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A Case Report:

A Unique case of Adenomatoid Odontogenic Tumour of Lateral Incisor: Pathogenetic Evaluation through Immunohistochemistry

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ABSTRACT

Background and Setting: The article reviews a rare case of a 9 year old female patient with a swelling in the anterior maxillary region, associated with the missing left lateral incisor. Her radiograph revealed an impacted, left lateral incisor that was surrounded by a well-defined radiolucency with corticated margins, on the distal aspect of the crown and root. Numerous hypotheses for the pathogenesis of AOT have been proposed over the years, but controversy still exists, as to precise odontogenic source of origin. Through this review we have extensively discussed the differential hypothesis regarding this enigmatous tumor.

The Adenomatoid odontogenic tumor (AOT) is a rare (0.6 to 38.5% of odontogenic tumors) benign tumor of epithelial origin that predominantly occurs in children and young adults (88% occurs in 2nd and 3rd decades of life). The tumor is found twice as frequent in females, as in males. Two forms of the tumors are identified: intraosseous and extraosseous. Seventy one per cent of cases were of the follicular type, with the impacted maxillary (64.3%) canine (60%), being predominantly affected. Expert morphological diagnosis is required to establish a differential diagnosis, especially from ameloblastoma, in order to prevent an extensive surgery.

The term Adenomatoid odontogenic tumor, a century old, benign tumor of odontogenic origin, was first proposed by Philipsen and Birn, which was later accepted by WHO in 1971. 1AOT may constitute about 2.2% to 7.1% of odontogenic tumors, as reported in a recent study. The differential diagnosis of AOT is crucial in terms of surgical management, and local excision is the treatment of choice for AOT. The increasing number of reports on AOT points to the fact that the tumor develops more frequently than formerly expected. 1The tumor has been called as the 2/3rds tumor, as 2/3rd cases appear in females, 2/3rd cases in maxilla, and 2/3rd cases appear in relation to impacted teeth. [2]

The AOT can be subtyped based on its clinical and radiological findings. The follicular or intraosseous type and extrafollicular or extraosseous types; of which the follicular type is more common and it is localized around the crown of a retained tooth which also include the upper part of the tooth root. [1]There are three well-established clinical variants of AOT namely the extraosseous [3] or peripheral (2.3%), and intraosseous: [3] pericoronal (70.8%) and extracoronal (26.9%). Multifocal AOT described by Larsson et al. was included in the bracket of multiple Adenomatoid odontogenic hamartomas. [4]

CASE REPORT

A 9-year-old female patient presented with a 1 month old, slow growing swelling in left anterior maxillary region. The swelling measured about 2 x 2.5 cm in size extraorally, extending anterio-posteriorly from philtrum of the lip to angle of the mouth, obliterating the nasolabial fold; and superior-inferiorly extending from the upper lip to lower border of nose. The overlying skin appeared normal and there was no associated pain. Intraoral examination revealed a diffuse swelling that extended from medial aspect of 21 to distal aspect of 53 obliterating the mucobuccal fold. 22 was found missing and a retained 52 was seen. The overlying mucosa appeared normal. The swelling was tender on palpation, soft, fluctuant, non-compressible, non-depressible and immobile. (Figure 1)

FIGURE 1: *Non-compressible, non-depressible and immobile swelling*

A provisional diagnosis of dentigerous cyst was made.

Radiographic examination revealed an impacted 22 surrounded by a well-defined, unilocular radiolucency with corticated margins on the distal aspect of the crown and root of 22. (Figure 2)

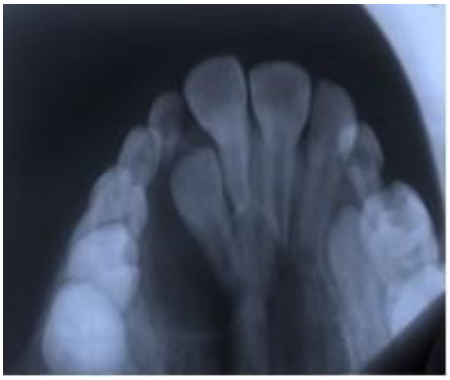
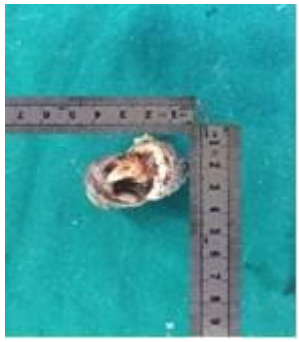


FIGURE 2: *Unilocular radiolucency with corticated margins on the distal aspect of the crown and root of 22*

Surgical enucleation of the cyst was suggested to be done under local anaesthesia.



Macroscopically, the specimen was oval in shape, soft to firm in consistency, brownish in color and measured about 1.5x1.2x1cm in size. (Figure 3)

Cut specimen revealed an embedded fully formed lateral incisor within the lesion, together with a yellow exudate.

Microscopically, hematoxylin and eosin stained section showed the tumor mass surrounded by a distinct fibrous capsule. The tumor mass exhibited spindle shaped epithelial cells arranged in the form of solid areas and whorls, (Figure 4 a) along with a ductal pattern that was lined by cuboidal to columnar cells, (Figure 4 b) within a scant fibrous stroma. Towards the periphery of a few areas with tumor cells arranged in form of strands were visible. (Figure 4 c) Eosinophilic matrix indicating an inductive phenomenon and few foci of calcifications were present. Based on these findings, the histopathological diagnosis of AOT was made. (Figure 4 d)

DISCUSSION

The clinical findings presented in this case substantiate the unique features documented in the literature, in terms of higher incidence in women; its occurrence in the 1st decade of life; and the maxillary lesion associated with an unerupted tooth. AOT cases have been reported in relation to impacted canine, but very few cases have been found in association with an impacted lateral incisor as reported here. [5]

History

Adenomatoid odontogenic tumor (AOT) is a relatively uncommon distinct odontogenic neoplasm that was first described by

Steensland in 1905. 5Due to the non-availability of photomicrographic documentation in the early days the search for an identifiable case of the AOT – a term stated by Philipsen and Birn in 1969 –was challenging, as the tumour terminology changed over the years. Ide et al. in their meta-analytic review of AOT, discovered that the 'cysticadamantoma' reported by Harbitz in1915 was probably the first irrefutable, confirmed, case of AOT in the 2nd half of the 19th century; reported throughout Europe, America and Japan. The suggestion to change the nomenclature of AOT to adenomatoid odontogenic cyst' was proposed by Marx and Stern. Many different names like ameloblastic adenomatoid tumor, adenoameloblastoma, adamantinoma, epithelioma adamantinum or teratomatous odontoma have been used before to describe the tumor currently called AOT. [5]

Pathogenesis: AOT is said to arise from:

- The enamel organ,
- The epithelial lining of dentigerous cyst,
- Epithelial rests of Malassez of the deciduous or permanent tooth, or
- Remnants of the dental lamina

However, none of the theoretical interpretation of the odontogenic source of origin has received support; therefore was a necessity to identify the pathogenesis of the tumor, using immunohistochemistry. [4]

Immunohistochemical analysis: Immunohistochemistry is commended for research purposes but not as a mundane tool to institute the diagnosis of odontogenic tumors, including AOT.

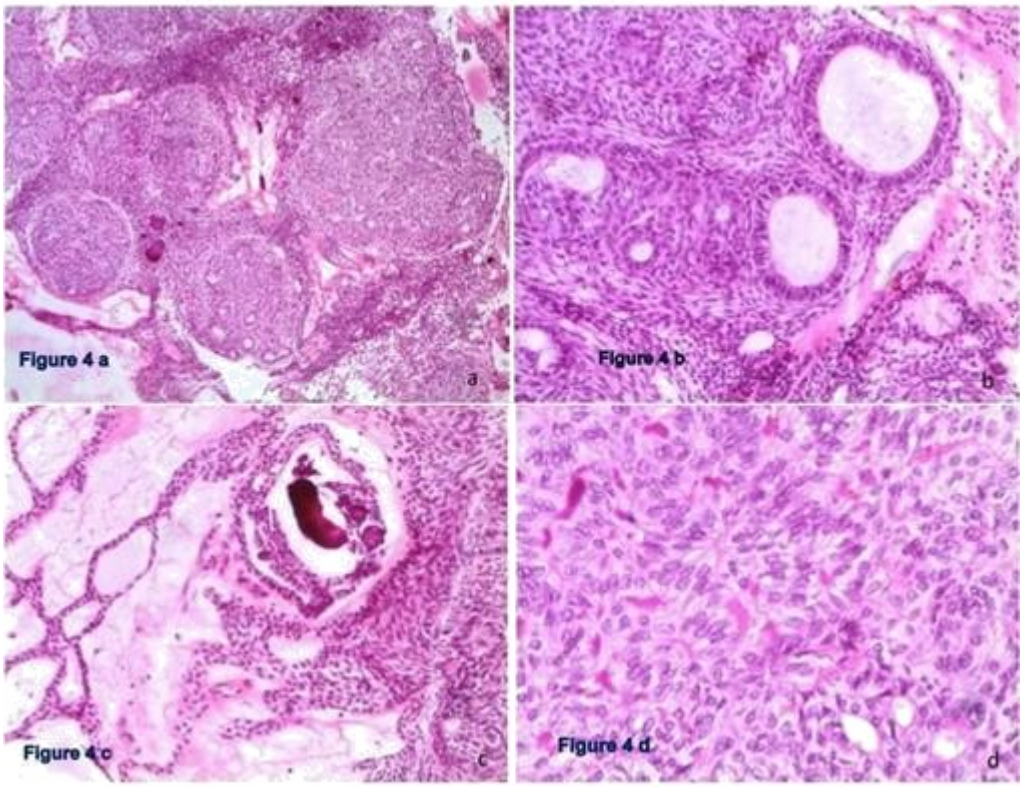
The epithelial cells of the AOT was positive for the CK14 labelling, indicating a secreting or post-secreting stage ameloblast in the adenomatoid structure of AOT. 1Embryologically, it is already known that during the enamel development, CK 14 is positive in the inner enamel epithelial layer which is substituted by CK19, when the ameloblasts are completely differentiated. The spindled areas and the cylindrical cells of the duct-like structures of AOT do not express CK 14 and this variation in the expression of CK14 indicated variability in the differentiation of the tumoral cells. The spindled structures, where the duct-like and adenomatoid structures were located, were found to arise from the post-secretory ameloblasts of the reduced enamel epithelium. The cuboidal cells of the duct-like and adenomatoid structures were considered equivalent to post-secretory ameloblasts in their early stage, that was capable of secreting enamel protein; and the absence of CK14 in these cells is understandable, because the same was also observed in normal ameloblasts. From the phase where the cells no longer express secretion, CK14 is expressed again. Hence the positive markers have indicated a role for reduced enamel epithelium in the histogenesis of AOT. [6]

The classical AOT phenotype has a cytokeratin (CK) profile similar to follicular cyst and/or oral or gingival epithelium based on positive staining with CK5, CK 19 and CK17 and is negative for CK4, 10, 13 and 18. Amelogenin that is seen in limited areas in AOT have been detected in ameloblasts and in the immature enamel matrix.

Takahashi et al. detected a positive staining for iron-binding proteins (transferring, ferritin) and proteinase inhibitor (alpha-one-antitrypsin) in various cells of AOT indicating their role to the pathogenesis of AOT. Bone morphogenic protein (BMP) was positive in the cementifying fibromas, dentinomas and compound odontomas whereas in AOT as well as ameloblastomas and calcifying epithelial odontogenic tumors, it was negative. [5]

Laminin was detected on the luminal surface of ductular, adenomatoid structures that was attuned with the reduced enamel epithelium in the enamel maturation stage. [1]

Luminal surface 6was also found to resemble the basal lamina next to the inner and outer enamel epithelium of the enamel organ The ductular areas were surrounded cells that were flat and fusiform, sometimes with morphology similar to that of the stellate reticulum. [6]



FIGURES 4a, 4b, 4c, 4d: *Histopathology of the specimen. Spindle shaped epithelial cells arranged in the form of solid areas and whorls, (Figure 4 a) along with a ductal pattern lined by cuboidal to columnar cells, (Figure 4 b) within a scant fibrous stroma. Towards the periphery of the lesion, a few areas with tumor cells arranged in form of strands were visible. (Figure 4 c) Eosinophilic matrix indicating an inductive phenomenon and few foci of calcifications were present. (Figure 4 d)*

PCNA that was predominant in the spindled and cord like areas of AOT, indicated a role of tumor growth for these areas. [6]

It was also positive in the small intercellular deposits of lighter eosinophilic material spread within the epithelial proliferation of spindled areas and cords, and on the orders between the tumor and connective tissue. [6]

It was weak in fusiform or stellated cells. [9]

The AOT cells hence have been thought to be able to secrete two types of substances, according to their practical ability: basal membrane material and enamel matrix. [6]

Thus the cytokeratin profiling of the AOT was found to be similar to the follicular cysts and gingival epithelium indicating its origin from the REE (reduced enamel epithelium).

There was also a focal co-expression of vimentin and of SMA at the base of the expansile duct-like zone. The focal α-SMA positive basal duct-like cells indicated a myoepithelial differentiation of a small population of cells. [6]

Mineralized and hyaline material did not show immunohistochemical reactivity for cytokeratin, as expected. [6] The rare formation of osteodentin next to the AOT can only be accepted as a secondary phenomenon in the tumor pathogenesis and therefore discussing the tumor as an odontogenic tumor with ectomesenchyme with or without hard tissue formation as per the WHO 2005, can be accepted. [8]

Extrafollicular variant theory by Philipsen, et al (1992): stated the possibility of a tooth erupting through the AOT and therefore of a possibility of the AOT arising from REE. The hamartomatous lesion would start at the REE and would not hinder dental eruption. [6]

Intraosseous or peripheral tumor in the jaw bones would depend on the three-dimensional position of the tumor and associated tooth.

In deeper impacted teeth, there would be more possibility of AOT to be intraosseous- follicular variant and if superficial, there would be more chances of an extrafollicular (in the case of tooth eruption) lesion. [6]

In tooth impactions next to the alveolar ridge, the tumor could occasionally involve the gingiva during or after the eruption process, which would justify the peripheral variant. [6]

The proliferation rate of AOT in terms of Ki-67-positive tumor cells was found to be low, indicating its benign nature. [1]

Neoplastic or developmental nature of the AOT was confirmed by the expression of 2 markers of the cell cycle, p16INK4A and Ki-67, and the results showed that neither p16INK4A expression nor Ki-67 expression was detected.

Based on these findings it was confirmed that the adenomatoid odontogenic tumour is not considered to be a neoplastic growth of the odontogenic epithelium but was rather a hamartomatous lesion. [7]

Differential diagnosis:

- Adenoid ameloblastoma and
- Adenomatoid odontogenic hamartoma [4]
- Dentigerous cyst [8]
- Calcifying odontogenic tumor when calcifications are present [8]

Treatment and prognosis

Since the tumor is well encapsulated. [2]conservative surgical enucleation is the treatment modality of choice. Whereas in case where there are periodontal intrabony defects caused by AOT, guided tissue regeneration. [7]with membrane technique is suggested, after complete removal of the tumor. [5] Recurrence is rare. [2]

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