Odontogenic gingival epithelial hamartoma (OGEH) is an extremely rare lesion characterized by an abnormal proliferation of odontogenic epithelium. This lesion is thought to arise from the rest of the dental lamina lying dormant in the gingival tissue after odontogenesis. Distinguishing OGEH from the granular cell variant of ameloblastoma and central odontogenic fibroma is important. To date, only eleven cases have been reported, and its pathogenesis remains unclear.

We report here on a case of OGEH, where the epithelial strands in the lesion were conspicuously positive for the antisera of cytokeratin 19 and ameloblastin. Tumor cells intensely expressed ameloblastin mRNA by in situ hybridization. To the best of our knowledge, this is the first case of OGEH to which ameloblastin immunohistochemical stain and in situ hybridization were applied.

Although our study is limited to a single case, the coexpression of cytokeratin 19 and ameloblastin might indicate the origin and specific cytodifferentiation of OGEH is quite different and unique, when contrasted to other odontogenic tumors.

Key Words: Odontogenic Gingival Epithelial Hamartoma-Ameloblastin-Cytokeratin 19
within the gingiva at the left third molar area, in which no tooth was found. Excision and curettage of the underlying alveolar ridge of the mandible were done.

The excised specimen was fixed with 10% neutral formalin. Paraffin sections prepared were stained with hematoxylin and eosin. Upon gross examination, the excised mass showed an oval pinkish-gray glistening firm nodule with no attached bone, and it measured $8.0 \times 6.0 \times 5.0$ mm. The external surface was smooth and the cut surface was soft, homogeneous tan. Histologically, the specimen showed nests, bands, cords and a trabecular pattern of odontogenic epithelial cells with intervening hyalinized myxoid stroma (Fig. 2A). The neoplastic cells were arranged in cords of two to three-cell layers and there were peripheral cuboidal to columnar cells and central small cells resembling basal layer cells (Fig. 2B). The epithelial cells had large vesicular nuclei and there was scanty to moderate amounts of granular cytoplasm (Fig. 2C, left). Squamous metaplastic cells with intercellular bridges were also occasionally found. Some cells showed a hydropic degeneration that formed a pseudoglandular pattern. There were no destroyed bony fragments but there was some tiny calcification (Fig. 2C, right). At the periphery of the lesion, it was well delineated from its fibrous pseudocapsule. PAS-positive granules were demonstrated in the cytoplasm of the epithelial cells. Immunohistochemistry using antibodies were performed by the avidin-biotin complex methods. The antibodies we used were as follows: pan-keratin (AE1/AE3, DAKO, Glostrup, Denmark, 1:80 dilution), cytokeratin 19 (DAKO, 1:80), cytokeratin 8 (DAKO, 1:80), smooth muscle actin (HHF35, DAKO, 1:100), S-100 protein (DAKO, 1:1,200), glial fibrillary acidic protein (Biogenesis, Newfield, UK, 1:3,000) and fibronectin (DAKO, 1:100). Immunohistochemistry for ameloblastin using an avidin-biotin-peroxidase complex method was done as follows. A synthetic peptide, YEYSLPVHPPPLPSQ, encoding for the human exon 3a of the ameloblastin (370-414, NM_016519) was also used to produce a polyclonal antibody from a rabbit. For in situ hybridization of the ameloblastin gene, the full length base pair of ameloblastin Y224 was cloned into the pBluescript SK(-) vector. The plasmids were linealized by EcoRI or Xhol for antisense or sense probe production, respectively. The single-stranded antisense and sense RNA probes were labeled with digoxigenin-UTP, and then they were generated by using T3 and T7 RNA polymerases (Boehringer Mannheim, Indianapolis, IN). The detection of in situ hybridization was carried out using the Genius Detection system (Boehringer Mannheim, Indianapolis, IN), in which the specific transcripts were detected with an anti-digoxigenin antibody conjugated to alkaline phosphatase. Immunohistochemically, the epithelial cells were strongly reactive for pan-keratin, ameloblastin and they were focally reactive for cytokeratin 19 (Fig. 3A) but they were negative for cytokeratin 8, smooth muscle actin, S-100 protein, or glial fibrillary acidic protein. Myxoid stroma was neg-
ative for fibronectin or PAS-stainability. *In situ* hybridization for ameloblastin revealed that ameloblastin was expressed in the epithelial glands of the lesion (Fig. 3B). The diagnosis we arrived at was odontogenic gingival epithelial hamartoma (OGEH), and this lesion was confined within the alveolar socket of the mandible, i.e. the intraosseous variant. During the thirty months of follow-up, she was in good health without recurrence.

**DISCUSSION**

The granular epithelial cells and myxoid stroma of the present case initially gave the impression of salivary gland tumor. However, the histologic findings such as nuclear polarization of granular epithelial cell nests with myxoid stroma, imply that this lesion had an odontogenic origin. Granular cells are usually found in OGEH, granular cell ameloblastoma and plexiform granular cell odontogenic tumor. Other differential diagnoses could include central odontogenic fibroma, granular cell variant (WHO type), calcifying epithelial odontogenic tumor and choristomatous salivary glands of the gingiva. Granular cell ameloblastoma can be differentiated from OGEH by the absence of stellate reticulum as well as pseudoencapsulation. A calcifying epithelial odontogenic tumor shows the proliferation of large polygonal odontogenic epithelial cells containing psammoma bodies in the amyloid like stroma. A pathological diagnosis of choristomatous salivary glands of the gingiva was excluded not only by the histology

![Fig. 3. (A) Immunoreactivity for cytokeratin 19 in the epithelial cells (cytokeratin 19 immunostain). (B) *In situ* hybridization for ameloblastin showing strong positivity in the nuclei of epithelial glands (arrows).](image)

<table>
<thead>
<tr>
<th>Authors (yr)</th>
<th>Sex/Age</th>
<th>Site</th>
<th>Radiology</th>
<th>Size (mm)</th>
<th>Continuity with oral epithelium</th>
<th>Calcification</th>
<th>Procedure</th>
<th>Clinical outcome</th>
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<tr>
<td>Baden, et al. (1968)</td>
<td>F/59</td>
<td>Gingiva, mandible</td>
<td>No bone resorption</td>
<td>Pea size</td>
<td>+</td>
<td>+</td>
<td>Mass excision &amp; bone excision</td>
<td>NER 2 yr F/U</td>
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<tr>
<td>M/55</td>
<td></td>
<td>Gingiva, maxilla</td>
<td>No bone resorption</td>
<td>2.5</td>
<td>+</td>
<td>-</td>
<td>Wide excision</td>
<td>NER 2 yr F/U</td>
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<tr>
<td>F/65</td>
<td></td>
<td>Gingiva, mandible</td>
<td>No bone resorption</td>
<td>0.7</td>
<td>+</td>
<td>-</td>
<td>Mass excision</td>
<td>NER 2 yr F/U</td>
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<td>Baden, et al. (1973)</td>
<td>F/60</td>
<td>Gingiva, mandible</td>
<td>Cupping of interdental bone</td>
<td>9 × 7</td>
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<td>-</td>
<td>Wide excision</td>
<td>NER 16 mo F/U</td>
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<td>Gardner (1973)</td>
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<td>No bone resorption</td>
<td>3 × 2</td>
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<td>-</td>
<td>Hemimandibulectomy*</td>
<td>NER 23 yr F/U</td>
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<td>Sciubba, et al. (1978)</td>
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<td>-</td>
<td>-</td>
<td>Wide excision</td>
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<td>Moskow, et al. (1989)</td>
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*: This case was initially misdiagnosed as ameloblastoma. yr, year; mo, months; NER, no evidence of recurrence; F/U, follow up; NR, not recorded.
Odontogenic Gingival Epithelial Hamartoma

There are two suggested hypotheses for the pathogenesis of this benign lesion. One is the origin from a dental lamina nest, the so-called "glands of Serres" after odontogenesis is started. Because odontogenesis is a highly complex process of interplay between epithelial and mesenchymal tissues (ectomesenchyme), errors are commonly encountered. Abnormally displaced, supernumerary tooth germs were pinched off during development, and these isolated foci failed to differentiate into a fully formed tooth, but rather they proceed to develop into OGEH. Gingival nests containing glands of Serres are encountered throughout the entire dentition, and they can regress or stay dormant as vestigial structures in children. The other theory is that OGEH arises from the proliferation of a basal layer of the surface epithelium after various provoking stimuli, such as inflammation, trauma and so on. The fact that the reported cases occurred in older adults suffering from chronic irritation on gingiva supports the latter theory. Sciubba et al. even suggested that this lesion is in a transitional status between a true odontogenic neoplasm and a developmental anomaly. In our opinion, the former theory is more plausible, i.e. OGEH originated from the pinched-off remnant of dental lamina rather than the basal layer of gingival epithelium. The supporting facts of the former are as follows; first, the site of the lesion generally shows the frequent absence of connection between the lesion and the overlying epithelium. Second, OGEH can occur in the intraosseous portion of the jawbone, where gingival epithelium is not a normal component, although Moskow and Baden’s cases are not typical examples of OGEH. Third, it frequently occurs in the third molar area, where remnants of the dental lamina may persist in adults, as well as in the premolar gingiva. Fourth, the immunohistochemical results in the present case support the dental lamina origin. The expression of cytokeratin 19 and ameloblastin may reflect that tumor cells retain an immature phenotype of odontogenic differentiation. The question about the cell of origin should not always be seen only from the viewpoint of cytokeratin immunohistochemistry, a specific type of cytokeratin is expressed in different stages of odontogenesis; all epithelial elements including fetal oral epithelium, tooth germ, as well as a variety of odontogenic tumors, express cytokeratin 19. Compared to the cytokeratin...
19, ameloblastin is more specific to enamel epithelium of the tooth’s organ. The expression of both cytokeratin 19 and ameloblastin in this study may reflect that tumor cells retain immature phenotype of odontogenic differentiation. In particular, the present study used a novel antibody against the epitope of ameloblastin exon 9, which is specific to the precursor ameloblastin in the cytoplasm of enamel epithelium, this is, however, excluding the degraded products of ameloblastin in the extracellular tissue. In our opinion, these results might support that OGEH is a benign tumor composed of relatively well-differentiated odontogenic epithelium that was derived from the pinched-off remnant of dental lamina.

REFERENCES