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Peripheral odontogenic tumor: a clinicopathologic study of 30 cases. General features and hamartomatous lesions

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BACKGROUND: Peripheral odontogenic tumors (POT), either neoplastic or hamartomatous, are rare. This study briefly summarizes the general features of POT and selectively reviews the histomorphologic spectrum of under-recognized hamartomatous lesions that we have designated peripheral odontogenic hamartomas (POH) in order to shed more light into the pathogenesis of POT.
METHODS: Archival material accessioned at our institutions between 1970 and 2004 was systematically searched to identify examples of POT/POH.
RESULTS: Among 39 660 biopsies, we retrieved 25 cases of 'classical' POT and five cases of 'unique' POH. Odontogenic fibroma and ameloblastoma were by far the most common. Of POH, two purely epithelial lesions showed multiple strands of basaloid rests [odontogenic gingival epithelial hamartoma (OGEH)] and a conglomerate of polyhedral epithelium, ghost cells and concentric calcifications (calcifying epithelial odontogenic tumor-like hamartoma), respectively. OGEH and peripheral squamous odontogenic tumor (PSOT) deserve to be a related entity. In two types of mixed POH, ectomesenchymal elements appeared juxtaposed to the squamous lining (gingival cyst-like organoid hamartoma) and ghost cells aggregated in the enamel organ of a microdont (peripheral odontoma). None of POH exhibited continuity with the surface epithelium.
CONCLUSION: On the basis of this relatively limited series of cases, POH, to conceptualize a unified histogenetic source, are speculated to arise from the soft-tissue remnants of dental lamina. Gingival rests of Serres seem to retain the ability to pursue epithelial–ectomesenchymal interactions that are necessary leading to odontoma formation.
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Introduction

Rare gingival equivalents have been observed for a variety of intraosseous odontogenic tumors and tumor-like conditions. These peripheral odontogenic tumors (POT) exhibit three principal histologic patterns – epithelial, ectomesenchymal, and so-called mixed (1–3). It is now well known that epithelial POT can arise either from the soft-tissue remnants of dental lamina or from the basal layers of surface epithelium (4). There is a copious indirect evidence that POT are directly linked to the rests of Serres (1–4); however, the view that the post-embryonic gingival epithelium retains the residual odontogenic potential is only circumstantial.

We herein report our experience with 30 cases of POT and allied lesions, particularly focusing on the salient histologic features of four different types of peripheral odontogenic hamartomas (POH) and one example of peripheral variant of squamous odontogenic tumor (SOT). The results of this study, taken together with a review of the literature, provide additional support that the gingival rests of Serres may be a cogent histogenetic source and are remarkable for their ability to spawn many different tumor types.

Material and methods

The surgical pathology files of the three institutions and the personal consultation files served as sources of material. Files were retrospectively reviewed for POT/POH during a 34-year period from 1970 to 2004. Only cases in which there was no confirmed evidence of bony involvement were accepted. All specimens were fixed in 10% buffered formalin and routinely processed for histology. Immunohistochemical investigation was done by the avidin-biotin-peroxidase complex (ABC) technique using cytokeratin (AE1/AE3; DakoCytomation, Glostrup, Denmark; 1:100), vimentin (V9;

DakoCytomation; 1:400), and S-100 protein (polyclonal; DakoCytomation; 1:2000).

Results

From the 39 660 specimens, we retrieved 30 cases of POT and related entities. The diagnoses of 25 well recognized POT included odontogenic fibroma of WHO-type ($n = 10$); ameloblastoma ($n = 9$); and SOT, calcifying epithelial odontogenic tumor (CEOT), calcifying odontogenic cyst, adenomatoid odontogenic tumor, ameloblastic fibroma, and odontogenic myxoma ($n = 1$ each). The lesions were all solitary except for one case in which two odontogenic fibromas were excised. Follow up data available showed no recurrence after simple excision but one patient with ameloblastoma experienced lymph node metastasis (5). The clinicopathologic aspects of the aforementioned POT will be presented in more detail in the near future.

The remainder ($n = 5$) was an under-recognized subset of POT. Because all cases were extremely small and lacked the diagnostic features of persistent and/or destructive growth, the term 'POH' is preferred to designate this type of lesions. In addition, because of their rarity, it has not been nowadays possible to assign several of POH to any currently defined specific category of POT (1–4); reluctantly, we utilized the descriptive term as discussed below.

Odontogenic gingival epithelial hamartoma
A 49-year-old woman had a 0.7 cm sessile mass on the right retromolar pad of 6 years' duration. Microscopically, within the dense fibrous tissue were multiple circumscribed nodules of basaloid epithelium, arranging in a double-strand array (Fig. 1a). Only a single focus of squamous metaplasia was noted (Fig. 1b). Epithelial islands were faintly positive for AE1/AE3. Serial sections confirmed a clear boundary between the deep-seated lesion and the unremarkable overlying epithelium.

Peripheral SOT
A 61-year-old woman complained of an elevated mass, 1.3 cm in diameter, on the palatal gingiva of the right second molar that had been enlarging for 1 month. There was no continuity with the periodontal ligament. Histologically, the lesion consisted of solid-cystic islands of benign squamous epithelium, extending up to the epithelial–stromal interface (Fig. 2a). Superficial portions showed prominent microcystic changes (Fig. 2b) but in its depth, epithelial nests were solid and clear in appearance. An AE1/AE3 immunostain highlighted multicentric connections with the surface epithelium along a considerable length of the lesion (Fig. 2c).

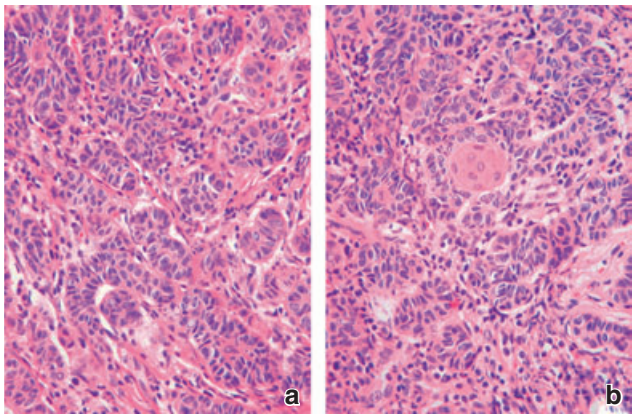

Figure 1 Odontogenic gingival epithelial hamartoma. (a) Multiple strands of basaloid cells [haematoxylin and eosin (H & E), ×200]. (b) Focal squamous metaplasia (H & E, ×200).

Peripheral CEOT (PCEOT)-like hamartoma
A 9-year-old girl presented with a 1.0 cm dome-shaped mass on the palatal gingiva of the left central incisor. On microscopic level, a well circumscribed nodule was located deep to the surface epithelium which did not exhibit proliferation downward (Fig. 3a). The lesion was composed of a sheet of polyhedral epithelium with intercellular bridges (Fig. 3b). Ghost cells and concentric calcifications were readily observed. Congo red-positive materials could not be detected. Squamous but not ghost cells exhibited AE1/AE3 positivity. S-100 protein was uniformly negative.

Gingival cyst-like organoid hamartoma
A 12-year-old boy revealed a delayed eruption of the upper right first molar. Minute radiopacities were present within the gingiva. Microscopically, thickened covering mucosa contained a unilocular gingival cyst (GC) lined by non-keratinizing squamous epithelium (Fig. 4a). GC was not attached to the surface epithelium. This lesion was very complex. Numerous areas of the wall proper showed epithelial rests embedded in a dental papilla-like immature stroma (Fig. 4b). AE1/AE3 was detected and the cyst epithelium stained more intensely than the rests. Focally, ectomesenchyme with condensation of its cells appeared in juxtaposition to the basal layer of cyst lining (Fig. 4c). Liesegang-ring type calcifications were scattered (Fig. 4d). There was no evidence for ameloblastomatous transformation or ghosting in the lining epithelium.

Peripheral odontoma
Two examples, one of which was previously reported (6), were identified. Another case was an 8-year-old girl who had a 0.8 cm mass on the lingual gingiva of the lower left lateral incisor. Histologically, a developing rudimentary tooth was centered in the submucosa (Fig. 5a). Both enamel and dentin were present (Fig. 5b). Within the enamel organ were ghost cells (Fig. 5c). They were negative for AE1/AE3 but weakly positive for S-100 protein. Vimentin was expressed in the dental papilla and surrounding follicle. The lesion was completely separated from the overlying epithelium.

Discussion

Some of the most complex developmental interactions, the reciprocal interplay of epithelium and ectomesenchyme, occur during the odontogenesis (4). Such a highly complex embryologic process is prone to invite

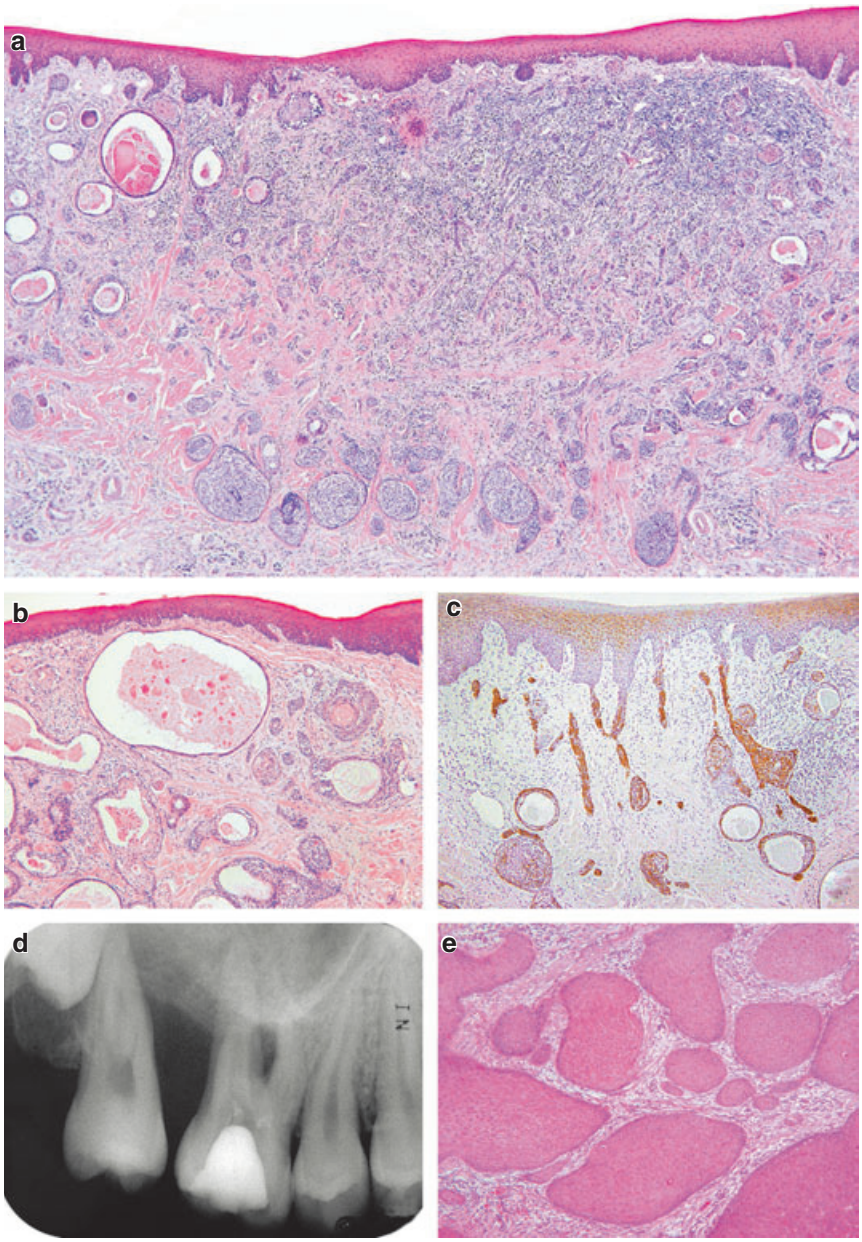

Figure 2 Squamous odontogenic tumor of peripheral (a–c) and central (d, e) types. (a) Solid-cystic nests of mature squamous epithelium [haematoxylin and eosin (H & E), ×40]. (b) Prominent microcystic degeneration (H & E, ×100). (c) Multifocal continuity with surface epithelium (AE1/AE3, ABC method, ×100). (d) A triangular radiolucency between the molar roots in a 14-year-old boy. (e) Large solid islands of benign squamous epithelium (H & E, ×100).

errors, resulting in an aberrant growth of odontogenic epithelium with or without inductive proliferation of ectomesenchyme (4, 7). These hamartomatous processes may remain dormant or undergo neoplastic transformation. As POT and POH represent a morphologic continuum without clearly definable cut-offs (4), studying POH is undeniably important to clarify the origin and nature of POT.

OGEH

The term odontogenic gingival epithelial hamartoma ('OGEH') has loosely been applied to encompass a variety of POT because of the incorrectness of the diagnostic criteria (7). Many such lesions are, in fact, examples of peripheral odontogenic fibroma (POF) of WHO-type (4, 8). Although gradually obsolete, we acknowledge the existence of bona fide OGEH (9, 10). This lesion occurs exclusively in adult woman and is characterized by its small size (< 1 cm). Histologically, double-stranded basaloid rests cluster in a nodular pattern. They tend not to be squamous and larger acanthomatous islands are difficult to find. The other noticeable feature is that the stroma is collagenous, lacking cellular arrays interwoven with hypocellular areas of POF. Most importantly, true

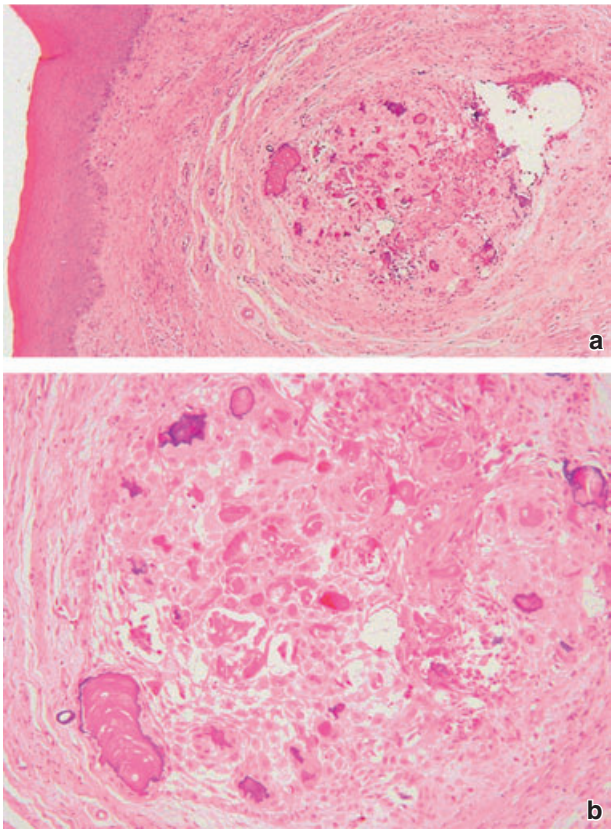

Figure 3 Peripheral calcifying epithelial odontogenic tumor-like hamartoma. (a) Deep-seated small nodule [haematoxylin and eosin (H & E, ×40]. (b) Hybrid lesion of polyhedral epithelium, ghost cells, and calcifications (H & E, ×200).

OGEH exhibit no communication with the surface epithelium. From the practical standpoint, the diagnosis of OGEH should be done only for a gingival tumor fulfilling the above characteristics.

PSOT

With the three previous instances (11–13), this brings to four the number of cases of peripheral SOT (PSOT). The morphologic diagnostic accuracy in two cases is difficult to verify (14, 15) and could well fit with peripheral ameloblastomas (PA), which is in agreement with comments made by others (3, 12, 16). Instead, we are impressed by the inseparable similarities between PA-like POF (17) with PSOT of Baden et al. (12). Comparing with SOT (Fig. 2d,e), PSOT have a peculiar propensity for keratocystic degeneration reminiscent of GC of infants. It is a cautionary note that all lesions show multiple surface epithelial involvements. Several lines of evidence supporting that PSOT appear to be a hamartomatous process of rests of Serres include: (i) the origin of periradicular SOT from rests of Malassez is unquestionable (4, 16); (ii) rare SOT in a pericoronal setting may arise from rests of Serres (18); (iii) rests of Serres can potentially give rise to microkeratocysts and in the form of GC fuse with the surface mucosa (19–21); (iv) atypical proliferation of an aborted GC joined the gingival epithelium (22); and (v) SOT in contact with the overlying mucosa (16, 23, 24) or in association with an unerupted tooth (25) evoked pseudoepitheliomatous hyperplasia of the gingiva that eventually intermingled. Considering the fact that the sequential maturation from deep-seated basaloid to superficial squamous rests

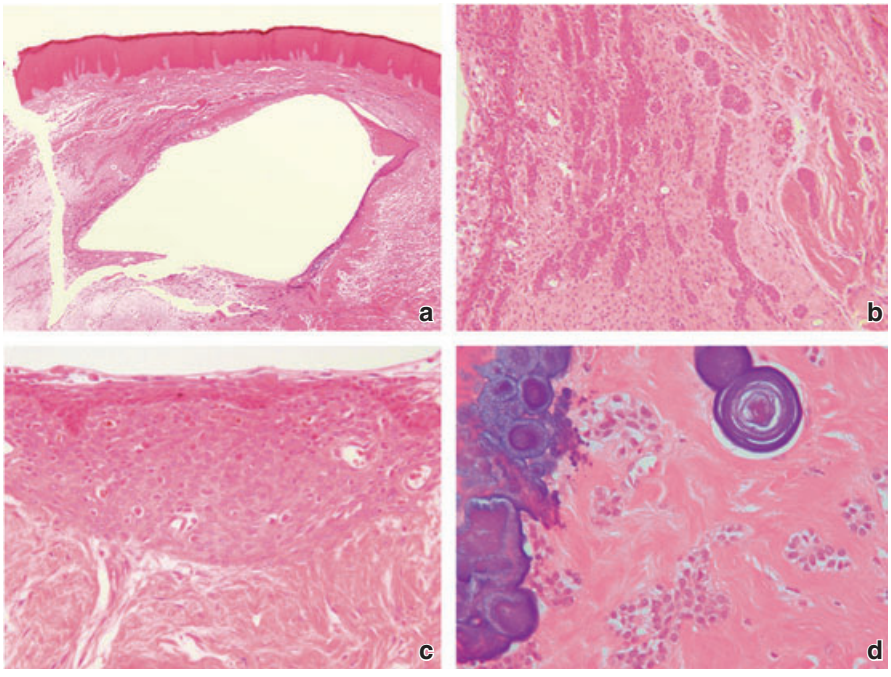

Figure 4 Gingival cyst-like organoid hamartoma. (a) Unilocular cyst lined by squamous epithelium [haematoxylin and eosin (H & E, ×15]. (b) Odontogenic rests in a cell-rich ectomesenchyme (H & E, ×200). (c) Condensed mass of ectomesenchyme lie next to cyst epithelium (H & E, ×400). (d) Calcified bodies with Liesegang pattern (H & E, ×400).

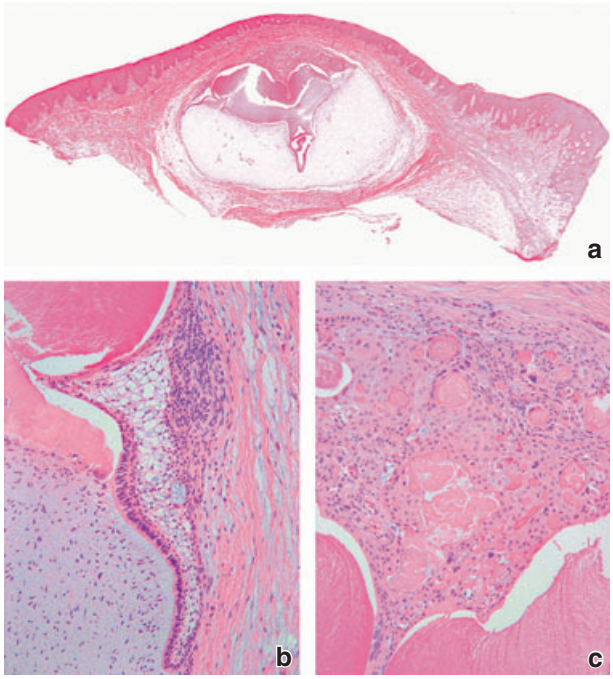

Figure 5 Peripheral odontoma. (a) Developing microdont located entirely within gingiva [haematoxylin and eosin (H & E), ×10]. (b) Enamel matrix and dentin (H & E, ×200). (c) Ghost cells in enamel organ (H & E, ×200).

is a consistent finding in the developing oral mucosa (19, 21), PSOT and OGEH are probably members of a spectrum of related entities.

PCEOT-like hamartoma

The present case is not classifiable within the standard nosology of odontogenic tumors (4). Ghost cells have been found in a variety of odontogenic tumors and cysts, so that their occurrence is of little significance in developing differential diagnosis. This case may be considered a spectrum of CEOT rather than of calcifying odontogenic cyst, not only because of squamoid appearance but also because of a lack of dentinoid. However, the presence of ghost cells and absence of amyloid-like material have never been documented in CEOT (1–3). There was one Japanese report of a morphologically identical lesion in the maxillary incisor region of an 18-year-old female (26).

GC-like organoid hamartoma

A review of the literature on pericoronal hamartomatous lesions (27, 28) and GC (29, 30) failed to disclose any similar description. The sequential differentiation leading to the inductive accumulation of ectomesenchyme in this lesion is hardly resolvable. Following a pathway in odontogenesis, the soft-tissue remnants of dental lamina can return to an active state and likely have the innate ability to induce ectomesenchyme. Of note is a case of unicystic ameloblastoma that contained mural combined nodules of epithelial rests and ectomesenchyme (31). The pathogenesis of this unusual phenomenon remains unclear.

PO

On very rare occasions, odontomas may occur peripherally (2, 3, 6). It is probable that so-called soft-tissue mesiodens is an erupted form of peripheral odontoma (PO) (32). Although a lack of consensus (1), a unique case of mixed POT exhibiting ghost cell formation and calcification could be diagnosed as PO in the earliest stage of development (33). Lesions of Sigal et al. (34) and Siar and Ng (17) are somewhat different; the former lacked the enamel coverage and the latter was associated with POF. With the exception of a single instance (32), it is unlikely that the traumatic episode is instrumental in the pathogenesis of PO. Although a locally uncontrolled hyperactivity of rests of Serres may be responsible under exceptional conditions (35), a hereditary basis is also operable to a certain extent (34).

Conclusions

Retrospective analysis of 39 660 biopsies disclosed 30 cases of POT/POH. Although data are limited, none of POH showed continuity with the surface epithelium, which suggests their shared origin from the rests of Serres. The full morphologic spectrum of POH offers evidence that gingival remnants of dental lamina may posses an inherent potential to diversely transform toward various tumor lines, exerting inductive influence on the adjacent connective tissue. The vast majority of their parent rests will disappear fairly soon after birth and some POH tend to undergo involution, therefore, clinically manifest cases of POT are exceptional.

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