous lateral incisor and canine exhibited grade II mobility. The right upper central incisor and premolars were also mobile. Percussion pain was not elicited overlying any of the teeth involved and electric pulp vitality testing was unremarkable. Three milliliters of straw colored fluid (and no cholesterol) was aspirated from the lesion.

On the right side, panoramic radiograph revealed well-defined unilocular radiolucency with impacted lateral incisor and canine (Fig. 2). The same was revealed even with the occlusal view of maxilla (Fig. 3). Paranasal sinus view revealed a well-defined, unilocular, ovoid radiolucency containing one impacted tooth.(Fig. 4). Computed tomography

(CT) showed a well-defined lesion with reactive bone formation involving the floor of nasal cavity on right side and also compressing the maxillary sinus. Symmetrically scattered radio-opacities and two impacted teeth were found within the radiolucency (Figs. 5, 6a, b). Based on these clinical and radiographic findings, a diagnosis of dentigerous cyst was made. During incisional biopsy, a thick fibrous capsule was encountered through the perforation of labial cortical plate and jelly-like specimen was collected. Histologic diagnosis of adenomatoid odontogenic tumor was made.

Under general anesthesia, the mass was approached intraorally via a reflected mucoperiosteal flap extending from 21 to 15. Bony perforation was noted over the apical region of 52 and the thin nature of labial cortical bone was comparable to that of an eggshell. The firm mass was separated from the adjoining bone all along the margin and removed along with the involved tooth (right upper lateral incisor). Tissue attachments were observed from the firm mass at lateral/posterior margin (belonging to a separate lesion). A triangular shaped paper thin depression with epithelial lining was seen on the anterior aspect of compressed maxillary sinus. A linear groove was seen beside the triangular depression, which might have harbored the root tip of lateral incisor. Tissue was excised from below the nasal floor. Another tooth (canine) was removed from the superior- anterolateral aspect. Epithelial lining (with alveolus) was enucleated from an area corresponding to multilocular site of occlusal radiograph (Fig. 7a–d). Right upper deciduous canine was extracted. Hemostasis was achieved, bony cavity thoroughly irrigated with normal saline and beta dine, and packed with ribbon gauze. Closure was done with 3.0 black silk. Pack was removed on second post-operative day. Suture removal was done on seventh post-operative day. Healing was satisfactory without any complications.

The surgical specimen was sent for histologic examination. The gross specimen measured approximately 5 cm in diameter. Three distinct regions could be identified within

Fig. 2 Panoramic radiograph

Fig. 3 Occlusal view of maxilla

Fig. 4 Paranasal sinus view

Fig. 5 CT scan (coronal section)

the cut section of the specimen. The most obvious area was a well developed maxillary lateral incisor and its crown portion circumscribed by solid tumor. There was a thin cystic epithelial lining attached to the posterior aspect of the solid tumor, which in turn was in close proximity to the lateral incisor. Corresponding with the gross observation, three parts i.e., solid tumor, tooth, and cystic lining could also be identified microscopically. The central tumor tissue consisted of solid sheets and clusters and well formed tubules of varying sizes lined by columnar epithelium. The tumor cells contained moderate amount of pale acidophilic vacuolated cytoplasm and round to oval nucleus with clefts and grooves and small nucleolus. Multiple dilated blood vessels of varying sizes and multiple focal areas of psammomatous calcifications were seen (Fig. 8). Section of cystic lesion showed inner surface lined by stratified squamous epithelium with 2–3 layer cell thickness and interlacing collagenous bundles and multiple small blood vessels (Fig. 9). Further, this cystic lining was in continuity with posterior aspect of AOT. Consequently, we landed into a state of uncertainty of whether the AOT was associated with the dentigerous cyst or the dentigerous cyst had transformed itself into an AOT (i.e., multiple pathology originating from a single genetical alteration or having an independent origin).

Discussion

Adenomatoid odontogenic tumor was first recognized by Staphne [5] in 1948 as a distinct pathological entity. According to the second edition of the WHO “Histological

Fig. 6 **a** CT scan (axial section at a level above the nasal floor). **b** CT scan (axial section at maxillary alveolus)

Fig. 7 Intra-operatively **a** exposure of lesion, **b** expulsion, **c** bony cavity, and **d** specimen

Typing of Odontogenic Tumors” [7], AOT is defined as: “A tumor of odontogenic epithelium with duct-like structures and with varying degrees of inductive change in the connective tissue. The tumor may be partly cystic, and in some cases, the solid lesion may be present only as masses in the wall of a large cyst.”

According to an extensive review done by Philipsen et al. [2], the intraosseous variants are more commonly found in the maxilla than in the mandible with a ratio of 2.1:1. Age distribution shows that more than two-thirds are diagnosed in the second decade of life and more than half of the cases occur within the teens. The female:male ratio

Fig. 8 The tumor consisted of solid nodules of various sizes. Within these, cuboidal or columnar epithelial cells formed nests or rosette-like structures. Foci of aggregates of eosinophilic hyaline droplet material and calcification were also noted. (hematoxylin and eosin, $\times 40$)

Fig. 9 Low power view ($\times 10$) showing tumor arising from 2 to 3 cell layered dentigerous cystic lining

for all age groups and AOT variants together is 1.9:1 with an even higher female preponderance (around 3:1) among certain Asian populations. The distribution of unerupted permanent teeth found in association with the follicular variant shows that all four canines account for 59 % and the maxillary canines alone for 40 %.

As previously mentioned, AOTs are usually solid but are occasionally cystic. Only 11 cases have been described that arise in association with a dentigerous cyst [6]. It is noted that the male to female ratio is 6:5 and nearly all cases occurred during the second decade of life, ranging from 8 to 39 years. Furthermore, most of the cases were patients of Asian origin. The common symptom

across majority of the cases was a maxillary swelling that was either painless or painful. The most commonly involved tooth was the maxillary canine (five cases); the others involved were the first premolar, third molar, second molar, and lateral incisor. Interestingly, only one case depicted a well-defined radio-opaque mass; all of the other lesions appeared as well circumscribed unilocular radiolucency around an unerupted tooth. Our patient is an Asian male with an AOT associated with an unerupted maxillary lateral incisor displacing the maxillary canine.

Philipsen et al. [8] postulate that the follicular type of AOT develops from nests of cells within the dental lamina, and therefore as a result surrounds the tooth. Furthermore, they suggest that the formation of the extra follicular variant is from the epithelial nests that are situated at the border of the conduit of tooth eruption. Consequently, the tooth would not be embedded in its eruption by the developing AOT.

As noted from macroscopic observations, the tumor portion in the current case has a tissue tag that is attached to the epithelial lining in the bony depression. Microscopic examination reveals that the tissue tag belongs to the epithelial lining of dentigerous cyst. This gives us three propositions, the first one being a dentigerous cyst with an unerupted lateral incisor would develop first and through a stimulus that is yet to be determined, the AOT would subsequently arise from the epithelial rests of the dental lamina within the odontogenic cystic lining, the second one that two different pathologies occurring concurrently in a single lesion and the third one that it is an entirely new variant. It is reported that AOT has also derived from a calcifying epithelial odontogenic cyst [9].

The potential for proliferation of cyst to tumor might be associated with cell kinetics in the lining epithelium, which is under the influence of growth factors such as the peptide epidermal growth factor (EGF) and its receptor (EGFR) by modulating cell growth and cell differentiation [10, 11]. On the other hand, a high proliferative activity in dentigerous cysts turning into AOT could also be related to the presence of inflammation in response of an infection or traumatism. Due to the fact that odontogenic tumors emerge from remnants of normal odontogenic apparatus, which is strictly regulated through several genes, studies have been done in an attempt to unravel the relation between these two processes. The normal genetic regulation takes place through different signaling pathways, including four major families: Transforming Growth Factors [TGF, which include Bone Morphogenic Proteins (BMPs)], Fibroblast Growth Factors (FGF), Hedgehogs (Hh), and Wingless (Wnt). Each family consists of several signals encoded by different genes [12]. Alterations in the pathway of these genes have been linked to a variety of developmental defects, and there is evidence of tumor formation resulting

from aberrant activation of this pathway in adult life [12, 13]. An autocrine mechanism of activation of this pathway is also suggested [14]. Furthermore, p53 gene is a tumor suppressor gene and plays an important role in the regulation of cell proliferation [15]. Mutations in the p53 gene yields a wild type p53 protein having a high cellular proliferation activity [16].

Although there are case reports of AOT arising from pre-existing odontogenic cyst [3, 6, 17–22] and the factors responsible for alteration in cell kinetics of lining epithelium of odontogenic cysts being delineated, the exact stimulus acting on the cell rests of the dental lamina in the epithelium of dentigerous cyst to transform into an AOT is unknown. There is still an uncertainty whether the tumor has arisen from the cyst or the two pathologies occurred concurrently in the same lesion. This alerts us for a careful attention toward anatomical variation, gross specimen sectioning, and meticulous histopathologic examination of the biopsied specimens, which can unfold the mystery behind origin of tumors. Hence, this must be the subject of further research with accumulation of more cases. Given that the number of reported cases to date is so small, we are even unable to speculate whether multiple pathologies occurring in single lesion could represent a distinct ‘hybrid’ variant.

The AOT and dentigerous cyst are both benign, encapsulated lesions and conservative surgical enucleation or curettage is the treatment of choice. The prognosis for a dentigerous cyst is good, and recurrences are very rare after complete removal of the lesion. There have been no reports of aggressive behavior on the part of AOT and recurrences are very rare.

Conclusion

Very few case reports of a combination of AOT and dentigerous cyst have been reported so far and it is believed to be a rarity. To define the kind of lesion or to determine its origin, further studies are needed to unravel the mechanisms of cytodifferentiation and tumor progression. Since both the lesions are encapsulated, there have been no reports of aggressive behavior or recurrence. Further investigations on the regulation of genes involved in the pathological development of AOT from dentigerous cyst, as well as the coordination among them may provide a better understanding of the process and establish new strategies, leading to the development of more efficient diagnosis, prevention, and treatment approaches.

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Conflict of interest None declared

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