Review Article

Inflammatory Odontogenic Cysts

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ABSTRACT

Cystic conditions of the jaw cause bony destruction and may cause resorption or displacement of adjacent teeth. Odontogenic cysts have developmental or inflammatory origins. To describe in detail the inflammatory odontogenic cysts, a manual search was done in hard copy books of oral and maxillofacial pathology, and an electronic search was done in the google website, oral and maxillofacial pathology E-books, PubMed, Research Gate, Academia, and Google scholar using the keywords "odontogenic cysts," "classification of the odontogenic cysts," "radicular cyst," "periapical cyst," "lateral inflammatory cyst," "residual cyst," "paradental cyst," "collateral inflammatory cyst," "treatment of inflammatory odontogenic cysts," and matching each odontogenic inflammatory cyst subtype with these words "gross description," "pathogenesis," "microscopical," clinical," "radiographical" appearance. Articles published till February 2021 were included in this review. In conclusion, an accurate diagnosis of an inflammatory odontogenic cyst requires information relative to its clinical, radiographical, macro- and microscopical findings. In many instances, two cysts that are classified differently may exhibit similar histopathological features. In such cases, clinical and radiographic findings are necessary to make a precise diagnosis.

Keywords: Inflammatory, Odontogenic Cysts, Oral, Radicular Cyst, Collateral Cyst.

Introduction

The number and variety of cysts that occur in the jaws are greater than those arising in any other part of the body. At least 90% of all jaw cysts are of odontogenic origin(1). Odontogenic cysts originate from the epithelial components' odontogenic apparatus or from its remnants that are entrapped within the bone or the gingival tissues. Concerning their pathogenesis, some of them are considered as "developmental" and others as "inflammatory."(2) Most jaw cysts have the same behavior and usually slowly growing and expanding. They vary mainly in their relationship to a tooth. Their radiographic features are generally useful guides to their nature, but their diagnosis ultimately depends on histopathology(1). Despite being lesions with benign biological behavior, they can reach considerable size if they are not diagnosed early and treated appropriately(2).

These lesions have an important set of clinical and histopathological features, which help to reach the final diagnosis.
This review is a try to summarize the critical features of inflammatory odontogenic cysts in the literature.

**Review of literature**

**What is a cyst?**

A cyst can be defined as a pathological cavity lined by epithelium with fluid or semi-fluid contents. However, clinically, the term encompasses a broader range of benign fluid-filled lesions, some of which do not possess an epithelial lining (pseudo-cyst). Therefore, the preferred definition is a 'pathological cavity having fluid or semi-fluid contents that have not been created by the accumulation of pus'.(3) A cyst is composed of three basic structures: (1) a central cavity (lumen), (2) an epithelial lining, and (3) an outer wall (capsule) (Figure 1). The cystic cavity usually contains fluid or semi-solid material such as cellular debris, keratin, or mucus. The epithelial lining differs among cyst types and may be keratinized or non-keratinized stratified squamous, pseudostratified, columnar, or cuboidal. The cystic wall is composed of connective tissue containing fibroblasts and blood vessels. (4).

**Odontogenic cysts**

Odontogenic cyst is a cyst in which the lining of the lumen is derived from the epithelium involved in tooth development. The epithelial lining of odontogenic cysts originates from residues of the tooth-forming organ. (4) Odontogenic cysts and tumors are the most frequent osseous destructive lesions of the jaws,(6) mostly in the mandibular posterior area. Radicular cysts are the most common cyst of the odontogenic inflammatory origin, most cases in females' anterior maxillary zone in their fourth decade of life.(7)

**Odontogenic cysts epithelial origin**

Epithelial rests of Series are remnants of the dental lamina, islands, and strands of epithelium that originate from the oral epithelium and remain in the tissues after inducing tooth development thought give rise to the odontogenic keratocyst, lateral periodontal and gingival cysts. Reduced enamel epithelium is derived from the enamel organ and covers the unerupted tooth's fully formed crown. The dentigerous (follicular) and eruption cysts originate from this tissue, as do the mandibular buccal and paradental cysts. Epithelial rests of Malassez are small islands and strands of odontogenic epithelium found in the periodontal ligament. They represent remnants of Hertwig's root sheath, an embryologic epithelial structure that surrounds a developing root. Although the rests of Malassez are present along the root's entire length, they are most plentiful in the apical region. Radicular cysts originate from these residues. These three odontogenic epithelium sources represent logical categories on which a histogenesis and classification of odontogenic cysts can be based (Figure 2).(3, 4).

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**Figure 1** Cyst: (A) and (B) Elements of a cyst.(4) (C) True (a) and pseudo-cyst (b).(5)

**Figure 2** Odontogenic cysts epithelial origin. (8).

**Table 1** Classifications of the jaws' cysts: (A) by Shear.(9) (B) Histopathological classification by Sapp.(4) (C) Latest WHO Classification.(10)

<table>
<thead>
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<th>A Epithelial-lined cysts</th>
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<td>1 Developmental origin</td>
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<td>(a) Odontogenic</td>
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<td>i Gingival cyst of infants</td>
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<td>ii Odontogenic keratocyst</td>
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<td>iii Dentigerous cyst</td>
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<td>iv Eruption cyst</td>
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<td>vi Developmental lateral periodontal cyst</td>
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<td>vii Botryoid odontogenic cyst</td>
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<td>viii Glandular odontogenic cyst</td>
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<td>ix Calcifying odontogenic cyst</td>
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<td>(b) Non-odontogenic</td>
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<td>i Midpalatal raphé cyst of infants</td>
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<td>ii Nasopalatine duct cyst</td>
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<td>iii Nasolabial cyst</td>
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<th>2 Inflammatory origin</th>
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<tr>
<td>i Radicular cyst, apical and lateral</td>
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<td>ii Residual cyst</td>
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<td>iii Paradental cyst and juvenile paradental cyst</td>
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<td>iv Inflammatory collatral cyst</td>
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<th>B Non-epithelial-lined cysts</th>
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<tr>
<td>1 Solitary bone cyst</td>
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<td>2 Aneurysmal bone cyst</td>
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Odontogenic cysts of inflammatory origin:
Inflammatory odontogenic cysts constitute about 55% of all oral cysts. They are benign osteolytic asymptomatic lesions, but that, depending on the size. They can destroy the surrounding bone and been infected. They can be classified as a radicular cyst (periapical cyst and lateral inflammatory cyst), residual cyst, and collateral cyst (paradental cyst, mandibular infected buccal cyst). These cysts require a source of low virulence and long duration infection, resulting in stimulation of the "epithelial root sheath of Hertwig remnant" (or epithelial remnants of Malassez). Some of these cysts, such as periapical cysts, inflammatory lateral root cyst, depend on endodontic infection, while collateral cysts require periodontal or pericoronary infection. (9, 11)

Pathogenesis of inflammatory cysts:
The formation of a radicular cyst occurs in three phases: 1. The phase of initiation, 2. The phase of cyst formation, and 3. The phase of cyst enlargement (Figure 3). (5) Inflammatory cysts of the jaws are lesions that are produced as a consequence of pulpal necrosis and therefore, are considered to be inflammatory. (2) Dental caries or trauma cause chronic inflammation, which eventually forms a periapical inflammation; continued inflammation stimulates cells of the rests of Malassez (initiation phase), and the epithelial cells undergo necrosis to form the cyst (formation phase), which may be sterile or become secondarily infected, while most are lined by epithelium-derived from rests of Malassez, maybe oral epithelium from a fistula or oral epithelium proliferating down a periodontal pocket which results in cyst formation. (9)

The infection is constituted mainly by anaerobic bacteria in the periapical region, stimulating and activating innate and acquired defense mechanisms, allowing vascular and cellular events to encourage radicular cysts' development. (11) Because epithelial cells derive their nutrients by diffusion from the adjacent connective tissues, progressive growth of an epithelial island moves the innermost cells of that island away from their nutrients. Ultimately these innermost cells undergo ischemic liquefactive necrosis, establishing a central cavity (lumen) surrounded by viable epithelium. At this point, an osmotic gradient is found across the epithelial lining (membrane), separating the connective tissue fluids from the necrotic contents of the newly formed cyst. This osmotic gradient's net effect is a progressive increase in fluid volume within the lumen, tending to expand the cyst by the internal hydraulic pressure generated. (4) So, enlargement of radicular cyst occurs at a relatively slow pace. Various factors influence the rate of expansion. These factors include: mural growth, hydrostatic enlargement, and bone-resorbing factor. (12, 13)

Histogenetic Classification of Odontogenic Cysts

<table>
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<tr>
<th>CYSTS DERIVED FROM RESTS OF MALASSEZ</th>
<th>Dentigerous cyst</th>
<th>Lingual cyst</th>
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<tr>
<td>Periodontal cyst</td>
<td>Dental keratocyst</td>
<td>Gingival cyst</td>
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<tr>
<td>Periapical cyst</td>
<td>Eruptive cyst</td>
<td>Oral keratocyst</td>
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<tr>
<td>Residual cyst</td>
<td>Parakeratogenous cyst</td>
<td>Nasopalatine duct cyst</td>
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Odontogenic cysts of inflammatory origin

| Bacteria | Mitogenic, stimulate the expression of cytokines and chemokines. Inflammatory mediators and pro-inflammatory cytokines released by the host tissue modulate the epidermal growth factor (EGF), causing increased cellular element proliferation. Furthermore, they trigger local fibroblasts into hyperactivity by expressing a keratinocytic growth factor. The epithelial cell rests of Malassez are commonly quiescent/stable cells in the G-0 phase of their cell cycle. These cells require to be exposed to extracellular signals to push them into the cell cycle properly. Extracellular signals are collectively known as Mitogen. Experimentally, a cell can be identified in the proliferative phase by expressing PCNA and Ki-67. Ki-67 marker is present in cells belonging to all stages of cell division except the G-0 phase. Studies reveal increased levels of PCNA and Ki-67 markers in the epithelial lining of radicular cysts. The actual binding of Mitogen to receptors present on the cell membrane surface initiates a series of intracellular reactions pushing the cell into the mitotic phase. (13, 15, 16) Probable growth factors (Mitogen) involved in the pathogenesis of radicular cysts include: (13)

1. EFG & KGF – released by stromal fibroblast
2. TGF-α – released by macrophages and lymphocytes
3. IGF (Insulin-like growth factor) – released by stromal fibroblasts.

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The lateral (radicular) inflammatory cyst is similar to the inflammatory periapical cysts and extends along the root's side portion. As well stems, ordinarily, the epithelial rests of Malassez or a preexisting dental granuloma. The inflammation source can be pulp necrosis extending through a side (lateral accessory canal) foramen. Toxins exit the foramen and infect the tissue of the periodontal ligament. The inflammatory response induces proliferation of epithelial rests of Malassez or the remnants of Hertwig's epithelial sheath and the formation of a cystic lesion. (11)

The collateral cyst seems to originate in the cervical epithelium, the reduced epithelium or epithelial remnants of Malassez. Though its exact origin is not yet understood, it is believed that an inflammatory process, such as periodontitis or pericoronitis, stimulates their development, and observations of scholars suggest that the formation of the enamel projection in the root bifurcation is related to its pathogenesis. (11) Figure 3 Shows diagrams summarize the pathogenesis of inflammatory cysts.

**Radicular cyst**

Radicular cysts are the most frequent form of jaw cysts. They are frequently referred to as dental cysts or periapical cysts, but the term ‘radicular cyst’ is preferred because the cyst arises about a tooth root. They are representing over one half to three-fourths of all oral cysts. A periapical cyst develops at the root apex of an erupted tooth with devitalized pulp (by dental caries or trauma). Occasionally they can also evolve at the openings of large accessory pulp canals on the root lateral aspect of teeth—pulpal inflammation and products of pulpal necrosis exit to form lateral radicular cysts. The recent decline in dental caries incidence has resulted in a corresponding reduction in periapical cysts' incidence. (3, 4, 17, 18).

**Radicular cyst clinical features**

Periapical cysts represent 60% of all odontogenic cysts, and of 7 to 54% of all the cysts in permanent dentition. They are most common in the anterior maxillary area (50% of cases), especially around incisors and canines, and more in females. The reason for this raised prevalence in the maxilla has been attributed to the increased risk of pulp damage to anterior maxillary teeth due to trauma and palatal invaginations. There is no age group with the highest incidence of the inflammatory periapical cyst, but reported cases mostly between the third and fourth decades. It is rare for such cysts to develop in association with deciduous teeth (0.5 to 3.3%). However, cysts associated with deciduous teeth occur more often in the mandible. (11, 19-22).

Because the periapical cyst is associated with a non-vital tooth, the patient may present with previous symptoms of tenderness, pain, swelling, or drainage in the affected area. Many periapical cysts are asymptomatic unless an acute inflammatory exacerbation occurs, being discovered only during current or routine radiographic examination. (20) In the case of acute (exacerbation) inflammation, toothache, swelling (Figure 4), increased tooth mobility, sudden extrusion, and light sensitivity arise due to mobility and displacement of adjacent dental elements. The severity of clinical
manifestations is directly associated with the degree of intensification. The pulp of the tooth of origin by cold, heat, and pulp test is negative, i.e., reveal pulp necrosis. (11)

The bony covering becomes increasingly thin, which may be demonstrated on palpation by the classic ‘eggshell cracking’ as the thin bone gives way. As the lesion expands beyond its bony confines, it then becomes a fluctuant swelling. The cyst's slow expansion usually causes displacement of related structures, such as the mandible's inferior alveolar bundle. Thus, the altered sensaion is not a common feature of mandibular cysts. (19) Even cyst may result in paresthesia due compression to inferior alveolar nerve. (23)

Figure 4 Radicular cyst clinical features: (A) Palatal swelling due to a periapical cyst. (24) (B) No clinical evidence of Periapical cyst.(19) (C) Lateral (radicular) cyst with intraoral swelling in the vestibule.(25).

Radicular cysts radiographic appearance

Periapical lesions are often diagnosed on a clinical and radiological finding. Radiographical differentiation between periapical granuloma and cyst could prove to be rather tricky. The general rule is "if the lesion is large in radiological imaging, then it should be considered a cyst." These cysts enlarge at the expense of the surrounding bony barrier, (13) still, the size of the lesion radiographically does not indicate whether the lesion is cystic in nature or an apical granuloma. (19, 26)

In Plain radiograph and CT, most radicular cysts appear as round- or ovoid-shaped, unilocular, radiolucent lesions in the periapical region, with a radio-opaque margin extending from the lamina dura of the non-vital tooth expanding cysts (Figure 5). Mostly, they are usually less than 1 cm in diameter. Cyst margin may not always be present in the case of infection. The associated tooth commonly has a deep restoration or large carious lesion. Root resorption may be seen. Quite often, more than one radicular cyst may be found in a patient. While MRI is not the first-line imaging modality but periapical cysts appear as a non-enhancing lesion at the tooth's apex. (19, 27-29)

The lateral inflammatory cyst appears as well-defined radiolucency associated with the lateral surface of a badly restored or grossly carious tooth. A corticated margin is continuous with the lamina dura of the root of the affected tooth, and the lamina dura will not be intact. It is associated with pulpal infection and a non-vital tooth (Figure 5). (30).

Figure 5 Radicular cyst radiographical appearance: radiolucency's associated with non-vital teeth in (A, B, C) periapical cysts, (D) lateral inflammatory cyst. (9, 31).

Radicular cyst gross descriptions

Radicular cysts are usually attached to a tooth root, maybe firm, or have a deflated capsule. The lumen can contain thin serous or straw-colored fluid, opaque yellow-white debris, muddy brown fluid from old hemorrhage, or frank purulent debris. Nodules of opaque yellow crystalline material, representing cholesterol, may be seen protruding into the lumen or within the wall. They extend from a few millimeters to several centimeters in diameter, although most measure less than 1.5 cm (Figure 6). (30, 32).

On aspiration, radicular cyst content typically varies from a watery, straw-colored fluid to semi-solid, brownish material of paste like consistency. Cholesterol crystals impart a shimmering (shining gold) appearance. The composition of cyst fluid is complex and variable. It is hypertonic compared with serum and contains: (3, 19, 33)
• Breakdown products of degenerating epithelial and inflammatory cells and connective tissue components.
• Serum proteins; the soluble protein level is 50-110 g/l. Cyst fluid contains higher immunoglobulin levels compared to plasma, probably due to local production by plasma cells in the capsule.
• Water and electrolytes.
• Cholesterol crystals.

Radicular cyst histopathological features

Periapical cyst lined by the stratified squamous epithelium of variable thickness, but when the epithelium is derived from maxillary sinus and thus lined with respiratory epithelium (pseudostratified ciliated columnar epithelium). Rushton hyaline bodies are amorphic, eosinophilic, linear to crescent-shaped bodies, found in the epithelium of 10% of periapical cysts. Its fibrous capsule with varying thickness with chronic inflammatory cells (plasma cells) may be particularly prominent and may have acute inflammatory cell infiltration (Figure 7). (34-36)

Cholesterol clefts may be few or form large mural nodules, in which case they are often associated with epithelial discontinuities and project into the cyst lumen towards the path of least resistance, i.e., into the cyst cavity, as the external surface of the cyst may consist of dense fibrous tissue and bone. They are the probable origin of cholesterol crystals found in the cyst fluid. Mural cholesterol clefts are associated with foreign-body giant cells. As in periapical granulomas, the cholesterol is probably derived from the breakdown of red blood cells due to hemorrhage into the cyst capsule, and deposits of hemosiderin are commonly associated with the clefts. (3, 37)

Dystrophic calcification may be observed in approximately 15% of these lesions. (38) It refers to the precipitation of calcium salts at primary sites of chronic inflammation or dead and dying tissues. It is usually associated with a high local concentration of phosphatase, increased local alkalinity in inactive or devitalized tissues. A chronic, long-standing cyst is a common location of dystrophic calcification. Dystrophic calcifications generally do not induce any signs or symptoms. (39)

Residual cyst

Residual cysts result from incomplete resection of cystic tissue in the periapical zone of a previously extracted pathological tooth. (40) A residual cyst, as the name implies, is a radicular, lateral periodontal, dentigerous, or any other cyst that has persisted after its associated tooth has been lost. (39)

Clinically, residual cysts present with similar characteristics to a radicular cyst. The majority of the residual cysts are asymptomatic. They occur in the alveolar process and body of the jawbones in edentulous areas. Occasionally, it can cause expansion of the affected jaw and pain if a secondary infection is present. The residual cyst is seldom found in children. They are mainly diagnosed between 40- and 60-years aged patients, more commonly in male patients (62.5%), with a male: female ratio of 3:2, and in both jaws, suggesting to be more common in segments of the mandible. It is the third or fourth most frequent cystic lesion in the jaws, representing approximately 10% of all odontogenic cysts. (11, 39, 41)

Radiographically, they appear as a well-defined round, oval, or elliptical unilocular radiolucency but, in contrast to a radicular cyst, there is no evident tooth involvement. They have a distinct sclerotic margin in the edentulous area, which may be thin or thick. Occasionally, in cases of long-standing lesions, calcified masses are seen; their appearances may vary from barely visible, refined grains of radio-opacities to large irregular particles that rarely cross diameter of 0.5 cm (Figure 8). (39) Buccal and/or lingual expansion can occur, with a displacement of the maxillary sinus's floor may happen in some cases. (11) Gross and histopathology of residual cysts are the same as the radicular cyst.

Collateral (inflammatory) cysts

Collateral cysts develop on the lateral, usually buccal, aspect of a partially erupted vital tooth and comprise about 5% of odontogenic cysts. Inflammatory collateral cysts are subdivided into two main types; paradental cysts (60%) are associated with partially erupted lower third molars, and mandibular buccal bifurcation cysts (over 35%) occur in children at the buccal surface of an erupting first molar. Rarely, collateral cysts may evolve from partially erupted teeth or from upper canines and lower premolars. The inflammatory stimulus is, therefore, pericoronitis, but the source of epithelium is uncertain. Craig's (paradental) cysts were first fully described in 1976, who postulated that the lining derived from the reduced enamel epithelium's proliferation. Although this is the most likely source, rest cells of Malassez may be involved, and more recently, an origin from sulcular or junctional epithelium has been demonstrated. (5, 9, 20).
Figure 7 Radicular cyst histopathological features: (A) Diagrammatic picture, (B) Epithelial lining (arrow) and a cholesterol nodule (H&E X100), (C) Acutely inflamed non-keratinized squamous epithelium lining a radicular cyst, (D) The wall of a radicular cyst showing cholesterol clefts (needle-like spaces) and foamy macrophages, (E) Eosinophilic hyaline material (Rushton bodies) within the cyst lining, (F) Abundant hemosiderin (brown) deposition. (G) Multinucleated giant cell associated with cholesterol clefts (H) Ciliated epithelium in a radicular cyst near maxillary sinus. (C to H: H&E X400).

Figure 8 Radiograph of a residual cyst. The lesion is at the site of a previously extracted tooth.

Collateral cysts pathogenesis
The etiopathogenesis is uncertain. They are of an inflammatory origin, associated with pericoronitis. Cyst formation may be exacerbated by a down growth of enamel on the involved tooth's buccal aspect or food impaction. Inflammatory collateral cysts may arise from reduced enamel epithelium, but recent studies suggest an origin from sulcular or junctional epithelium.

Collateral cysts clinical features
It is a rare odontogenic cyst since its prevalence ranges from 1% to 5% of odontogenic inflammatory cysts. Paradental cysts localized at the lower first molar, mainly in age 8 to 9 years, whereas cysts localized to the second molar appeared between 13 and 20 years of age. It is more frequent in men. It occurs near the cervical margin of the lateral surface of the root of partially or fully erupted vital teeth due to an inflammatory process of the periodontal pocket and is usually associated with the buccal and distal of erupted molars, where there is associated with pericoronitis history. The majority of lesions do not exceed 15 mm in diameter.
More than 50% of the reported cases are related to the mandibular 3rd molars, occurring later than those associated with the 1st or 2nd molars and, more rarely, with anterior teeth. It is often painless. In some cases, it has mild signs, and symptoms like discomfort, halitosis, swelling, acute pain, pain during occlusion, delayed eruption, suppuration, and trismus may be present. The pain may be related to pericoronitis only (semi-enclosed bone). Usually, it does not cause bone expansion. Absence of bone expansion and not being palpable lesion, its consistency cannot be perceived. The tooth-related paradental cyst has pulp vitality. If the tooth is non-vital, the possibility is more for a lateral radicular (infective) cyst. (11, 42)

Collateral cysts radiological appearance

According to the radiographic analysis, the paradental cyst can vary, depending on the overlap of anatomical structures, presence of infection, size, and lesion location. Usually, the lesion's image is well-defined radiolucent, cortical, and usually located laterally (common distal), limited by a thin radiopaque line and associated with a partially erupted mandibular third molar (Figure 9).(11) The cyst has a "semi-lunar, ellipsoid, or crescent shape" and does not purpose for bone expansion. Paradental cysts were found in the root bifurcation region at the limit of the buccal cemento-enamel junction. In the buccal location, the cysts from the paradental portion show radiolucency, extending above the face of the root of the molar with a thin radiopaque line.(11) The radiolucency sometimes extends apically, but an intact periodontal ligament space provided the evidence that the lesion did not originate at the apex.(30) This circular shape is associated with the lateral roots and periapical region, making diagnosis difficult. In cysts located in the distal and rarely on the mesial aspect, the radiolucent acquires a lunate shape, being outlined by a radiopaque line on the edge toward the bone.(11) Periosteal reaction common. Onion skin deposition of bone appears as parallel opaque layers on buccal aspect is not visible unless by occlusal radiograph, while distal aspect shows well-circumscribed radiolucency.(43) The presence of the 'Colgan's sign,' which is the preservation of the distal follicular space in the radiograph, is a useful diagnostic feature to distinguish a paradental cyst from the dentigerous cyst.(42).

Figure 9 Paradental cyst radiographical appearance: Expansion of the vestibular cortical bone (onion skin appearance).(43) (B) Bilateral paradental cysts associated with erupting mandibular third molar teeth. The cysts are distal and buccal to the involved teeth.(9).

Collateral cyst gross descriptions

The cyst is adjacent to the root of an impacted or partially impacted tooth. It is open towards the coronal aspect and is in continuity with the reduced enamel epithelium and the pericoronal pocket (Figure 10).(9)
without any evidence of carcinomatous transformation. However, there is no evidence that cyst epithelium is at particular risk, and there is, therefore, no justification for cysts as precancerous lesions. (9).

Summary and conclusions:
The role of general dental practitioners and pediatric dentists in detecting pathological lesions that may develop asymptotically for a long time should be emphasized, as early detection of the lesion allows the use of less radical methods of treatment. For this purpose, periodic radiographic images should be taken. An accurate diagnosis allows the use of less radical methods of treatment. For this purpose, detecting pathological lesions that may develop asymptomatically for a long time should be emphasized, as early detection of the lesion allows the use of less radical methods of treatment. For this purpose, periodic radiographic images should be taken. An accurate diagnosis allows the use of less radical methods of treatment.

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