Dental Germ Tumor: An Unusual, Cystic, Mixed Epithelial–Mesenchymal Odontogenic Tumor

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Received: 7 October 2019 / Accepted: 25 January 2020 / Published online: 5 February 2020
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Abstract

Although odontogenic lesions have been extensively described and studied, anomalous, challenging cases occasionally come to the attention of the pathologist. Here, we report the clinical and microscopic characteristics of an unusual cystic lesion of odontogenic origin. A 16-year-old male presented with swelling and pain to palpation of the right mandible as well as numbness of the right lower lip. Radiographically, the corresponding lesion was well-defined and radiolucent with internal radiopaque foci. It extended from the right first premolar posteriorly, approaching the angle of the mandible, and involved the mandibular first molar which was impacted and displaced. The second and third right mandibular molars were also impacted and displaced. The patient was treated by excisional biopsy under general anesthesia. The histopathologic examination revealed the presence of multicystic areas lined by a thin, non-keratinizing squamous epithelium that resembled the epithelial lining of a dentigerous cyst. In continuity with the cystic lining, areas of myxoid tissue reminiscent of dental papilla were observed. The myxoid tissue formed structures that were surfaced by an epithelium comprising a basal layer of ameloblast-like cells with reverse polarity of the nuclei. Above the basilar cells, additional layers of epithelial cells composed a structure resembling the enamel organ. Subjacent to the basilar ameloblast-like cells, a condensation of mesenchymal cells with polarized nuclei opposite to the ameloblast-like cells was present. These mesenchymal cells resembled odontoblasts. In addition, numerous mineralized structures amongst the odontogenic epithelial tissue were present. To date, the patient remains well and without evidence of recurrence after 36 months of follow-up.

Keywords Odontogenic tumors · Primordial odontogenic tumor · Archegonous odontogenic cyst · Odontoma · Ameloblastic fibro odontoma

Introduction

In 2017, the WHO classified ameloblastic fibro-odontomas into the spectrum of odontomas as an immature state of these lesions [1]. Other similar lesions demonstrating histologic features of varying stages of odontogenesis have been

described in the literature. In 2014, Mosqueda Taylor et al. described a new entity which they named primordial odontogenic tumor (POT) with the presentation of six cases [2]. All the described tumors comprised of variably cellular loose fibrous tissue with areas analogous to dental papilla. They were covered by epithelium similar to the internal epithelium of the enamel organ [2]. Subsequently, in 2015, Slater et al. added a similar case to the literature and confirmed POT as a new entity [3]. In 2016, Argyris et al. described a lesion they believed to be a primordial odontogenic cyst with induction phenomenon and dentin material or an archegonous cystic odontoma (ACO) [4]. Ide et al. commented on their findings, stating that the lesion mentioned above could be an odontogenic cystic hamartoma or an odontogenic cyst presenting as an associated odontogenic hamartoma in its capsule [5]. The lesions described by these authors and the

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resulting discussions demonstrate the apparent controversy as to their classification that continues through today.

We recently examined a case with similar features to these odontogenic lesions and aim to add relevant information to this topic. Here, we report the clinical and histopathologic features of an unusual odontogenic lesion.

Case Report

A 16-year-old male patient presented with right-sided swelling and pain to palpation of the mandible combined with numbness of the right lower lip. The patient's medical and family history were without significant findings or current medical treatments.

The extraoral examination revealed facial asymmetry of the body and angle of the right mandible. Vestibular expansion was identified intraorally. The right mandibular molars were absent, although the patient did not recall a history of dental extractions.

A panoramic radiograph showed a well-defined, corticated, radiolucent lesion with multiple radiopaque foci. It extended from the right first premolar to an area anterior to the mandibular angle. Additionally, the lesion was associated with an impacted first molar and had caused displacement of the second and third right mandibular molars. The root of the right second premolar was also displaced (Fig. 1).

The clinical and radiographic differential diagnosis included an odontoma, in its immature or mature variants, adenomatoid odontogenic tumor, calcifying epithelial odontogenic tumor, and calcifying odontogenic cyst.

The patient was treated with enucleation and curettage, extraction of the right first mandibular molar, and cryotherapy under orotracheal intubation and general anesthesia. The lesional tissue was submitted to pathology for histopathologic evaluation.

Fig. 1 Radiographic characteristics. A panoramic radiograph shows a well-defined, radiolucent lesion with multiple radiopaque foci extending from the right first premolar posteriorly to approximate the mandibular angle. The lesion was associated with an impacted first molar and it displaced the second and third right mandibular molars. The lesion also displaced the root of the second right premolar

Gross examination showed multiple fragments of soft and hard tissue and a molar tooth. The soft tissue measured $10.5 \times 8.0 \times 3.0$ cm and had a rough surface on one side.

The histopathologic examination revealed cystic areas lined by a thin, non-keratinizing squamous epithelium that resembled a dentigerous cyst. Structures of dental germ-like formations projected into the cystic lumen (Fig. 2a, b). Areas of myxoid tissue resembling dental papilla presented as a proliferation of round to spindle-shaped cells in a myxoid stroma (Fig. 2c). These structures were covered by ameloblast-like cells demonstrating reverse polarization of the nuclei. The ameloblast-like cells were separated from the adjacent mesenchyme by an eosinophilic line interpreted as a basement membrane.

Above the ameloblast-like cells were polygonal epithelial cells similar to the stratum intermedium, and areas showed characteristics of the stellate reticulum (Fig. 2c–e). These features were analogous to the enamel organ. Subjacent to the ameloblast-like cell layer was a condensation of mesenchymal cells. These cells resembled odontoblasts and most had polarized nuclei opposite to the ameloblast-like cells (Fig. 2e). We hypothesized that these structures appeared in continuity with the cystic epithelium in areas where signals of a mesenchymal induction-like phenomenon occurred (Fig. 2f–h).

Numerous mineralized structures arranged concentrically were compatible with Liesegang rings (Fig. 3a), and enamel matrix-like material was identified amongst odontogenic epithelial tissue (Fig. 3b–d). Hyalinized material, interpreted as dentinoid material, was seen only focally (not shown).

Immunohistochemistry was performed for cytokeratins (CKs) 14 and 19, and the results showed positivity for both proteins in the ameloblast-like cells. Based on the histologic and immunohistochemical findings, a diagnosis of a benign odontogenic tumor was made.

After treatment, the patient was followed for 36 months without evidence of recurrence.

Discussion

The anatomic location, radiographic features, and histologic characteristics confirmed the diagnosis of an odontogenic lesion. Some of the microscopic features were similar to those of POT and ACO [2, 4].

ACO was described by Argyris et al. in 2016 as an odontogenic lesion presenting as a radiographic unilocular radiolucency in the area of a missing tooth in an 18-year-old patient. The authors named the lesion “primordial odontogenic cyst with induction phenomenon and dentinoid material” or an “archegonous cystic odontoma”. The name was based on the histologic characteristics of a cystic cavity lined by thin, non-keratinized stratified squamous epithelium

Fig. 2 Histologic characteristics: **a** The cystic area of the lesion with solid dental germ-like structures protruding into the cystic lumen (arrow) (H&E, original magnification $\times 40$). **b** Higher magnification shows details of the dental germ-like structures including ectomesenchymal tissue (dental papilla), polarization of enamel cells, and stellate reticulum (H&E, original magnification $\times 100$). **c** Multiple germ-like sprouts (H&E, original magnification $\times 40$). **d** Higher magnification of one of these structures (H&E, original magnification $\times 100$). **e** Higher magnification demonstrating the polarization of both epithelial (*) and mesenchymal cells (+). Note the presence of a structure similar to the enamel organ with ameloblastic, intermedium stratum, and stellate reticulum-like cell layers (H&E, original magnification $\times 200$). **f** Cystic wall of the lesion showing two to three layers of nonkeratinized cuboidal epithelial cells. Below the cystic epithelial cells, cellular rarefaction indicative of induction was observed (H&E, original magnification $\times 200$). **g** Continuity of the cystic wall presenting a structure suggestive of the initial phase of a dental germ. Note that part of the epithelial surface was lost during technical preparation (arrows) (H&E, original magnification $\times 40$). **h** Higher magnification of figure B depicting the condensation of mesenchymal cells (arrow heads) (H&E, original magnification $\times 100$)

with a fibroblastic connective tissue wall showing induction phenomenon. Focally, ameloblastic fibroma-like tissue and deposits of dentinoid material were observed [4].

ACO was discussed and renamed by Ide et al. as a complex odontogenic cyst with mural hamartoma or an odontogenic cystic hamartoma [5]. Unlike our case, lesions reported by these authors did not show evidence of differentiated odontoblasts. It is noteworthy that the authors

described areas of ameloblastic fibroma/ameloblastic fibro-odontoma; however, in our case, these areas were absent [5, 6].

The primordial odontogenic tumor (POT), a newly included entity in the WHO classification, was first described by Mosqueda-Taylor et al. [1, 2]. It most commonly occurs in the posterior mandible and is associated with unerupted teeth, either in a pericoronal position or surrounding the

Fig. 3 **a** Globules of calcification were seen among epithelial cells of the cystic lining (H&E, original magnification $\times 200$). **b** In rare areas, matrix-like enamel was identified (H&E, original magnification $\times 200$). **c** In very few areas, mineral tissue similar to enamel matrix surrounded by ameloblast-like cells was seen (H&E, original magnification $\times 400$). **d** Abundant mineralized material was noted among cells showing similarities to cells of the reduced enamel epithelium (H&E, original magnification $\times 400$)

whole tooth as a “dentigerous cyst-like” radiolucency [7]. The radiographic characteristics in the present case showed radiopaque flecks, whereas POTs are reported as entirely radiolucent lesions [1, 2]. Microscopically, POTs comprise a myxoid stroma, rich in fusiform and ovoid cells and closely resembling dental papilla, completely surrounded by a single palisaded layer of cuboidal to columnar cells with reverse nuclear polarization. The latter resembles the internal enamel epithelium observed during tooth development [7, 8].

In our opinion, the histopathological features of the present case showed some similarities with POT, but the induction phenomenon was more evident. In contrast to the single tumor sprout usually observed in POT, the present tumor showed multiple structures protruding towards the interior of the cyst with the semblance of an immature compound odontoma in its early stages of development. Moreover, the polarization of mesenchymal cells suggests inductive activity and a differentiation to odontoblasts. Although the condensation of the mesenchymal cells in POT is interpreted as an induction phenomenon, the mesenchymal cells are not polarized unlike what was observed in the current case [9].

To further elucidate the differentiation stage of the ameloblast-like cells, we performed an immunohistochemical analysis of CK14 and CK19. It is known that in normal secretory ameloblasts CK14 is substituted by CK19. In our case, the ameloblast-like cells were positive for both proteins which indicates lack of terminal differentiation for secretion [10]. The histologic characteristics and immunohistochemical

profile suggest the tumor represents an aborted dental germ similar to POT yet the nuclei polarization of both the ameloblast and odontoblast-like cells indicate a more advanced phase of odontogenesis.

It is also noteworthy that the cystic epithelium was continuous with the rest of the lesion. This implicates the cystic epithelium as a feature of the lesion and not a separate process, as previously reported by others with designations of dentigerous cyst with mural hamartoma or dentigerous cyst associated with an odontoma [5, 11, 12]. We hypothesize that the cystic epithelium was either a component of the lesion or perhaps even the tissue of origin. It is important to note that lesions of the dental germ spectrum are usually associated with impacted teeth. In the surgical treatment of other odontogenic lesions, extraction of the associated impacted tooth is recommended in order to avoid recurrence [7, 13]. This leads us to hypothesize that a structure related to the tooth may have a role in lesional recurrence. The reduced enamel epithelium could be causative of this phenomenon and deserves further investigation.

In conclusion, we believe that POT and the lesion reported—a dental germ tumor—develop during the primordial stage of tooth development and may represent varying aborted phases in the process of odontogenesis. The current case may be considered a variant of POT or a new entity presenting a more advanced phase of odontogenesis. Both lesions could be considered in the spectrum of odontoma, as proposed by the WHO. Further molecular studies analyzing genes and transcription factors related to odontogenesis

could be performed to further shed light on this interesting topic.

Acknowledgements The authors would like to thank Ms. Audra Renyi for the English edits of this article.

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