Development and Growth of Adenomatoid Odontogenic Tumor Related to Formation and Eruption of Teeth

Fumio Ide · Kenji Mishima · Kentaro Kikuchi · Norio Horie ·
Shigeo Yamachika · Kazuhito Satomura · Tetsuo Shimoyama ·
Hideaki Sakashita · Ichiro Saito · Kaoru Kusama

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Abstract The number of published cases of adenomatoid odontogenic tumor (AOT) has steadily increased, and about half were reported in Asian populations. Although the clinicopathologic profile of AOT has been extensively reported, factual knowledge of its pathogenesis is rudimentary at best, and there is controversy as to precisely which odontogenic epithelium it arises from. AOT is a successional tooth-associated lesion which develops during

the mixed dentition. The permanent successor differs from its deciduous predecessor in that it has an eruptive pathway from the dental follicle to the gingiva, the gubernaculum dentis. With this background in mind, the present review focuses mainly on the early development of AOT. We successfully demonstrated a close spatial relationship between AOT and the gubernaculum dentis in a typical case. From further observations of the same AOT in which an enclosed permanent canine showed enamel hypoplasia, it is possible to pinpoint areas around the crown of a developing successional tooth in continuity with the gubernaculum dentis as starting points. In addition, we discuss the unifying histogenetic concept of three clinical variants, namely, pericoronal (follicular), extracoronal (extrafollicular), (see Article note) and peripheral.

Although widely quoted by clinicians and pathologists, the prefix “follicular” implies that AOT develops in connection with the dental follicle of ectomesenchymal origin. In this review, we chose to use the more descriptive terms “pericoronal” and “extracoronal” in accordance with the 2004 report by Rick [1]. In 2007, Philipsen et al. [2] also began to put these headings in brackets as additional subtitles.

F. Ide (✉) · K. Mishima · I. Saito
Departments of Diagnostic Pathology and Oral Pathology,
Tsurumi University School of Dental Medicine, 2-1-3 Tsurumi,
Tsurumi-ku, Yokohama 230-8501, Japan
e-mail: ide-f@tsurumi-u.ac.jp

F. Ide · K. Kikuchi · K. Kusama
Division of Pathology, Department of Diagnostic
and Therapeutic Sciences, Meikai University School
of Dentistry, Sakado, Japan

F. Ide · N. Horie · T. Shimoyama
Department of Oral Surgery, Saitama Medical Center,
Saitama Medical University, Kawagoe, Japan

S. Yamachika · K. Satomura
Second Department of Oral and Maxillofacial Surgery,
Tsurumi University School of Dental Medicine,
Yokohama, Japan

H. Sakashita
Second Division of Oral and Maxillofacial Surgery,
Department of Diagnostic and Therapeutic Sciences,
Meikai University School of Dentistry, Sakado, Japan

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Introduction

The relative frequency of adenomatoid odontogenic tumor (AOT) corresponds to 2.2–7.1%, making it the fourth most common odontogenic tumor [1, 2]. Accordingly, current understanding of its clinical, radiologic and pathologic attributes is comprehensive. It is well-established that AOT appears as three clinical variants (pericoronal [70.8%], extracoronal [26.9%] and peripheral [2.3%]) [2], and these variations conform in all respects to categorization as benign [1, 3, 4]. Because of its distinctive microscopic features, the diagnosis of AOT is not difficult [1, 3]. Lesions that pose differential diagnostic problems include adenoid ameloblastoma [1, 3, 4] and adenomatoid odontogenic hamartoma

[1, 5], both of which have been discussed in the literature [1, 3] and need not be pursued further here. Although there were very rare cases of AOT with two separate tumors in the same region [6, 7], an unusual example of multifocal AOT described by Larsson et al. [8] might well fall into a spectrum of multiple adenomatoid odontogenic hamartomas [5].

Different hypotheses for the pathogenesis of AOT have been proposed [1]. It could theoretically arise from the enamel organ [9, 10], the epithelial lining of dentigerous cyst [11], epithelial rests of Malassez of the deciduous or permanent tooth [12, 13], or remnants of the dental lamina [10, 14]; however, none of these has received wide support [1]. A clinical finding of note is that the vast majority of AOT arise in association with the successional tooth during active dental development [1, 2]. Within this framework, current concepts on the origin and growth of AOT are detailed in the present article, on the basis of our multi-institutional experience and by a thorough review of the relevant literature. We also discuss in detail how the three clinical variants of AOT (pericoronal, extracoronal and peripheral) are formed at length.

Discussion

Gubernaculum Dentis and AOT

Background

Accumulating evidence now shows that AOT is unique among odontogenic tumors, because of a very limited period (87% are seen in the second and third decades, with 65% in the former) [2] and a quite restricted anatomic location (80% in the incisor-canine region) [1, 2] for its onset. Naturally, the pathogenesis of AOT appears to be different from that of other epithelial odontogenic tumors. In 1992, Philipsen et al. [15] theorized that the gubernaculum dentis may be implicated in the development of AOT, a view which we share. This normal structure has been described in many anatomy textbooks [16–19] and other formal accounts [20–22], although it generally goes unnoticed. It consists of a fibrous band (gubernacular cord) running in the bony channel (gubernacular canal) that connects the pericoronal follicular tissue of the successional tooth with the overlying gingiva, and opens on the alveolar bone crest behind the deciduous predecessor. Remnants of dental lamina form strands within this track. The gubernaculum dentis in the mixed dentition is an eruption pathway of the successional tooth [16–22].

Since the gubernaculum dentis contains a concentration of dental lamina, its significance in the pathogenesis of ameloblastoma was suggested more than a century ago

[23]. This proposal applies to odontogenic keratocyst, no less [24]. According to Philipsen et al. [15], AOT may arise from these epithelial residues in close proximity to the crown of a permanent tooth, and some of them can move during tooth eruption along the gubernacular canal. This attractive hypothesis might more appropriately explain why AOT rarely arises in association with the deciduous tooth (three convincing [6, 25, 26] and one possible [27] cases with the exception of one debatable example [28]). The question thus arises as to why some AOT relates to the permanent molar which has no deciduous predecessor, although it consists of less than 4% of pericoronal lesions (see Refs. [2] and [30] for an additional list of references) [1, 27, 29, 31–39]. Suffice it to say that unlike the deciduous tooth, the permanent molar also has a molar gubernacular cord [18, 20, 22]. Unfortunately, there was only a schematic drawing of gubernaculum dentis in their landmark report [15], and subsequent experience has not added support to this concept [1, 2].

Literature Review and Case Presentation

From a search of the literature, the gubernacular canal was fortuitously demonstrated on radiographs in seven cases of pericoronal AOT into which a permanent canine protrudes [40–46]. One gross specimen showed a gubernacular cord that was accidentally pulled out of a gubernacular canal during surgery [44]. We made exception to the acceptance of case 2 reported by Abrams et al. [47] not showing a definite radiographic presentation. This feature was not specifically recorded in six reports [40–44, 46], and the remaining one misinterpreted it as a widened nutrient canal [45]. Although the veritable cases were all in the mandible [40–46], differences in the structural complexity between the maxilla and mandible could be cited as a rationale for this bias. Being a forgotten structure, other authors probably overlooked it.

In the present case, conventional dental radiographs showed features diagnostic of pericoronal AOT containing a permanent canine (Fig. 1a). On computed tomography scan, an extremely expanded gubernacular canal was found to extend into the bony crypt (Fig. 1b–d). It is easy to speculate that this may guide a canine with AOT in eruption. Grossly, a thickened gubernacular cord was continuous with a fibrous capsule of AOT and the dental follicle (Fig. 2a, b). Microscopically, it was replete with remnants of dental lamina (Fig. 2c, d). Since surgeons are now encouraged to preserve the teeth involved in AOT (see Ref. [30] for details) [1, 48], it becomes difficult to clarify a kinship of AOT with the successional tooth and its gubernaculum dentis at the histologic level. New imaging techniques are, instead, successful in revealing their spatial relationships.

Fig. 1 Adenomatoid odontogenic tumor (AOT) in an 11-year-old girl. **a** Panoramic radiograph. Spatial relationship between AOT and the gubernaculum canal. **b** Cross-section image of CT. Bone resorption of the inner lingual cortical plate by AOT is evident. **c, d** Panoramic images of CT

Early Development of AOT

Background

Enamel is a unique hard tissue that once formed it is never remodeled [19]; therefore, alterations in enamel during its development are permanently recorded and can provide valuable clues regarding the timing of damaging events. Although only soft tissues were processed in the majority of AOT, there were a few reports describing the gross appearance of a lesional tooth [12, 32, 36, 47, 49, 50]. As far as we know, three cases of pericoronal AOT showed areas of enamel hypoplasia on the involved crown [6, 51, 52], all of which were focal (occlusal surfaces of an upper deciduous canine [6] and lower permanent first premolar [52] and cervical area of an upper first premolar [51]). This suggests that most AOT may start to grow after the crown

formation reaches completion, thus leaving no trace of enamel hypoplasia [12, 32, 36, 49].

Enamel Hypoplasia

On gross examination of the above AOT, diffuse hypocalcification was detectable from the incisal edge to the cervical margin of a permanent canine, and the lingual surface was more severely affected (Fig. 3). There was neither change in shape nor reduction of thickness, but spotty enamel defects were evident in the form of pits at the cervical one-third of the crown. It is generally recognized that the crown formation of a permanent lower canine takes place at the age of 4–5 months and is finished when a child is 4–6 years of age [19]. Based on these findings, the present AOT obviously disturbed ameloblasts when two-thirds of the crown was formed (at least 4 years

Fig. 2 Relationships between AOT (asterisk), the gubernacular cord (arrowhead) and the dental follicle (arrow). **a** Intraoperative finding. **b** Gross appearance. Gubernacular cord was partly removed to reveal the crown. **c** Scanning photomicrograph (H&E, $\times 1.5$). **d** Photomicrograph of strands of dental lamina in the gubernacular cord (H&E, $\times 400$)

of age) [19]. At the end of enamel maturation (below 6 years of age) [19], AOT was mainly located lingual to the crown (see Figs. 1b and 2b). Excluding a tumor-free dental follicle surrounding a partly formed root (a matter discussed later), the actual size of AOT was less than 10 mm at the age of 11 years (compare Figs. 1b with 2c). That is to say, it grew very slowly above 7 years. Combining the previous information and present findings, it is entirely possible that most, if not all, of AOT may cease to proliferate and can remain stationary for a considerable amount of time.

Brief Summary

Regarding a fairly common canine-associated AOT in the maxilla (47% of lesions with an unerupted tooth) [32], an origin from enamel organ of a normal or supernumerary series is unacceptable, since a missing permanent canine is unusual and a supernumerary tooth is very rare in this region [19]. Even if AOT occurs in the enamel organ itself while amelogenesis is still in progress, a partially formed or malformed crown should be inevitable. However, this is not the case just described. If AOT arises from active enamel epithelium of the cervical area at the end of crown formation, the apical elongation of Hertwig's epithelial sheath does not occur, and the root is not mapped out [19]. Given a quite narrow age range as mentioned above, there is no reason to believe that AOT derives from epithelial rests of Malassez that persist throughout the life span of a permanent canine. Similarly, it is impossible to reconcile an origin of AOT from these epithelial residues around the root of a deciduous canine, with its permanent molar position [2, 30].

Unifying Histogenetic Concept of AOT

Background

Philipsen et al. [15] and Reichart and Philipsen [29] conceptualized a unified pathogenesis for diverse clinical settings (pericoronal, extracoronary and peripheral) of AOT. As to various modes of presentation, we expand here their argument and reemphasize that the three variants are best considered together [53].

Extracoronary Variant

Reichart and Philipsen [29] subdivided extracoronary AOT into four subtypes (E_1 – E_4) based on radiographic appearance. Although it is conceivable that E_1 subtype (no relation to tooth structures either erupted or unerupted) may exist, such cases take place only very rarely, if at all [32]. In any event, it is theoretically possible that normal eruption of its associated tooth may leave AOT either on a lateral root surface (E_2 ; inter-radicular [Fig. 4a] or E_4 ; superimposed [Fig. 4b]) or at a root apex (E_3 ; radicular/periapical [Fig. 4c, d]). Which of these subtypes (E_2 – E_4) will develop depends primarily on the spatial relationship between a growing AOT and erupting teeth [15]. In whatever way the relationship arises, AOT may commence around the crown of a developing permanent tooth. At an earlier stage, it appears to be nothing more than an enlarged dental follicle radiographically [12, 47, 48, 54–58].

Fig. 3 Gross appearances of a permanent canine with diffuse hypocalcification. *Arrows* indicate pitted enamel defects

Pericoronal Variant

There may be two subtypes of pericoronal AOT, perhaps with different causes and arising at different stages of AOT development (Fig. 5a, b). In one subtype, expanding AOT merely embraces the crown of an adjacent tooth at a distinctly later stage [29]. It is not uncommon to see AOT associated with two or more teeth (6% of pericoronal lesions) [1, 6, 32, 47, 48, 50, 58]. Although superimposition often results in a “dentigerous” appearance radiographically (Fig. 5b), its relationship to the crown of an unerupted tooth is not a dentigerous one. There is microscopic evidence that a thick fibrous tissue clearly separates AOT from the crown (Fig. 5c). Since tooth-tumor relationships were not preserved on histologic sections in most of AOT as described earlier, such a feature has only been presented once [59]. This type of pathogenesis appears to be very much the exception.

In the other subtype, AOT envelops a fully matured crown at a relatively early stage, and later assumes a classic “dentigerous” relationship following tumor growth combined with active tooth eruption (Fig. 5d, e). Grossly, about 80% of this subtype showed circumferential attachment to the neck of an unerupted tooth (Fig. 5d)

[34], and histologically, incipient lesions revealed that the ameloblastic layer remains intact on the crown surface [58, 60]. With time, a characteristic pericoronal radiolucency extending apically far beyond the cemento-enamel junction becomes apparent (see Fig. 1a) [1, 32, 60], and in more than half of cases [60], a single tooth is almost totally enclosed (Fig. 6a) [43]. Not surprisingly, the crown is always enveloped asymmetrically on gross sectioning [36, 41, 43, 51, 54, 60–67], and AOT limited to one aspect of the tooth is not uncommon [60–62]. We draw attention to the fact that tumor extensions along the root surface are close to zero (see Fig. 2b, c) [39, 41, 43, 51, 60, 61, 63–67]. As we have seen, a thick band surrounding part of the root is a hyperplastic dental follicle in response to eruption disturbance but not a tumor-specific fibrous capsule, although imperceptibly blending with each other (see Fig. 2a, b). Follicular growth and root elongation in a circumscribed environment facilitate resorption of the bony crypt (see Fig. 1b). This assists in enlargement of AOT and in turn, increasing forces displace an enclosed tooth away from its direction of eruption (Fig. 6b). Dilaceration occurs when a growing apex of the root collides with the inner cortical bone [36, 41, 46, 49, 51, 60, 65].

Fig. 4 Periapical radiographs of extracoronal AOT. **a** Inter-radicular type in a 22-year-old female. **b** Superimposed type in a 20-year-old male. **c** Radicular type in a 19-year-old female. **d** Periapical type in a 23-year-old male

Peripheral Variant

Certainly, peripheral AOT is a debatable lesion [47, 53]. With regard to their genuine extraosseous origin, the previously reported cases do not withstand critical reevaluation [53]. It is basically an upper incisor-associated lesion (80% of peripheral lesions) [53] and usually appears as a labial gingival mass overhanging the crown (93% of peripheral lesions) [2, 14, 53]. If small AOT is located coronolabially to an erupting permanent incisor (just behind the resorbed root of a deciduous incisor), active eruption forces may push it up toward the marginal gingiva, culminating in a hybrid central and peripheral process [15, 53]. This type of AOT is unreasonably given the suffix of peripheral (Fig. 6c). In certain cases [47, 68], gingival swelling regressed with time, leaving a residual bone defect at its base. Whether to designate it a gingival AOT which erodes into the underlying alveolar bone or a superficial intraosseous AOT which expands outward into the overlying gingiva is a matter of semantics (for review, see Refs. [15, 29, 50] and [53]) [1, 68–71]. This dilemma is apparent

in two articles of Philipsen et al. [15, 50]; Takeda and Kudo's case [70] that demonstrated central and peripheral involvement was not included as a peripheral AOT in 1991 [50] whereas it did in 1992 [15]. In practice, when confronted with gingival AOT showing a moat-like defect of the alveolar crest, it is strongly advisable to think of an erupted intraosseous lesion first [1, 14, 47, 53].

Brief Summary

Evidence in support of a unifying histogenetic concept of three potential variants is strong. Many clinical observations that after surgical exposure, an impacted tooth associated with AOT begins to erupt spontaneously (see Fig. 5a), and tumor tissue tends to regress are applicable to this view (see Refs. [30] and [53] for an additional list of references) [47, 58, 66, 67, 71]. Orthodontic movement of teeth in relation to AOT is also a case in point (see Refs. [30] and [53] for specific details) [44, 48, 49, 52, 57]. Given time, a fully erupted tooth carries a residual AOT to the gingiva (peripheral variant) [44, 47, 53] or leaves it

Fig. 5 Pericoronal AOT.

a Radiograph of AOT associated with the lower second molar in a 15-year-old boy. Inset depicts the tooth eruption 8 months after marsupialization. **b, c** Panoramic radiograph of canine-related AOT in a 16-year-old girl. Photomicrograph shows boundary between the crown and contiguous cystic AOT separated by the dense fibrous tissue. Asterisk indicates the enamel space (H&E, $\times 1.5$). **d** Cut surface of canine-containing dentigerous AOT in a 22-year-old female. **e** Photomicrograph of true dentigerous AOT in a 17-year-old female enclosing the upper first premolar. Arrow indicates the cemento-enamel junction (H&E, $\times 1.5$)

Fig. 6 **a, b** Gross and radiographic appearances of pericoronal AOT in a 22-year-old female. Arrow indicates the root apex. **c** Clinical photograph of peripheral AOT in a 15-year-old male

within the alveolar bone surface (extracoronal variant) [4, 13, 33, 47, 60, 71–74]. More often than not, AOT itself forms a barrier, causing tipping of the crown and/or spacing between the neighboring teeth (see Fig. 6c) [53, 69, 73]. The fact that there are no significant differences in age, gender and anatomic location among the three clinical variants is additional supporting evidence [14, 32, 50, 53].

Conclusions

The majority of readers may not be familiar with the gubernaculum dentis. As illustrated in standard histology

textbooks such as Ten Cate's [19], the gubernacular canal and its fibroepithelial content that connect the dental follicle of an erupting successional tooth to the lamina propria of the gingiva clearly can be seen long the lingual surface of the deciduous dentition. At a more practical level, we are only now, 20 years after Philipsen et al. [15], just beginning to understand the histogenetic relationship between AOT and gubernaculum dentis. It is reasonable to conclude that dental lamina in the gubernacular cord of a developing permanent incisor, canine or premolar seems to be an embryonic source of more than 96% of AOT [1, 2]. Undoubtedly, it commences during the mixed dentition in which post-natal odontogenesis goes on (in the first decade).

With regard to the most common canine-related AOT (68% of all cases) [32], tumor growth may start around the completely formed crown (at nearly 5 years of age) [19], and there is a different mode of tooth envelopment, either complete or partial. As tumor expansion and tooth eruption continue, a widened gubernacular canal is a pathway of least resistance (see Fig. 1b–d). On the whole, AOT has grown unnoticed for more than 5 years (in the second decade) [1, 2]. Extracoronary AOT may arise by eruption of its associated tooth past a coronally positioned tumor. Clinical conditions known as pericoronary AOT may be formed by two different paths. Although there are arguments both in favor and against an origin from a pre-existing dentigerous cyst [1, 11, 29, 32, 47], it is essential to keep an open mind that a true “dentigerous” AOT does not imply a derivation from the lining epithelium. Enamel hypoplasia of the involved crown, if present, provides a golden opportunity of studying the natural history of AOT (see Fig. 3). There is no doubt that peripheral AOT forms when an associated tooth erupts into the gingiva passing through the intraosseous phase of its eruption pathway, so that a soft-tissue mass becomes an outstanding clinical feature. Hence it is not necessary to unreasonably propose an extrasosseous origin [14, 47, 53].

Future Perspectives

Do all AOT have an origin from rests of dental lamina confined in and immediately adjacent to the gubernacular canal? The answer is no. There are cases of AOT which arise far after the age of the active dental development and of AOT associated with deciduous teeth which lack the gubernaculum dentis. These exceptions support the ability of AOT to develop from dental lamina outside of the gubernacular canal. In a similar manner, many odontogenic tumors and developmental cysts that would arise from rests of dental lamina occur frequently in locations nowhere close to the gubernaculum dentis.

Another major gap in our knowledge is a surprisingly high frequency of pericoronary AOT associated with the canine (60% of pericoronary lesions of which 40% with the upper canine) [1, 2, 29] and of extracoronary AOT attached to the canine root (89% of extracoronary lesions) [1, 50]. Although the canine is commonly impacted, neither the increased number nor long-term persistence of remnants of dental lamina in this region can be taken for granted [19]. A significant predominance in the maxilla (64% of all cases) [2] as well as in females (F:M ratio of 1.9:1) [2] also remains unexplained. In pericoronary AOT, 66% occur in the maxilla and 34% in the mandible, whereas the corresponding figures in extracoronary AOT are 58 and 42%, respectively [2, 27], adding a poorly understood possible

difference. These topographic predilections need further research.

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