Paradental cyst is an inclusion cyst of the junctional/sulcular epithelium of the gingiva: histopathologic and immunohistochemical confirmation for its pathogenesis

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Objective. The aim of this study was to characterize the histologic and immunohistochemical profiles of paradental cyst-lining epithelia to clarify its histopathogenesis.

Study Design. Ten surgical specimens of paradental cysts were examined for clinical profiles and to determine the histopathologic characteristics of the lining epithelia. Immunohistochemical profiles for keratin (K) subtypes, as well as for perlecan, UEA-I lectin binding, and proliferating cell nuclear antigen (PCNA), were determined and compared.

Results. The paradental cyst was clinically characterized by its occurrence in young adults (mean age, 36.8 years; male, 42.8, female 27.8). Eight of the 10 cases arose in the retromolar area. The cyst wall was basically granulation tissue that was attached to the periodontal ligament space. Thin irregular anastomosing epithelial cords lined the cyst walls of immature granulation tissue with vascular dilation and hemorrhage. The intercellular space of the lining epithelia was widened with inflammatory cell infiltrates. Immunohistochemically, the lining was positive for K13, K14, K17, K19, UEA-I binding, and perlecan, suggesting its junctional/sulcular epithelial character.

Conclusion. The results showed that the paradental cyst was lined by epithelial cells with characteristics of the junctional/sulcular epithelium. The cyst can thus be considered as a kind of inclusion cyst arising in the periodontal pocket, most frequently of the mandibular third molars of young adults. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:227-237)

The disease entity of the paradental cyst, also known as the inflammatory paradental cyst, inflammatory collateral cyst, and mandibular infected buccal cyst, was established as 1 of 2 types of inflammatory jaw cysts in the second version of the World Health Organization (WHO) classification in 1992.1 The cyst has also been referred to as Craig’s cyst in acknowledgment of the work of Craig, who examined a series of 49 cases and helped clarify the cyst’s clinicopathologic characteristics;2 Craig’s findings were similar to those previously reported by Main, who had analyzed 8 cases.3 Subsequent reports have confirmed the inflammatory pathogenesis of the paradental cyst.4 Even after reviewing 342 cases in the literature, Philipsen et al. concluded that reduced enamel epithelium, epithelial rests of Malassez, or remnants of the dental lamina are the possible sources of cyst-lining epithelia and that the histologic features are indistinguishable from those of the inflammatory radicular cyst.5 Thus, it remains unclear whether the differential diagnosis of the paradental cyst is histopathologically possible or what the origin of the lining epithelium of the paradental cyst is.

Jaw cysts are one of the most common diseases encountered in routine oral pathology services. However, their differential diagnoses at the histopathologic level are not always easy because the epithelial linings of the cyst wall are easily modified by inflammation, even though the diagnosis of cystic jaw lesions is made by considering clinical and radiographic information along with histopathologic specimens. Histopathologic differential diagnosis is especially important when

Statement of Clinical Relevance

This study proposes a possible histopathogenesis of the paradental cyst based on histopathologic and immunohistochemical investigations. The cyst is a kind of inclusion cyst arising in the periodontal pocket, most frequently of the mandibular third molars of young adults.
neoplastic lesions such as cystic ameloblastoma or keratocystic odontogenic tumor (KCOT) are clinically suspected.

To resolve this challenging issue, we have introduced several combinations of immunohistochemistry for epithelial linings in our diagnostic services, since we have found that hematoxylin and eosin (H&E)-stained sections occasionally do not work in the differential diagnoses of inflamed cystic jaw lesions6-11 or of odontogenic tumors with cystic changes.12-15 So far, we have defined immunohistochemical profiles specific to the six most common cystic lesions: unicystic ameloblastoma, KCOT, dentigerous cyst, lateral periodontal cyst, radicular cyst,6,7 and nasopalatine duct cyst.11 However, we have not included the paradental cyst as an object for differential diagnosis because we have considered that its occurrence was much rarer than that of the 6 cystic lesions mentioned above and because the diagnosis of the paradental cyst is apparently easier due to its characteristic location. At the same time, however, we have occasionally encountered paradental cyst cases showing some characteristic histopathologic features that have not been well documented in the literature. Furthermore, we have come to realize that the histopathogenesis of paradental cysts still remains poorly understood. Thus, we wanted to apply our immunohistochemical method for better understanding the histopathogenesis of paradental cysts.

The purpose of this study was to analyze the clinicopathologic and histologic characteristics of 10 paradental cyst cases documented in our hospital to determine the relationship between the cyst-lining epithelia and the gingival junctional/sulcular epithelium. This investigation was possible because we had recently determined the immunohistochemical profiles of the junctional/sulcular epithelium.16

MATERIALS AND METHODS

Patients and specimens

Surgical specimens of 10 cases of paradental cysts were collected for the present study from the surgical pathology files of the Division of Oral Pathology, Niigata University Graduate School of Medical and Dental Sciences, during a 15-year period from 2000 to 2014. During the same period, a total of 2329 jaw cyst cases were documented. The 10 paradental cyst cases were typical cases, diagnosed on the basis of not only histopathologic findings but also clinical and radiologic findings. The surgical samples were fixed in 10% formalin and decalcified with Planck-Rychlo’s solution, which contained 8.5% hydrochloric acid and 5% formic acid, for up to 48 hours when cyst walls were surgically removed along with teeth. The specimens were then routinely processed and embedded in paraffin. In addition, 20 biopsy samples from epulides, which contained junctional/sulcular epithelia in the inner surface, and 10 cases each of the other five major cystic jaw lesions such as unicystic ameloblastoma, KCOT, dentigerous cysts, lateral periodontal cyst, and radicular cyst were selected for control experiments. Serial sections cut at 4 μm from paraffin blocks were used for H&E and immunohistochemical staining. The experimental protocol for analyzing surgical material was reviewed and approved by the Ethical Board of the Niigata University Graduate School of Medical and Dental Sciences (Oral Life Science).

Clinical findings

In addition to clinical data (patient age and gender and cyst location) of paradental cyst cases that were documented in patients’ clinical records, the relationship with the affected tooth and the condition of associated teeth (vitality and periodontal disease) were carefully determined in every case by analyzing simple radiographic and computed tomography (CT) images in comparison with the documented clinical records and by referring to the conventional criteria for paradental cyst.4,5

Histopathology

Tissue sections from the 10 cases of paradental cyst were reviewed histopathologically, and their characteristic features were analyzed in terms of lining epithelia, blood vasculature, and inflammatory cells within the cyst walls.

Antibodies

Mouse monoclonal antibodies against human keratin 10 (K10, DE-K10, immunoglobulin [Ig] G1), K13 (DE-K13, IgG2a), K17 (E3, IgG2b), K19 (RCK108, IgG1), and proliferating cell nuclear antigen (PCNA) (PC10, IgG2a) were purchased from Dako (Glostrup, Denmark). A monoclonal antibody against K14 (CK-B1, IgM) was obtained from Sigma Chemical Co., (St Louis, MO). Rabbit polyclonal antibodies against the core protein of perlecan were raised in rabbits, as described elsewhere.17

Immunohistochemistry

Immunohistochemical staining was performed by using the ChemMate Envision system (Dako).7 For K13, K14, and K19, sections were autoclaved in citric acid buffer (pH 6.0) at 121°C for 10 minutes. For K17, sections were autoclaved in 0.01 M Tris buffer (pH 9.0) containing 0.001 mol/L ethylenediaminetetra-acetic acid.
(EDTA) at 121°C for 10 minutes. After the pretreatment, the sections were rinsed in phosphate-buffered saline (PBS) containing 0.5% milk protein (Morinaga Milk Industry Co. Ltd., Tokyo, Japan) and 0.05% Triton X-100 (T-PBS) and treated with 0.3% hydrogen peroxide in methanol for 30 minutes at room temperature to block endogenous peroxidase activities. After rinsing in T-PBS, the sections were incubated with 5% milk protein in T-PBS for 1 hour at room temperature to block nonspecific protein-binding sites. They were then incubated overnight at 4°C with the primary antibodies diluted in T-PBS. After incubation, the sections were rinsed in T-PBS and incubated with the secondary antibodies, which were conjugated with peroxidase-labeled dextran polymers, for 1 hour at room temperature. After rinsing in T-PBS, they were treated with 0.02% 3,3'-diaminobenzidine in 0.05 M Tris-HCl buffer (pH 7.6) containing 0.005% hydrogen peroxide to visualize the reaction products. Finally, the sections were counterstained with hematoxylin. For control studies on antibodies, the primary antibodies were replaced with preimmune mouse IgG subclasses (Dako). For Ulex Europaeus agglutinin I lectin (UEA-I) binding immunohistochemistry, sections were stained using the lectin-antilectin method.6 UEA-I and rabbit polyclonal antibodies against UEA-I were obtained from E-Y Laboratories Inc. (San Mateo, CA). The lectin concentration was 1 mg/mL. Staining results were evaluated as positive when staining intensities of epithelial cells were evident from those of connective tissue areas and their positive areas occupied recognizable extents of the epithelial zone.

**RESULTS**

**Age and gender**

The age and gender distribution in the 10 cases of paradental cysts are summarized in Table I. Those cases accounted for 0.4% of the 2329 of jaw cysts documented in the file during the same period. They were ranked sixth among jaw cysts, of which radicular cysts were the most common (1136 cases, 48.8%), followed by dentigerous cysts (328, 14.1%), KCOTs (159, 6.8%), nasopalatine duct cysts (61, 2.6%), and lateral periodontal cysts (29, 1.2%). The mean age of the patients was 36.8 years (42.8, male; 27.8, female) with ages ranging from 17 to 65 years. There were 6 male (60%) and 4 female (40%) patients. The data indicated that paradental cysts occur in young adults but not in children, and with no obvious gender predilection.

**Tooth association**

Of the 10 paradental cysts, 8 (80%) were associated with the third molars or with second molars which lacked a distally neighboring third molar; 9 (90%) were mandibular, and 1 (10%) was maxillary. One of the 8 cysts was located on the mesial side of the third molar, while the others were on the distal side (see Table I). Radiographically, they were identified as unilocular radiolucencies next to tooth roots without any tooth root resorption. Most showed ovoid shapes, with swelling toward their distal ends and looked different from simple periodontal pockets (Figure 1, case #7). Their longest diameters ranged from 8 to 18 mm, with a mean of 11 mm on panoramic radiographs. In

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age (y) and sex</th>
<th>Location</th>
<th>Tooth site</th>
<th>Symptoms</th>
<th>Associated tooth pulp</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>17 M Mandible</td>
<td>Second molar, distal (no third molar)</td>
<td>No, bone resorption found during dental treatment for other teeth</td>
<td>Vital</td>
<td>Extirpation</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>27 M Mandible</td>
<td>Third molar, distal</td>
<td>Repeated pain</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>22 F Mandible</td>
<td>Third molar, distal</td>
<td>Acute pain</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>28 F Mandible</td>
<td>Third molar, distal</td>
<td>Continuous pain</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>29 F Mandible</td>
<td>Third molar, distal</td>
<td>Repeated gingival swelling</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>32 F Mandible</td>
<td>Third molar, distal</td>
<td>Food impaction, pain</td>
<td>Vital</td>
<td>Extirpation</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>47 M Mandible</td>
<td>Third molar, distal</td>
<td>No, found during dental treatment</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>45 M Mandible</td>
<td>First and second premolar, buccal</td>
<td>Periodontitis</td>
<td>Vital</td>
<td>Extirpation</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>56 M Maxilla</td>
<td>Third molar, palatal</td>
<td>No, found during dental treatment for multiple caries with periapical lesions and for periodontitis</td>
<td>Vital</td>
<td>Extirpation with tooth</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>65 M Mandible</td>
<td>Lateral incisor, distal</td>
<td>Repeated pain, gingival swelling, periodontitis</td>
<td>Vital</td>
<td>Extirpation</td>
<td></td>
</tr>
</tbody>
</table>

Table I. Clinical summary of 10 cases of paradental cyst investigated in the present study
addition, younger patients (cases #1-7; ages 17-47 years) did not suffer from periodontitis but from focal pericoronitis around their third molar teeth, whereas older patients (cases #8-10; ages 45-65 years) had extensive periodontitis, which might have caused the deepening of the periodontal pockets. All of the teeth associated with the cysts were determined to be vital by electric pulp testing (see Table I).

**Histopathology**

The paradental cysts were located along tooth roots within the range from the enamel-cementum junction (case #4, Figure 2A; rectangle area indicated by dashed line, a high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00565) to the apical ends (case #2, Figure 2B; rectangle, eSlide: VM00579). The cyst wall was composed of granulation tissue, measuring 1 to 3 mm in thickness on H&E-stained sections. In case #3, the cyst wall granulation tissue extended to the bifurcation zone of tooth roots (Figure 2C; rectangle, eSlide: VM00572). The cystic lumen was not smooth surfaced but was indented, with immature granulation tissue protrusions (Figures 2D to 2G). The cyst wall granulation tissue showed edematous changes, but there was no definite layering of granulation tissues in the different organizing processes, which is characteristic of the walls of radicular cysts, the other major type of inflammatory cysts. The inner surface of the cystic lumina was lined by extensively anastomosed cords of stratified squamous epithelial cells without keratinizing tendencies (Figures 2F and G). The congestive status of blood vascular channels seemed to result in hemorrhage at surgery (Figure 2G). In 2 of the 10 specimens, some connection was identified (Figure 2D, arrow) between the cyst linings (Figure 2D, open asterisk) and the junctional/sulcular epithelia (Figure 2D, closed asterisk) forming the bottom of the periodontal pockets (Figure 2D, double circle), although there was no direct continuity between the periodontal pockets and the cystic lumina.

The lining epithelia in anastomosing cords were characterized by their wide intercellular space (Figure 3A). Occasionally, microcystic changes with eosinophilic (Figure 3B, open asterisk) or pale-colored fluid contents (Figure 3B, arrows) as well as round-shaped hyaline bodies (Figure 3B, closed asterisk) were observed within the lining epithelia. Blood capillaries and venules were prominently dilated with red blood cell (RBC) retention between the anastomosing epithelial cords (Figure 3C). Those RBCs tended to coagulate with each other, to be hemolyzed within the vascular channels, or to be extravasated over the epithelial compartment (Figure 3D). However, there were no obvious hemosideroses in the tissue specimens investigated, which indicated that the hemorrhagic changes were related to surgical intervention.

In 2 cases, the round-shaped hyaline bodies were observed in close association with deeply eosinophilic epithelial cells (Figure 3E). Some of those deeply stained cells contained pyknotic or fragmented nuclei or even lacked nuclei, and they were occasionally indistinguishable from round-shaped eosinophilic hyaline bodies, some of which were composed of granular materials or contained calcified centers (Figure 3F).
Immunohistochemistry for lining epithelia

The 10 cases showed basically the same staining profiles. Among the keratin subtypes, K13 (Figure 4A), K14 (Figure 4B), and K19 (Figure 4C) were demonstrated in almost the whole layer of the linings. K17-positive (+) cells were occasionally found in the surface part, but their appearance was not stable (not shown). There were no positive reactions for the other K subtypes (not shown). Perlecan was characteristically localized mainly on the cell border, showing vesicular patterns in nearly the whole epithelial layer (Figure 4D). UEA-I binding was
mainly shown on the cell border of the upper half of the epithelial layer (Figure 4E). PCNA+ cells were scarcely observed (Figure 4F). We also investigated the immunohistochemical profiles for K14 in the dentigerous cyst, which is included in the differential diagnosis with the paradental cyst, unicystic ameloblastoma, KCOT, lateral periodontal cyst, and radicular cyst, whose immunohistochemical modes for K10, K13, K17, K19, UEA-I binding, perlecan, and PCNA have been documented.\(^7\) As a result, K14 was sporadically positive in the surface layer of the lining epithelia of the dentigerous cyst, lateral periodontal cyst, and radicular cyst (data not shown), while it was not obviously demonstrated in unicystic ameloblastoma and KCOT (data not shown). The immunohistochemical profiles of paradental cyst linings are summarized in Table II, where the profiles of the linings of the other 5 major jaw cysts are compared.

Hyaline bodies within the anastomosed epithelial processes (see Figures 3E and 3F) were immunohistochemically positive for K13 (Figure 5A), K14 (Figure 5B), K19 (Figure 5C), and faintly for
The results indicated that the round-shaped hyaline bodies were derived from the lining epithelial cells. There were occasionally eosinophilic conglomerates of round-shaped calcified materials within fibrous tissues, which did not look like epithelial components (Figure 5E). However, immunohistochemically, those round-shaped materials were positive for keratin (K13; Figure 5F), K14 (Figure 5B), and K19 (Figure 5C), although their staining intensities and extents differed by case. At higher magnification, the cell border of the lining epithelial cells was positive for perlecan (D) and UEA-I binding (E). There was no definite PCNA labeling among the epithelial cells (F).

Table II. Immunohistochemical profiles of lining epithelia compared five major jaw cysts with the paradental cyst

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Unicystic ameloblastoma*</th>
<th>Keratoctyic odontogenic tumor*</th>
<th>Dentigerous cyst†</th>
<th>Lateral periodontal cyst†</th>
<th>Radicular cyst†</th>
<th>Parodontal cyst</th>
<th>Junctional epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin 10</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Keratin 13</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keratin 14</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keratin 17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keratin 19</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>UEA-I</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perlecan</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCNA</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Modified from reference 7.
†Only surface.
‡Only basal.

UEA-I, Ulex Europaeus agglutinin I lectin; PCNA, proliferating cell nuclear antigen.

K17 (Figure 5D). The results indicated that the round-shaped hyaline bodies were derived from the lining epithelial cells. There were occasionally eosinophilic conglomerates of round-shaped calcified materials within fibrous tissues, which did not look like epithelial components (Figure 5E). However, immunohistochemically, those round-shaped materials were positive for keratin subtypes (K13; Figure 5F).

Junctional/sulcular epithelia covering the inner surface of epulis samples showed irregular-shaped rete ridges that were anastomosed with each other in the background of acute and chronic inflammation. Compared with the outer surface epithelia, their intercellular spaces were more enhanced (Figure 6A). Immunohistochemically, those cell borders were positively labeled for perlecan (Figure 6B) as well as for UEA-I (Figure 6C), and junctional/sulcular epithelial cells in the upper zone were positive for K13 (Figure 6D), K14 (Figure 6E), and K19 (Figure 6F) were more extensively localized in the epithelial layer, although their extents varied from case to case. In cases with severe inflammation, K17 tended to be positive only in the surface zone (Figure 6G).

**DISCUSSION**

The present study reconfirmed the clinical characteristics of the paradental cyst: it mostly arises in the periodontal space of the mandibular third molar of young adults. Histopathologically, the cyst wall is granulation tissue, and its inner surface is lined by an irregular-shaped squamous epithelial layer, which indicates its inflammatory origin. Based on its immunohistochemical profiles, we were also able to demonstrate that the nature of the lining epithelium resembles that of the junctional/sulcular epithelium of the gingiva. Thus, our present definition of the paradental cyst is that of an
inflammatory cyst generated by inclusion of the gingival sulcular or junctional epithelia of adjacent vital teeth. Paradental cysts most often arise in the distal aspect of the third molar of younger adults between 20 and 30 years old but also arise around teeth affected by periodontitis in older men. The cyst wall, attached to the upper part of tooth roots, is composed of fibrous granulation tissue lined with nonkeratinous epithelium with reticulately anastomosed rete ridges, between which are dilated and congestive blood capillaries. Immunohistochemically, the lining epithelium shows the same profile as the junctional/sulcular epithelium. Both are positive for K13, K14, K17, K19, UEA-I binding, and perlecan.

In addition to the histologic features already documented, the present study adds the following characteristic findings: (1) anastomosed epithelial cords of the cyst lining, which have a wide intercellular space; (2) vascular dilation with congestion or hemorrhage, which seems to be generated by mechanical stress during surgery; (3) retention of tissue fluid containing foreign bodies within the epithelial compartment or along the inner surface of the cyst wall; and (4) association between the junctional epithelium and the cyst-lining epithelium. Surgical intervention was considered as a cause of hemorrhage because RBCs were intact, although some were hemolytic and not associated with hemosiderosis. The anastomosing
epithelial cords may cause mechanical stress to blood vessels between the cords, which may result in a circulatory disturbance with a tendency toward hemorrhage. Their characteristic wide intercellular space must be one of the most important tissue architectural features of the junctional/sulcular epithelium, which allows the intercellular passage of leukocytes as well as tissue fluids, including gingival crevicular fluid (GCF). Such a characteristic tissue architecture should be an infrastructure of microcyst formation within the lining epithelium. The presence of foreign bodies also suggests the continuity between cystic lumina and periodontal pockets in the process of paradental cyst formation.

Immunohistochemically, the lining epithelium is positive for K13, K14, and K19, perlecan, and UEA-I binding. The results indicate its junctional/sulcular epithelium characteristics. The keratin expression profiles for the junctional/sulcular epithelium or the periodontal pocket epithelium have been documented in the literature. We have chosen K14 and K19 as the junctional/sulcular epithelium markers in our diagnostic services because these 2 keratin subtypes are most stably localized in the whole layer of the junctional epithelium in formalin-fixed surgical human specimens. As to the inter-epithelial-cellular deposit of perlecan, we have reported its significance as one of the constituents of the intraepithelial stroma, which functions as a growth factor reservoir for cellular growth in such tissue circumstances without blood circulation as inside epithelial compartments. The absence of UEA-I binding has been shown to be specific to ameloblastoma, and thus its presence in paradental cysts indicates that it is a reactive lesion as opposed to a neoplastic one.

A summary of the immunohistochemical profiles of lining epithelia of major jaw cysts is provided in Table II. The pathogenesis of the paradental cyst, including the origin of its lining, has remained unclarified. However, we now consider it possible to objectively evaluate the differentiation degrees of the lining epithelium with the aid of combined immunohistochemistry in order to speculate on their origins. Judging from the immunohistochemical profiles (Table II), the paradental cyst can be regarded as an independent cyst entity in which the lining either shows the junctional/sulcular-epithelial differentiation or keeps the junctional/sulcular-epithelial character. The unstable and faint expression of K17 indicates that the paradental cyst differs from pure odontogenic lesions such as ameloblastoma or KCOT. Among those jaw cyst types, K14 was not demonstrated in the whole epithelial layer, but their stainings were occasional and sporadic, which was different from those in the junctional/sulcular-epithelial or the paradental cyst. The presence of perlecan indicates junctional/sulcular-epithelial characteristics, in which cellular migration is allowed, as seen in the sulcular or normal junctional epithelium. Those combined immunohistochemical profiles, summarized in Table II, indicate the resemblance between junctional/sulcular epithelia and paradental cyst linings.

Philipsen et al. stated that histologic features are indistinguishable from those of the inflammatory, peri-epithelial or radicular cyst. However, it is now possible to distinguish these 2 cysts by immunohistochemistry.
They also listed 3 candidates for the origin of lining: reduced enamel epithelium, cell rests of Malassez, and remnants of the dental lamina, which are stimulated by inflammation in the pathogenic processes of paradental cysts. Epithelial rests of Malassez have been considered to be the source for radicular cysts. Because they are the only epithelial component within the periodontal space between the tooth root and the alveolar bone of erupted teeth, there is no doubt about the role of epithelial rests of Malassez in the histopathogenesis of radicular cysts. However, the Epithelial rests of Malassez theory cannot explain why paradental cysts arise mainly in the third molar region.

Based on the present results, the most probable pathogenesis suggests periodontal pocket-related processes. Such pathogenic pathways have already been proposed by several groups. We agree with the suggestion of Vedtofte and Praetorius that paradental cyst is initiated by pericoronitis. However, it is difficult to accept their conceptual speculation on the lining epithelial origin from epithelial rests of Malassez or reduced enamel epithelium as mentioned previously. Although reduced enamel epithelium has been considered the origin of the paradental cyst by other groups, this seems unlikely because, in contrast with dentigerous cysts, paradental cysts never arise in the tooth crown. The role of remnants of the dental lamina in conditions occurring in adulthood seems to be doubtful, and in terms of immunohistochemical profiles, the paradental cyst differs markedly from the dentigerous cyst.

Terms such as “globulomaxillary cyst,” “branchial cyst,” and “nasopalatine duct cyst” have also been widely applied for many years for cysts arising in their specific locations, based on the assumption that such cysts result from fetal tissue remnants. However, given the lack of solid scientific support for the histopathogenesis of such entities, we believe it is time to abandon these 3 terms.

Colgan et al. concluded that food impaction at the site of erupting teeth was the major cause of paradental cysts by showing foreign body reactions in their series. We also found foreign bodies in the present study. The union between the oral epithelium and the cyst lining epithelium has also been reported, and we have demonstrated the continuity between the two in Figure 2D. The presence of foreign bodies also suggests the continuity between cystic lumina and periodontal pockets during the process of paradental cyst formation, including tooth eruption steps. In other words, the cystic space may be completed by closure of periodontal pockets, hence the paradental cyst is a kind of inclusion cyst of the junctional/sulcular epithelium, which is generated by a mechanism similar to that for epidermal inclusion cyst of the skin.

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