A clinicopathologic study on central odontogenic fibroma: with special reference to amyloid variant

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Objective. The aim of this study was to clarify the clinicopathologic features of central odontogenic fibroma (OF), especially the amyloid variant, and to discuss its association with the Langerhans cell variant of calcifying epithelial odontogenic tumor (CEOT).
Study Design. The clinicopathologic features and immunophenotypes of 17 OFs, including 6 amyloid variants, were analyzed. The Langerhans cell variant of CEOT is reviewed, and its relationship with OF is discussed.
Results. Most OFs (13 of 17) were located at the anterior region of the jaws, often with root resorption. The amyloid variant exhibited the typical clinicopathologic features of OFs, characterized by dispersed small epithelial nests embedded in a fibrous stroma. Immunohistochemically, the epithelial component in all central OFs, including the amyloid variants, exhibited dispersed staining for CK10/13 but was negative for CK7 and CK8/18. Langerhans cells were positive for S-100 and Langerin in the epithelium of OFs, including the amyloid variants.
Conclusions. The amyloid variant of OF is a rare benign tumor exhibiting the typical clinicopathologic features of conventional OFs and should not be diagnosed as CEOT even in the presence of amyloid deposits. Previously reported cases described as "Langerhans cell variant of CEOT" should be classified as the "amyloid variant of OF," given that it shares features more in common with OFs than with CEOTs. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;126:513–520)

Odontogenic fibroma (OF) is an uncommon benign neoplasm characterized by variable amounts of inactive-appearing odontogenic epithelium embedded in a mature, fibrous stroma. According to the World Health Organization, 2 subtypes are recognized: epithelium-poor (formerly known as the "simple type") and epithelium-rich (also known as the "complex or WHO type"). Topographically, OF can be further subclassified into 2 subtypes, central (intraosseous) and peripheral (extraosseous) type, which have been described to derive from the dental follicle or the periodontal ligament.[1] Central OF is rare, with a predilection for females, and occurs more commonly in the maxilla than in the mandible, especially the anterior region of the maxilla, and usually presents as a well-circumscribed radiolucency that may cause root resorption.[2-5]

Some other variants, including the amyloid and ossifying variants, have also been described. The amyloid variant of central OF is rare and is characterized by amyloid deposits and intercalation of Langerhans cells into the epithelial elements. Eversole[6] described 4 such cases that exhibited the typical histologic appearance of OFs, but with the addition of amyloid deposits. These deposits stained positively for Congo red and demonstrated green birefringence with polarized light. The epithelial element showed a core of cytokeratin (CK)–positive cells surrounded by a network of Langerhans cells.[6] It has also been reported that Langerhans cells are commonly detected in the nests and strands of odontogenic epithelia in both central and peripheral OFs.[3,6,7] Recently, the Langerhans cell variant of the intraosseous calcifying epithelial odontogenic tumor (CEOT) has been described; it consists of scattered small nests and cords of epithelial cells, with loose fibrous connective tissue stroma and abundant amyloid substance with no calcification.[8-12]

Because of the limited number of cases reported in the literature, the clinicopathologic features, biologic behavior, and histogenesis of the amyloid variant of central OF are not fully understood, and its relationship with the Langerhans cell variant of CEOT remains to be clarified. Here, we present a report on 17 cases of central OFs, including 6 cases of the amyloid variants. Clinicopathologic features and immunophenotypes were analyzed, with special reference to the amyloid variants. Furthermore, the relationship of the amyloid variants of central OFs to the conventional OFs and CEOTs is discussed.

Statement of Clinical Relevance

The amyloid variant of odontogenic fibroma is a rare benign tumor with no recurrence after local curettage and should not be diagnosed as calcifying epithelial odontogenic tumor that is locally invasive with occasional recurrence and malignant transformation.

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MATERIALS AND METHODS

Cases diagnosed as central OFs or CEOTs between 1999 and 2015 were reviewed from the files of Peking University School and Hospital of Stomatology, after obtaining approval from the University Institutional Ethics Committee. Standard hematoxylin and eosin−stained slides from all cases were reviewed to confirm the diagnosis according to the *World Health Organization Classification of Odontogenic Tumors*.[1] Congo red staining was performed to assess the amyloid deposits. Seventeen cases of central OFs, including 6 cases of amyloid variants, were identified. Six cases of intraosseous CEOTs were also retrieved for comparative purposes. Four-μm-thick serial sections were cut, and immunohistochemical staining was performed by using a standard streptacidin-biotin-peroxidase complex method (LAB-SA kits; Zymed Laboratories, San Francisco, CA). The primary antibodies included CK5/6, CK7, CK10/13, CK8/18, CK19, CK20, CD1α, S-100, Langerin, and Ki-67. Details of the primary antibodies used are listed in Table I. Clinical data were collected from surgical and pathology records. Follow-up information was obtained by performing clinical interviews or reviewing medical records of the patients.

RESULTS

Clinical features

Clinical data from the 17 central OFs are summarized in Table II. Patients (7 males, 10 females) ranged in age from 10 to 76 years (median age 33 years). Twelve cases involved the maxilla, and 5 occurred in the mandible; in most cases (13 of 17), the OFs were located at the anterior and premolar region of the jaws. Palatal depression was noted in 6 cases, including 4 amyloid variants and 2 conventional central OFs. Radiographically, all the cases exhibited a well-circumscribed unilocular or multilocular radiolucency, and 13 were accompanied by root resorption of the involved teeth (Figures 1A and 1B). All of the cases were treated with curettage except for 1, where partial resection of the mandible was performed; no recurrence was recorded 6 to 170 months after conservative surgery.

Pathologic features

Microscopically, the tumor was composed of fibrous tissues with variable collagen density ranging from loose to more mature collagen fibers, accompanied by scattered small epithelial nests and cords (Figures 1C and 1D). The cytoplasm of the epithelial cells stained pale and occasionally brightly eosinophilic. The nuclei were relatively dense and contained a single nucleolus. Some ovoid, densely purple calcifications were found in 1 case. Congo red staining revealed amyloid deposits in 6 cases, and green birefringence was demonstrated with polarized light; these cases were identified as the amyloid variants (Figures 2A and 2B). No calcification was found in the amyloid variants.

Immunohistochemical findings

Immunostaining was performed on 6 amyloid variants of OFs, 6 conventional central OFs, and 6 intraosseous CEOTs. CK5/6 and CK19 expression, but not CK20, was detected in all cases (data not shown). The epithelial component in all central OFs, including the amyloid variants, was found to exhibit dispersedly staining for CK10/13 but was negative for CK7 and CK8/18, whereas CEOTs were positive for CK7 and CK8/18 but negative for CK10/13 (Figure 3). Langerhans cells were detected in the epithelial nests and cords in all the central OFs, including the amyloid variants, which stained positively for CD1α, S-100, and Langerin. The mean ratio of Langerhans cells to epithelial cells in these cases was approximately 40%. However, the ratio of Langerhans cells to epithelial tumor cells was no more than 2% in CEOTs (Figure 4). In addition, the Ki-67 index was no more than 2% in all central OFs, including the amyloid variants, whereas it ranged from 2% to 5% in CEOTs. Most of the proliferating cells characterized by Ki-67 immunostaining were fibroblasts in central OFs but epithelial cells in CEOTs (see Figure 4).

Table I. Primary antibodies used for immunohistochemistry

Antibody	*Company*	*Clone*	*Pretreatment*	*Dilution*
CK5/6	Zymed, Carlsbad, CA	D5/I6 B4	Citrate HIER	Ready to use
CK7	Zymed, Carlsbad, CA	OV-TL12/30	Citrate HIER	Ready to use
CK10/13	Zymed, Carlsbad, CA	DEK-13	Citrate HIER	Ready to use
CK8/18	Zymed, Carlsbad, CA	Zym5.2	Citrate HIER	Ready to use
CK19	Zymed, Carlsbad, CA	A53B	Trypsin (20')	Ready to use
CK20	Zymed, Carlsbad, CA	Ks 20.8	Citrate HIER	Ready to use
CD1a	Zymed, Carlsbad, CA	MTB1	Citrate HIER	Ready to use
Langerin	Zymed, Carlsbad, CA	12D6	Citrate HIER	Ready to use
S-100	Zymed, Carlsbad, CA	15E2E2+4C4.9	None	Ready to use
Ki-67	Dako, Carpinteria, CA	MIB-1	Citrate HIER	1:100

Table II. Clinical information of the central odontogenic fibromas

Case	*Age/Gender*	*Site, tooth notation*[*]	*Duration (months)*	*Symptom and oral examination*	*Treatment//Follow-up*	*Radiographic feature*	*Association with impacted teeth*	*Resorption of tooth root*
1[†]	33/M	Max, 22−26	60	Depression over the anterior maxilla, loose teeth	Currettage /6 months	Unilocular radiolucent	No	23−26
2[†]	59/F	Max, 13−15	9	Depression over the anterior maxilla, loose teeth	Curettage /12 months	Unilocular radiolucent	No	14
3[†]	38/M	Max, 23−26	18	Depression over the maxilla, loose and displaced teeth	Curettage /21 months	Unilocular radiolucent	No	24
4[†]	32/F	Max, 12−15	24	Depression over the anterior maxilla, loose teeth	Curettage /12 months	Unilocular radiolucent	No	13−15
5[†]	40/F	Max, 15−21	48	Depression over the anterior maxilla with pain, loose teeth	Currettage/90 months	Unilocular radiolucent	No	11−12
6[†]	58/M	Max, 13−26	3	Swelling, loose teeth	Currettage/120 months	Multilocular radiolucent	No	23−26
7	29 / F	Man, 44−46	24	Swelling	Curettage/78 months	Unilocular radiolucency	No	45
8	10 / M	Man, 35−37	1	No symptom	Curettage/70 months	Unilocular radiolucency	No	36
9	33 / M	Man, 46−47	10	Swelling	Curettage/70 months	Unilocular radiolucency	No	47
10	22 / F	Max, 23−27	32	Swelling	Curettage/26 months	Unilocular radiolucency	No	No
11	29 / F	Man, 43−46	4	Swelling, loose teeth	Partial resection of jaw/ 92 months	Unilocular radiolucency	No	44
12	25 / F	Max, 22−24	12	Depression over the anterior maxilla	Curettage/26 months	Unilocular radiolucency	No	22
13	36 / F	Max, 23−25	2	No symptom	Curettage/26 months	Unilocular radiolucency	No	24
14	34/ M	Max, 23−25	120	Depression over the anterior maxilla	Curettage/170 months	Unilocular radiolucency	No	NS
15	76 / M	Max, 22−24	1	Swelling	Curettage/60 months	Unilocular radiolucency	Yes	No
16	13 / F	Man, 47−48	120	No symptom	Curettage/108 months	Unilocular radiolucency	Yes	48
17	36 / F	Max, 15−17	5	Swelling, loose teeth	Curettage/120 months	Unilocular radiolucency	No	16

[*]The tooth notation is according to Federation Dentaire Internationale (FDI) tooth notation system.

[†]Amyloid variants of the odontogenic fibromas.

Dur, duration; *F,* female; *L,* left; *M,* male; *Man,* mandibular; *Max,* maxillary; *NS,* not stated; *R,* right.

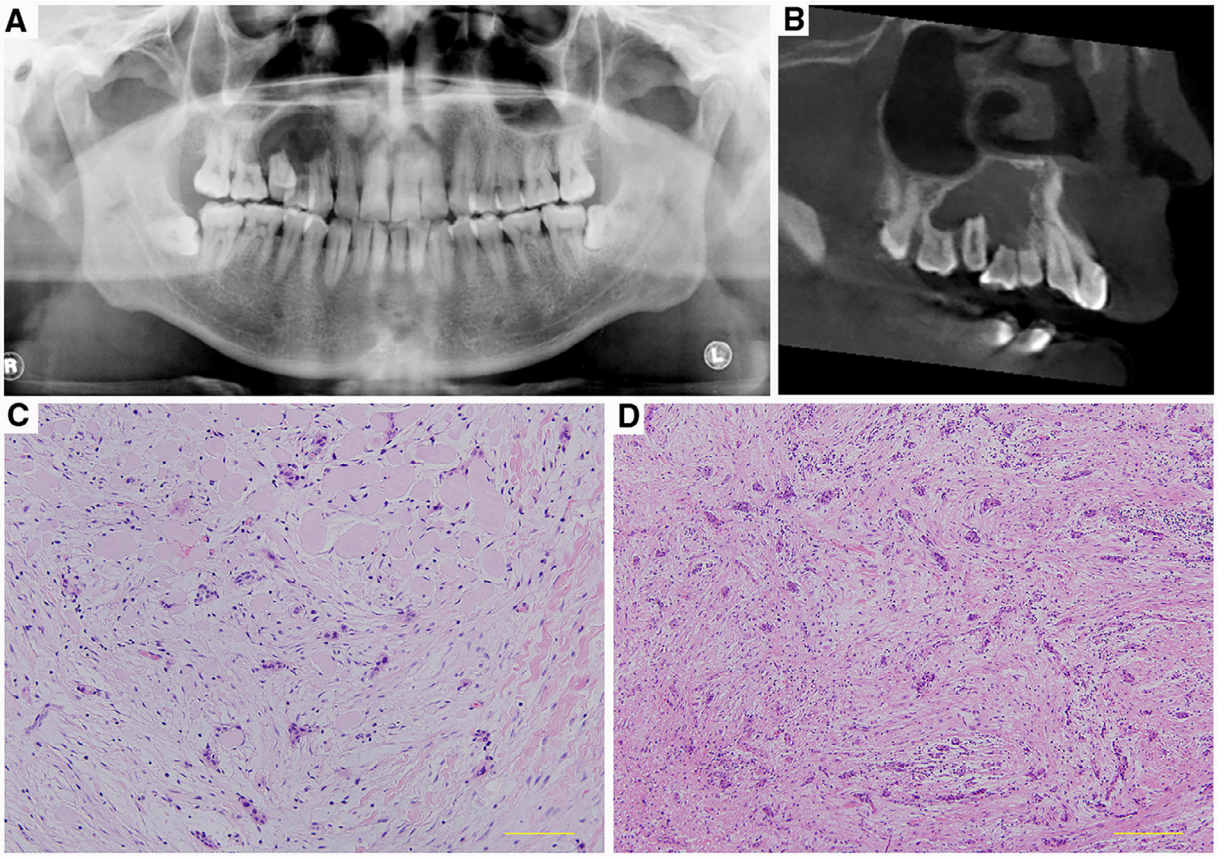

Fig. 1. Radiographic and pathologic features of amyloid variants of central odontogenic fibromas (OFs) (case #1). **A and B,** Radiographic examinations revealed unilocular radiolucent areas from the right incisor to the first molar with root resorption. **C and D,** Microscopically, the tumor consisted of fibrous connective tissue with scattered epithelial nests and cords. (hematoxylin and eosin [H&E], original magnification: × 200 and × 100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04885.*

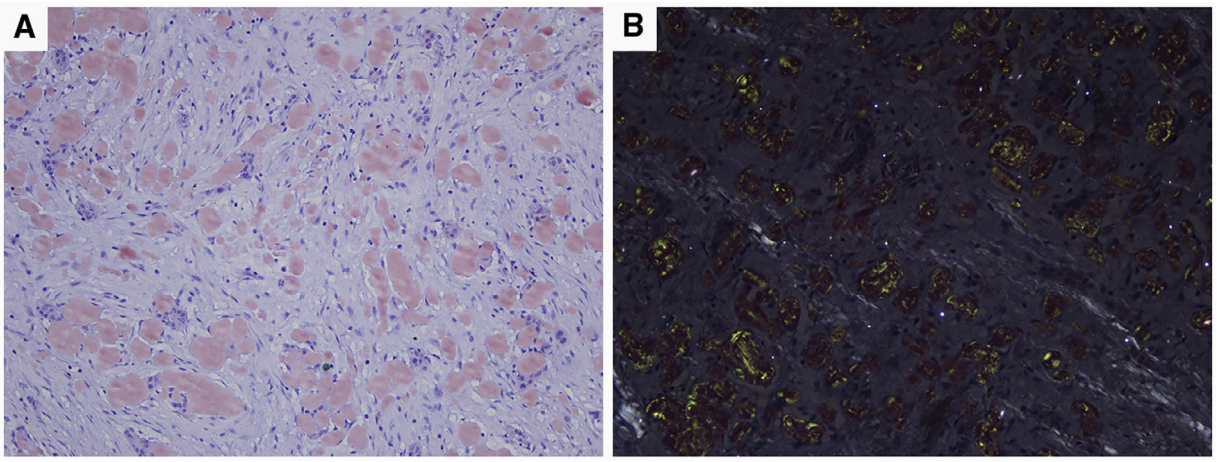

Fig. 2. Amyloid deposits in central odontogenic fibroma (OF). **A,** Congo red staining revealed amyloid deposits as homogeneous eosinophilic globular masses. (Congo red stain; original magnification × 200). **B,** Amyloid deposits showed green birefringence with polarized light. (Congo red stain; original magnification × 200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04886.*

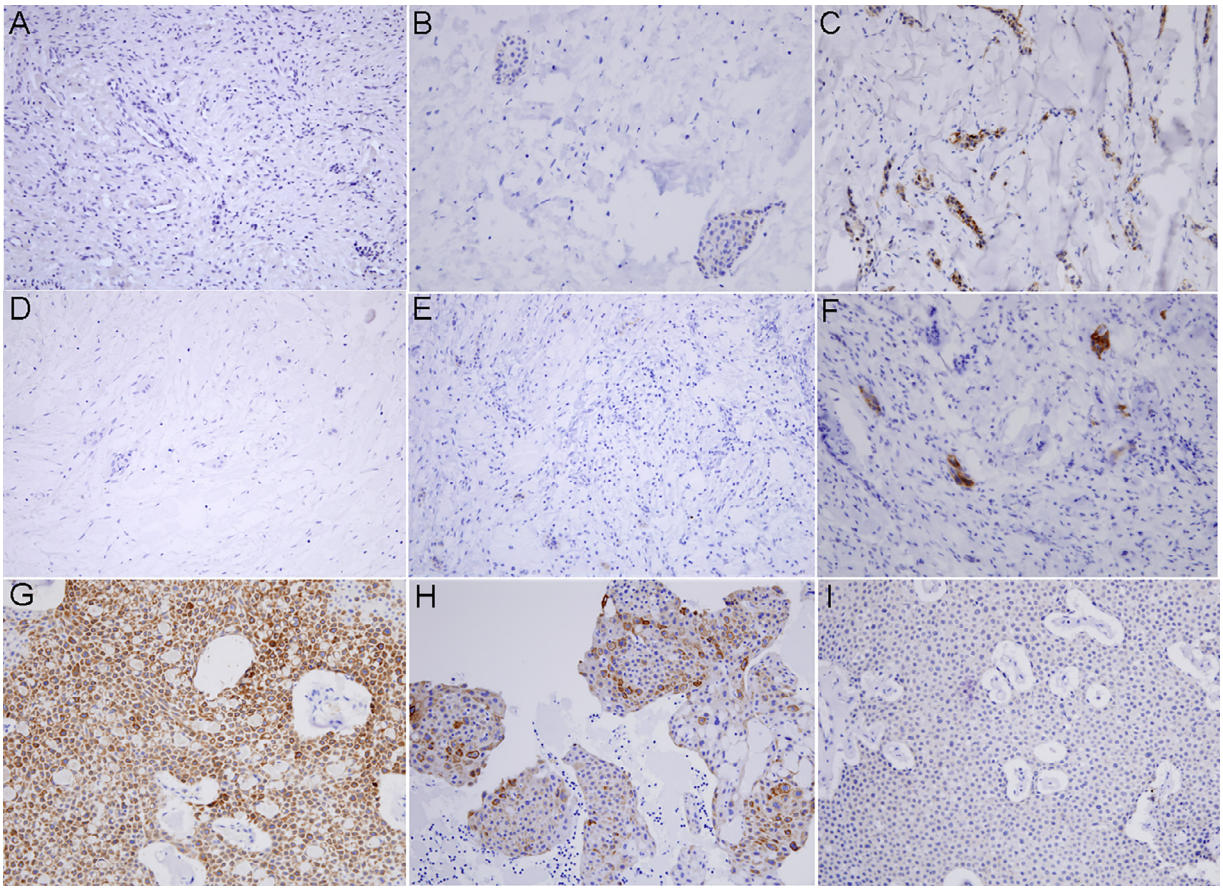

Fig. 3. Keratin profiles in conventional odontogenic fibromas (OFs), amyloid variants of OFs and calcifying epithelial odontogenic tumors (CEOTs) (immunohistochemistry; original magnification × 200). **A–C,** Conventional OFs. **A,** CK7. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04889*. **B**, CK8/18. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04895*. **C**, CK10/13. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04896*. **D–F,** Amyloid variants of OFs. **D,** CK7. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04897*. **E,** CK8/18. **F**, CK10/13. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04898*. **G–I,** CEOTs. **G,** CK7. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04899*. **H,** CK8/18. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04900*. **I,** CK10/13. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04909*.

DISCUSSION

Central OF is a rare benign tumor arising in the jaws and is classified as a mesenchymal odontogenic tumor. It occurs more often in the maxilla than in the mandible, especially the anterior region of the upper jaw.[2-4] Radiographically, these tumors exhibit well-circumscribed radiolucency with or without expansion, often with root resorption or displacement of the adjacent tooth. The clinicopathologic features in the present case series were in general agreement with those of previous reports and were characterized by dispersed small epithelial nests and cords embedded in a mature fibrous stroma, with predominance of maxillary location in comparison with mandibular location (2.4:1). Interestingly, 6 cases in the current series contained amyloid deposits that stained positively for Congo red and exhibited green birefringence with polarized light and, thus, were identified as the amyloid variants of central OFs.

Eversole described 4 cases of this amyloid variant in a series of 65 OFs.[6] All 4 cases involved the maxilla, showing a well-delineated radiolucency with root resorption. They were characterized by typical histologic appearance of OFs, with additional features, such as amyloid deposits and intercalation of Langerhans cell into the epithelial elements. In the present series, all 6 amyloid variants were found to involve the upper jaw, exhibiting well-circumscribed radiolucency with root resorption. Interestingly, palatal depression was noted in 5 of the 6 cases, and this is unusual for a solid tumor of the jaw. Initially, therefore, these lesions were clinically and

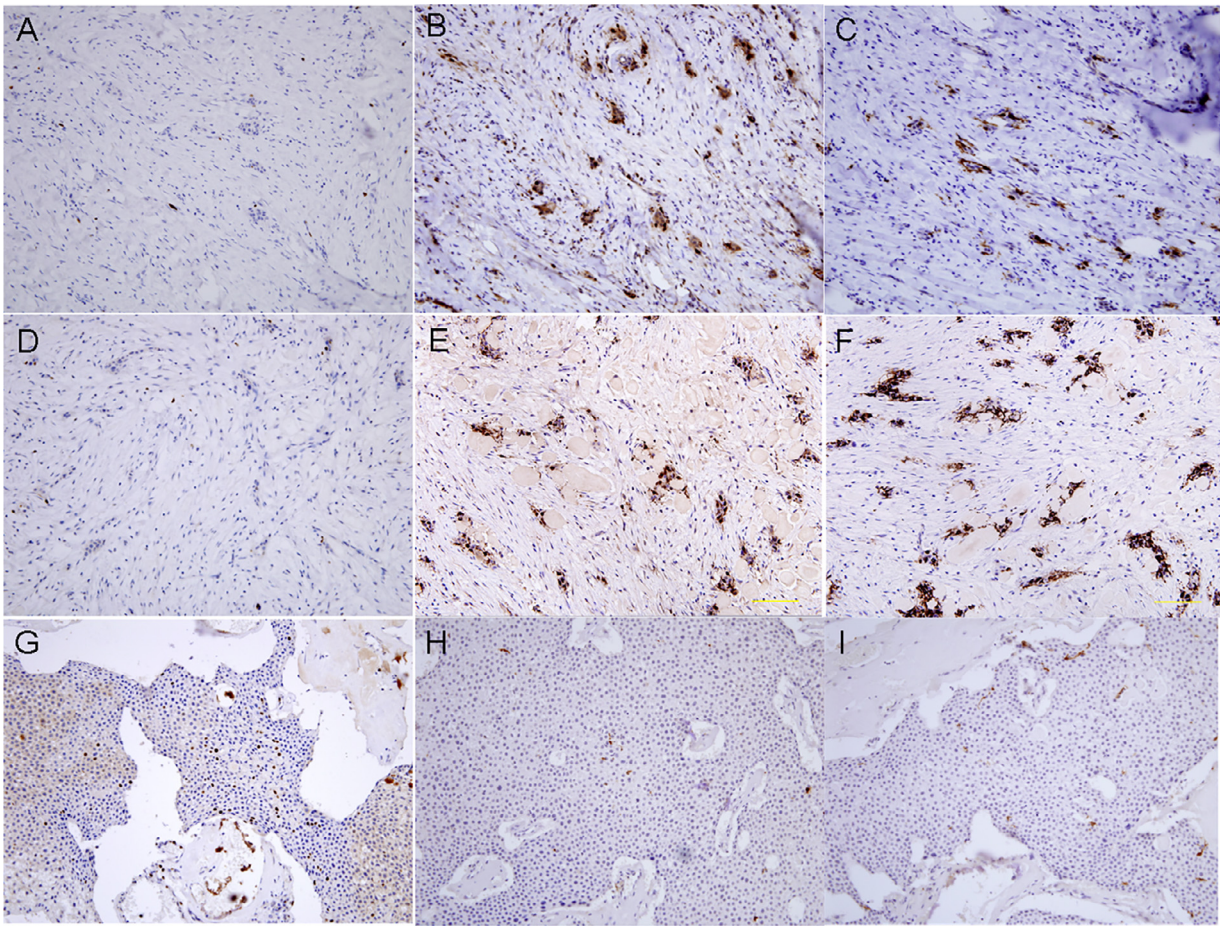

Fig. 4. Ki-67 index and Langerhans cells in conventional odontogenic fibromas (OFs), amyloid variants of OFs and calcifying epithelial odontogenic tumors (CEOTs) (immunohistochemistry; original magnification × 200). **A**−**C,** Conventional OFs. **A,** Ki-67. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04910.* **B,** S-100. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04911.* **C,** CD1a. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04912.* **D**−**F,** Amyloid variants of OFs. **D,** Ki-67. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04913.* **E,** S-100. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04915.* **F,** CD1a. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04916.* **G**−**I,** CEOTs. **G,** Ki-67. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04917.* **H,** S-100. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04918.* **I,** CD1a. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide:VM04920.*

radiologically mistaken for cysts and were subsequently found to be solid tumors during surgery. All of the cases were treated with curettage, and no recurrence was recorded after conservative surgery. Histopathologically, these tumors were characterized by dispersed small epithelial nests and cords embedded in a mature, fibrous stroma with amyloid deposits that stained positively for Congo red and demonstrated green birefringence with polarized light. No calcification was found in any case. Furthermore, the epithelial component exhibited CK-positive cells surrounded by a network of Langerhans cells that were positive for CD1α and S100, which was also detected in conventional OFs.

Recent reports have described the Langerhans cell variant of CEOT that consists of scattered small nests and cords of epithelial cells with loose fibrous connective tissue stroma, together with abundant amyloid substance with no calcification.[8-12] Our review of the English language literature revealed 7 so-called Langerhans cell variants of CEOT (Supplemental Table S1), 2 of which were from our own records and were reclassified as the amyloid variant of central OF in this study. On the basis of the findings of this study, we propose that this special subtype be referred to as the "amyloid variant of central OF" rather than "Langerhans cell variant of CEOT" because it shares features more in common with OFs than with CEOTs.

First, central OFs occur more often in the maxilla than in the mandible, exhibiting well-circumscribed radiolucency that may cause root resorption.[2-5] In contrast, most CEOTs occur in the mandible and exhibit a mixed radiolucent/radiopaque lesion, often associated with an unerupted tooth.[13] To date, 7 Langerhans cell variants of CEOT have been described, 6 (85.7%) of which involved the maxilla, especially the anterior region. No associated impacted tooth was detected in any of these 7 cases; however, root resorption, which is often reported in conventional OFs,[3,6,14] was found in 4 cases.

Second, these special subtypes exhibit the typical histologic appearance of OFs, apart from amyloid deposits, whereas conventional CEOTs are predominantly composed of epithelial tumor components. Although Langerhans cells are commonly detected in the epithelial components of both conventional OFs and this special subtype,[3,6,7] they are dramatically fewer in number in CEOTs.[12] Immunostaining for keratins and Ki-67 was performed in 6 amyloid variants of OFs, 6 conventional central OFs, and 6 intraosseous CEOTs. The epithelial components in OFs, including 6 amyloid variants, exhibited dispersed staining for CK10/13 but were negative for CK7 and CK8/18, whereas the epithelial components in conventional CEOTs were positive for CK7 and CK8/18 but negative for CK10/13. The Ki-67 index in all of the OFs was no more than 2%, whereas that in conventional CEOTs ranged from 2% to 5%.

The presence of amyloid-like protein deposits within these tumor subtypes is the most probable reason for their classification as a variant of CEOTs. Although it is common that these Congo red−staining amyloid deposits are observed in CEOTs, they can also be found in several other odontogenic tumors, such as adenomatoid odontogenic tumor, calcifying cystic odontogenic tumor, and developing odontoma.[15-17] The nature of this amyloid material has been referred to as *odontogenic ameloblast-associated protein* by biochemical analysis.[15,18] Its expression has been detected in the junctional epithelium as well as in the epithelial cell rests of Malassez.[19,20] With regard to histogenesis, OF is believed to originate from dental follicle or the periodontal ligament,[1] whereas CEOT often involves an unerupted tooth and may originate from the reduced enamel epithelium.[21] The so-called Langerhans cell variant of CEOT usually causes apparent root resorption of the apical part of the involved tooth, suggesting that it may originate from the dental follicle or the periodontal ligament, with the epithelial elements derived from the rests of Malassez. This is consistent with the histogenesis of OFs. Furthermore, CEOT is considered a locally invasive tumor that often requires local resection. Malignant transformation has been reported occasionally, and recurrence is not rare,[22] whereas OFs are benign lesions that can be successfully treated with local enucleation. To date, no recurrence has been described in any reported cases of the Langerhans cell variant of CEOT. This also supports classification of this special subtype as an amyloid variant of central OFs.

CONCLUSIONS

In summary, the amyloid variant of central OF is characterized by inactive-appearing odontogenic epithelium embedded in a mature fibrous background, with amyloid deposits and intercalation of Langerhans cell into the epithelial elements. It is a rare but consistent subtype of OF that can be cured by local enucleation. Previously reported cases described as "Langerhans cell variant of CEOT" may, therefore, be the same entity.

SUPPLEMENTARY MATERIALS

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.oooo.2018.08.019.

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