Hamartomatous proliferations of odontogenic epithelium within the jaws: a potential histogenetic source of intraosseous epithelial odontogenic tumors

F. Ide^{1,2,3}, K. Obara², H. Yamada², K. Mishima², I. Saito², N. Horie³, T. Shimoyama³, K. Kusama¹

¹Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, Saitama; ²Department of Pathology, Tsurumi University School of Dental Medicine, Yokohama; ³Department of Oral Surgery, Saitama Medical Center, Saitama Medical School, Saitama, Japan

BACKGROUND: The jawbone is replete with a vestige of odontogenesis. The overall consensus is that intraosseous remnants of the enamel organ and dental lamina are the only histogenetic option for central epithelial odontogenic tumors. Curiously, incipient tumors or possible precursor conditions of residual odontogenic epithelium have rarely been reported in the literature.

METHODS: We microscopically evaluated 39 660 biopsy samples to determine the presence of a tumor-like odon-togenic epithelial nodule in the maxilla and mandible.

RESULTS: Seven intraosseous specimens that associated with a focal proliferation of odontogenic epithelium were retrieved. Six hamartomatous processes showed four different morphologic patterns comparable with the tumor nests comprising ameloblastoma (n = 1), squamous odontogenic tumor (n = 1), calcifying epithelial odontogenic tumor (n = 2) and calcifying cystic odontogenic tumor (n = 2). Among six lesions, four were the intrafollicular development. The remaining case of interest was multiple hyperplastic clear rests of Malassez in association with an impacted tooth.

CONCLUSION: Although it is impossible to predict the fate of these microscopic structures of hamartomatous character, the present case series indicates that any of the dormant embryonic residues of odontogenic epithelium can return to an active state, capable of non-reactive, probably neoplastic proliferation of pathological significance.

| Oral Pathol Med (2007) 36: 229-35

Keywords: dental follicle; dental lamina; enamel organ; epithelial remnants; hamartoma; jawbone; rests of Malassez

Introduction

After the completion of odontogenesis, residual epithelium of tooth-forming apparatus establish residence both in the bone and in soft tissue of the jaws (1-4). These developmental inclusions persist into adult life and are divided into four main types: rests of Malassez in the periodontal ligament (Hertwig's root sheath remnants), rests of dental lamina in the alveolar bone (2), rests of enamel organ deep in the body of jawbone (5–7), and rests of Serres in the gingiva. Such embryonic residues stay dormant for a long period of time but can resume active growth at a later time, resulting in the formation of epithelial odontogenic tumors (1-4). Our group already demonstrated that the gingival rests of Serres possess an inherent potential to give rise to a variety of peripheral odontogenic tumors, continuing throughout life (8). An additional cogent source of central epithelial odontogenic tumors is the pericoronal follicular tissue which houses abortive ameloblastic epithelium because of their common dentigerous relationship to mature unerupted or impacted teeth (1, 2).

The purpose of this article was to describe the pathologic characteristics of seven instances of singular odontogenic epithelial proliferations within the jawbones. Although these microscopic processes do not deserve further histological subclassification, the present unique and often challenging findings are histogenetically significant and worth noting.

Materials and methods

The hematoxylin and eosin-stained slides from the archival files of the Department of Pathology at the Meikai and Tsurumi Universities between 1970 and 2004 were reviewed (8). Clinical data, including radiographic appearance and follow-up, were sought from the medical records. All cases that associated with microscopic foci of proliferating odontogenic epithelium were thoroughly examined through sectioning at many levels, with appropriate special and immunohistochemical stains.

Correspondence: Dr Fumio Ide, Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, 1-1 Keyakidai, Sakado, Saitama 350-0283, Japan. Tel: +81 49 279 2773, Fax: +81 49 286 6101, E-mail: idef@dent.meikai.ac.jp Accepted for publication June 27, 2006

Results

Of 39 660 biopsies reviewed, we retrieved seven intraosseous specimens that contained a tumor-like nodule of odontogenic epithelium. They were chance findings and not removed on suspicion of tumor occurrence. Although a part of lesion was left at the surgical margins in all cases, neither regrowth nor recurrence has been recorded, with a follow-up period of 4 months to 120 months (mean 48 months). As these microscopic conditions obviously lacked the neoplastic quality, we included them in the range of hamartomas (8). Two intrafollicular soft masses associated with supernumerary teeth could be, in a broad sense, categorized into the spectrum of lesions known as the developing odontomas (2); however, because of their peculiar histologic findings, they are described in this study.

Ameloblastoma-like lesion

A 9-year-old boy had an impacted supernumerary tooth in the palatal aspect of an upper left central incisor. A well-formed 6-mm tooth and the surrounding soft tissue were submitted for microscopic evaluation. Within the collagenous sac was a 1.5-mm nodule of ameloblastic epithelium (Fig. 1a). Palisaded columnar basal cells showed diagnostic features for early ameloblastoma including hyperchromatism and reverse polarization of nuclei and subnuclear vacuolization. Central to the ameloblast-like cells, areas reminiscent of the stellate reticulum could be identified (Fig. 1b). There was no stroma of dental papilla-like immature ectomesenchyme. At a microscopic level, distinguishing this lesion from small ameloblastoma was difficult (Fig. 1c,d).

Squamous odontogenic tumor (SOT)-like lesion

A 47-year-old man related a localized loosening of a vital lower left second premolar. Radiographs showed a cup-shaped bone loss of the alveolar crest (Fig. 2a). A microscopic finding of note was a focal proliferation of benign odontogenic epithelium, usually two cell layers thick, along the lateral root surface of a removed tooth (Fig. 2b). The lesion eroded the crestal bone (Fig. 2c), but did not extend beyond the apical third of the root. The double strands of bland epithelial cells were basaloid in appearance and markedly similar to the cord-like rests of Malassez. They were positive for pancytokeratin (AE1/AE3, DakoCytomation, Carpinteria, CA, USA, 1:50; Fig. 2d). A mild chronic inflammatory infiltrate was evident in the fibrous stroma.

$Calcifying \ epithelial \ odontogenic \ tumor \ (CEOT)-like \ lesion$

Case 1. A 14-year-old boy was admitted with a 5-mm pericoronal radiolucency of a horizontally impacted lower right second molar. At operation, the tooth crown was invested by thickened sac and cystic structure could not be verified. Histologically, the myxofibrous follicle contained anastomosing sheets of squamoid epithelium (Fig. 3a,b). Within the epithelial nests were Liesegang ring-type calcifications (Fig. 3c) and Congo red-positive materials (Fig. 3d). In many areas, CEOT-like foci were



Figure 1 (a, b) Epithelial mass resembling follicular ameloblastoma (H&E, a, $\times 100$; b, $\times 400$). (c, d) A 9-mm cystic ameloblastoma of the alveolar crest between lower left premolars in a 43-year-old man (H&E, c $\times 10$; d $\times 400$).

Central epithelial odontogenic hamartoma Ide et al.



Figure 2 (a) Superficial bone loss of the alveolar crest. (b, c) Proliferation of bilayered rests of Malassez and residual bone (H&E, b \times 200; c \times 400). (d) AE1/AE3 reactivity (ABC method, \times 400).



Figure 3 (a) Calcifying epithelial odontogenic tumor (CEOT)-like focus (rectangle) and reduced enamel epithelium (arrows) (H&E, \times 5). (b) Squamoid epithelium (H&E, \times 400). (c) Liesegang ring-type calcification (H&E, \times 200). (d) Amyloid-like material (Congo-red, \times 400). (e, f) CEOT-like phenotype of the stratum intermedium (H&E, \times 400).

seen in direct continuity with the reduced enamel epithelium (Fig. 3a,e,f).

Case 2. The patient was a 16-year-old man who had a retained lower left deciduous canine. Radiographs revealed a small supernumerary tooth and an apparently

normal permanent canine embedded just below the apex of a retained tooth. Microscopically, an ill-organized tooth-like structure enveloped by the fibrous sac consisted of enamel matrix, tubular dentin and dentinoid. There were CEOT-type epithelial sheets among the hard



Figure 4 (a) Calcifying epithelial odontogenic tumor (CEOT)-type epithelial sheet (H&E, \times 400). (b) CEOT-like change in the reduced enamel epithelium (H&E, \times 400).

tissues (Fig. 4a). Liesegang ring-type calcifications were often seen in association with the reduced enamel epithelium (Fig. 4b). Cong-red stain was focally positive in CEOT-like foci.

Calcifying cystic odontogenic tumor (CCOT)-like lesion

Case 1. An 11-year-old boy presented with a pericoronal mixed radiolucent/radiopaque lesion of an unerupted upper right lateral incisor (Fig. 5a). The enlarged follicle was excised and the crown was surgically exposed. Histological examination revealed multiple large solid nests of basaloid epithelium within a hemosiderin-deposited fibrous sac (Fig. 5b). A 1.5-mm radiopaque mass surrounded by thick capsule was composed exclusively of ghost cells exhibiting calcification (Fig. 5c). The dental hard tissue was less evident (Fig. 5d). AE1/AE3 highlighted basaloid and ameloblastic epithelium but not ghost cells.

Case 2. A 6-year-old boy had a 6-mm soft nodule of 1 year duration on the palatal gingiva of an upper right deciduous incisor. Compared with the adjacent deciduous incisors, this tooth was markedly mobile. At operation, the bulk of the lesion was found as an intrabony mass in the alveolar crest and an erupting

permanent incisor appeared uninvolved. Microscopically, a solid mass was attached to the root of a shedding tooth (Fig. 6a). Deep in the fibrous tissue was a nonencapsulated conglomerate of dentinoid, ghost cells and ameloblastic epithelium (Fig. 6b). Often, ghost cells were surrounded by a foreign body giant cell reaction (Fig. 6c).

Hyperplastic clear cell rests of malassez

The patient was a 54-year-old man who had a completely impacted lower right third molar. Histologically, multiple large rounded islands of the clear epithelium were present in the periodontal ligament of a removed tooth (Fig. 7a). Some of them had an appearance reminiscent of sebaceous cells (Fig. 7b). Neither peripheral palisading nor stellate reticulum was evident (Fig. 7c). Periodic acid-Schiff positive, diastase-labile fine granules were contained in many of clear cells. The hyperplastic clear cell nests showed some cytologic resemblance to the so-called clear cell tumor (Fig. 7d,e). There was no inflammatory infiltration. Postoperative examination ruled out the possibility of metastatic disease.

Discussion

The jawbone is host to epithelial odontogenic tumors (1-4). Considering that almost all types of incipient or early tumors have been observed (7, 9, 10), it is theoretically acceptable that in situ or precursor epithelial lesions may exist, either separately or adjacent to tumors. However, previous descriptions of microscopic tumor-like alterations of intraosseous odontogenic epithelial remnants are exceptional (5, 7, 9). This disparity could be explained in part by the possibility that such fortuitous discoveries are of academic and research interest only and overlooked during routine tissue diagnosis. Recently, Bouquot et al. (7) found 84 rests and five incipient tumors of odontogenic epithelium outside the periodontal ligament space in 5034 jawbone biopsies. The latter subclinical lesions included one ameloblastoma, two SOT and two CEOT. Unfortunately, it is difficult to compare their latent tumors with our hamartomas because of the lack of detailed data (7).



Figure 5 (a) Small radiopaque masses within a pericoronal radiolucent lesion. (b) Basaloid epithelial island (H&E, \times 200). (c, d) Calcified ghost cells (H&E, c ×40; d ×400).



Figure 6 (a) Solid tumor attached to a shedding deciduous tooth (H&E, \times 8). (b) Mass of dentinoid, ghost cells, and ameloblastic epithelium (H&E, \times 100). (c) Foreign body reaction (H&E, \times 400).



Figure 7 (a) Two larger clear rests of Malassez (H&E, \times 40). (b) Sebaceous-like appearance (H&E, \times 200). (c) Cells with clear or granular cytoplasm (H&E, \times 400). (d, e) Clear cell odontogenic carcinoma of the lower left mandible in a 55-year-old man (H&E, e \times 200).

Ameloblastoma-like lesion

The present intrafollicular epithelial mass exhibited features analogous in structure to follicular ameloblastoma (1, 2, 11). However, because of small quality, this microscopic ameloblastoma-like lesion provides a diagnostic dilemma. It is interesting that unsuspected small ameloblastomas have been reported in the interradicular (12–14), periapical (15, 16), paradental (17) and pericoronal (10, 18, 19) settings. Moreover, ameloblastomatous changes of intraosseous odontogenic epithelial residues, although uncommon (20, 21), have incidentally been discovered in the body of jaw (5, 22), interdental alveolar crest (9), periodontal ligament (23), dental follicle (24) and cyst wall (25). These observations indicate that all types of epithelial rests can produce ameloblastomas (1–4). It must be borne in mind, however, that the maxillary incisor region in our patient is an unusual site for conventional ameloblastoma (26, 27). From the practical standpoint, one such rest, or even a few, does not justify the diagnosis of ameloblastoma (11), but this information should be noted in the pathology report.

SOT-like lesion

Squamous odontogenic tumor is a hamartomatous proliferation of rests of Malassez in the periodontal

ligament (1, 2, 4). Dental lamina may also be the potential source for rare cases in association with the crown of unerupted or impacted teeth (28). To our knowledge, a developing SOT is composed primarily of rounded or angular shaped islands of well-differentiated squamous epithelium and not of double-stranded basaloid epithelial rests (29, 30). If the present small lesion is in an immature stage of tumor evolution, primitive epithelial islands with probable origin from the rests of Malassez would be expected to enlarge and mature to take on the characteristics of SOT (1, 2, 4). It remains uncertain whether chronic mild periodontitis in our patient is the cause of, a contributor to, or an incidental juxtaposition regarding the occurrence of SOT-like lesion. Diagnostic consideration must also be given to central odontogenic fibroma, epithelium-rich type (2, 3, 31); however, the mature collagenous stroma in this case was not an integral mesenchymal component.

CEOT-like lesion

The sheets of squamoid epithelium, amyloid-like materials and Liesegang ring-type calcifications all help distinguish our pericoronal lesions from ordinary calcified follicular tissues (20, 21, 32). There were a few reports of intrafollicular (33, 34) and perifollicular (10) tumors with features of CEOT. Considering a fairly common association of CEOT with an impacted tooth (1, 2, 35), there may be a logical sequence of such incipient lesions progressing to destructive tumors. As shown in the present cases and other reports (34, 35), CEOT-type epithelium were seen in direct contact with, and in apparent transition from, the stratum intermedium of the reduced enamel organ. This finding supports that CEOT associated with the crown of impacted teeth may have an origin from the reduced enamel epithelium (1, 2).

CCOT-like lesion

Ghost cells typify the so-called calcifying odontogenic cyst that has now been designated as CCOT (3). Our cases differ from conventional CCOT in two respects: location and size. Although CCOT exhibits a wide variety of clinical features (1, 2), it would not be expected to localize in the perifollicular space or the superficial alveolar crest. Both lesions were quite small and showed very limited or no intrinsic potential for persistent growth. As demonstrated in case 2, a small intrabony CCOT in a child may facilitate its eruption in the same way as an eruption cyst. In consideration with the report that peripheral CCOT is a lesion of adult with a mean age of 63.5 years (36), several peripheral examples in pediatric patients may represent the gingival manifestation of central CCOT following tooth eruption and not a true soft-tissue process (37, 38).

Hyperplastic clear cell rests of Malassez

Not uncommonly, the clear appearance has been recorded in small inactive epithelial islands of dentigerous cyst (39), lateral periodontal cyst (40), opercula (20) and periodontal ligament (23, 41). Of note is that the larger proliferated rests of Malassez averaging eight to 10 times the size of the normal resting type as observed in our case were found in patients over 50 years (5, 23). Unlike conventional small rests, the present hyperplastic clear nests exhibit many overlapping features of neoplastic or pre-neoplastic rests of Malassez in carcinogenadministered rats (42). We are not certain whether clear cell odontogenic carcinoma is thought to be histogenetically related to the periodontal ligament rests of clear cell type (41).

Conclusions

This study further emphasizes the importance of submitting all excised tissues for histologic evaluation. Presumably, the occurrence of microscopically recognizable intraosseous hamartomas of residual odontogenic epithelium may be more frequent than has been reported in the literature (7, 9). As the present epithelial proliferation was present in only a small part of the lesion, there has been considerable debate in deciding how much epithelial element is necessary for such a microscopic mass to be diagnosed as neoplastic (11, 25). Their histogenetic significance warrants further discussion and can be ascertained by compiling larger series of cases.

References

- Sciubba JJ, Fantasia JE, Kahn LB. *Tumors and cysts of the jaws*. Washington, DC: Armed Forces Institute of Pathology, 2001; 71–127.
- Reichart PA, Philipsen HP. Odontogenic tumors and allied lesions. London: Quintessence Publishing Co., 2004; 25–270.
- Philipsen HP, Reichart PA, Slootweg PJ, Slater LJ. Neoplasms and tumour-like lesions arising from the odontogenic apparatus and maxillofacial skeleton: introduction. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *Pathology and genetics of head and neck tumours*. Lyon: IARC press, 2005; 283–6.
- 4. Massey D. Potential pitfalls in diagnostic oral pathology. A review for the general surgical pathologist. *Adv Anat Pathol* 2005; **12**: 332–49.
- 5. Hodson JJ. Epithelial residues of the jaw with special reference to the edentulous jaw. J Anat 1962; 96: 16–24.
- Sicher H, Bhaskar SN, eds. ORBAN's oral histology and embryology, 7th edn. St Louis: C. V. Mosby Co., 1972; 307 pp.
- Bouquot JE, Gnepp DR, Dardick I, Hietanen JHP. Intraosseous salivary tissue: jawbone examples of choristomas, hamartomas, embryonic rests, and inflammatory entrapment. Another histogenetic source for intraosseous adenocarcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90: 205–17.
- 8. Ide F, Obara K, Mishima K et al. Peripheral odontogenic tumor: a clinicopathologic study of 30 cases. General features and hamartomatous lesions. *J Oral Pathol Med* 2005; **34**: 552–7.
- Moskow BS, Baden E. Odontogenic epithelial hamartomas in periodontal structures. J Clin Periodontol 1989; 16: 92–7.
- 10. Curran AE, Damm DD, Drummond JF. Pathologically significant pericoronal lesions in adults: histopathologic evaluation. *J Oral Maxillofac Surg* 2002; **60**: 613–7.

- Gardner DG. Some current concepts on the pathology of ameloblastomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 82: 660–9.
- Quinn JH, Fullmer HM. A small ameloblastoma of the mandible. Oral Surg Oral Med Oral Pathol 1953; 6: 949–52.
- England LC. Ameloblastoma of the mandible. Report of a case. Oral Surg Oral Med Oral Pathol 1960; 13: 648–50.
- Levin MP, Kratochvil J, Nolan J. Ameloblastoma of the mandible: a case report. J Periodontol 2003; 74: 883–6.
- Harada H, Kado Y, Kumagai S, Nakagawa K, Yamamoto E. A case of ameloblastoma localized in the apex of the lower canine. *J Jpn Soc Oral Tumor* 1993; 5: 310–4.
- 16. Hollows P, Fasanmade A, Hayter JP. Ameloblastoma a diagnostic problem. *Br Dent J* 2000; **188**; 243–4.
- Batista AC, Filho HN, Rippert ET. Periapical radiolucency in the mandibular molar region. *J Oral Maxillofac Surg* 2002; **60**: 186–9.
- Eisig S, Boguslaw B. Maxillary ameloblastoma: report of an unusual case. J Am Dent Assoc 1990; 121: 135–6.
- Chindia ML, Guthua SW, Mwaniki DL. Ameloblastoma after surgical removal of an impacted mandibular molar. A case report. *Int J Oral Maxillofac Surg* 1991; 20: 73–4.
- 20. Cutright DE. Histopathologic findings in third molar opercula. *Oral Surg Oral Med Oral Pathol* 1976; **41**: 215–24.
- Kim J, Ellis GL. Dental follicular tissue: misinterpretation as odontogenic tumors. J Oral Maxillofac Surg 1993; 51: 762–7.
- 22. Thoma KH. The pathogenesis of the odontogenic tumors. *Oral Surg Oral Med Oral Pathol* 1951; **4**: 1262–80.
- Reeve CM, Wentz FM. The prevalence, morphology, and distribution of epithelial rests in the human periodontal ligament. *Oral Surg Oral Med Oral Pathol* 1962; 15: 785–93.
- Hodson JJ. Observations on the origin and nature of the adamantinoma with special reference to certain mucoepidermoid variations. *Br J Plast Surg* 1957; 10: 38–59.
- 25. Generson RM, Porter JM, Stratigos GT. Mural odontogenic epithelial proliferations within the wall of a dentigerous cyst: their significance. *Oral Surg Oral Med Oral Pathol* 1976; **42**: 717–21.
- Goldberg J. Bluish swelling of facial gingiva. Gen Dent 2003; 51: 81.
- Navarro CM, Principi SM, Massucato EMS, Sposto MR. Maxillary unicystic ameloblastoma. *Dentomaxillofac Radiol* 2004; 33: 60–2.
- 28. Cillo JE, Ellis E, Kessler HP. Pericoronal squamous odontogenic tumor associated with an impacted

mandibular third molar: a case report. *J Oral Maxillofac Surg* 2005; **63**: 413–6.

- Swan RH, McDaniel RK. Squamous odontogenic proliferation with probable origin from the rests of Malassez (early squamous odontogenic tumor)? *J Periodontol* 1983; 54: 493–6.
- Warnock GR, Correll RW, Pierce GL, Baker DA. Triangular-shaped radiolucent area between roots of the mandibular right canine and first premolar. J Am Dent Assoc 1985; 110: 945–6.
- Ide F, Sakashita H, Kusama K. Ameloblastomatoid, central odontogenic fibroma: an epithelium-rich variant. *J Oral Pathol Med* 2002; **32**: 612–4.
- 32. Yonemochi H, Noda T, Saku T. Pericoronal hamartomatous lesions in the opercula of teeth delayed in eruption: an immunohistochemical study of the extracellular matrix. *J Oral Pathol Med* 1998; **27**: 441–52.
- Blank DM, Solomon M, Berger J. A microscopic focus of calcifying epithelial odontogenic tumor arising in an operculum: an incidental finding. *J Oral Surg* 1981; 39: 454–6.
- Ficarra G, Hansen LS, Stiesmeyer EH. Intramural calcifying epithelial odontogenic tumor. *Int J Oral Maxillofac Surg* 1987; 16: 217–21.
- Ai-Ru L, Zhen L, Jian S. Calcifying epithelial odontogenic tumors: a clinicopathologic study of nine cases. J Oral Pathol 1982; 11: 399–406.
- Manor Y, Mardinger O, Katz J, Taicher S, Hirshberg A. Peripheral odontogenic tumours-differential diagnosis in gingival lesions. *Int J Oral Maxillofac Surg* 2004; 33: 268–73.
- Swan RH, Houston GD, Moore SP. Peripheral calcifying odontogenic cyst (Gorlin cyst). J Periodontol 1985; 56: 340–3.
- Claman LJ, Rossie KM, Records LE, Colbert G. Peripheral calcifying odontogenic cyst in a child: case report of an unusual lesion. *Pediatr Dent* 1987; 9: 226–8.
- Gorlin RJ. Potentialities of oral epithelium manifest by mandibular dentigerous cysts. Oral Surg Oral Med Oral Pathol 1957; 10: 271–84.
- Wysocki GP, Brannon RB, Gardner DG, Sapp P. Histogenesis of the lateral periodontal cyst and the gingival cyst of the adult. *Oral Surg Oral Med Oral Pathol* 1980; **50**: 327–34.
- Bascones J, Llanes F. Clear cells in epithelial rests of Malassez. Oral Oncol 2005; 41: 99–100.
- 42. Takeda Y, Hatakeyama S, Sashima M, Morita H, Fujisawa Y, Suzuki A. Proliferation of epithelial rests in periodontal ligament of rats induced by 1-butyl-1-nitrosourea. *Jpn J Oral Biol* 1982; 24: 520–2.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.