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Review

Cysts and Pseudocysts of the Oral Cavity: Revision of the Literature and a New Proposed Classification

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Abstract. *This article includes a comprehensive and up-to-date review on the cysts of the oral cavity. Several classifications of odontogenic (OC) and non-odontogenic (non-OC) oral cysts and the surrounding regions have been proposed. We suggest a new critical classification based on an established relationship between anatomical area, histological origin and clinical behavior (frequency, rate of recurrence, malignant potential). Moreover, the differential cytokeratin (CKs) expression of the various cysts is reported as epithelium-specific markers of differential diagnosis. Finally, issues related to differential diagnosis and therapeutic approaches of the cysts included in the two groups are described.*

Oral cysts (1-8) are divided into two major groups based on odontogenesis: odontogenic cysts (OCs) and non-odontogenic cysts (non-OCs). The first group is characterized by specific odontogenic markers, histological similarities with odontogenic structures and anatomical considerations (9).

The second group (1, 3) includes cysts that originate from specific areas or organs of the oral cavity such as salivary cysts, naso-palatine duct/mid-palatine cysts and nasolabial cysts. In this group are included also some cysts, that are ubiquitous in the body, such as dermoid cysts, lympho-epithelial cysts, and aneurysmal bone cysts.

OCs arise from the tooth-producing tissues; alternatively, they originate from the remnants of dental lamina epithelium entrapped within the gingival named epithelial rests of “Serres” (8-10), or the epithelial remains of the "Malassez" (2, 10-12). These cellular remnants fall within the concept of the post-functional state of the dental lamina, which has limited growth potential. These two types of embryological residues can generate two different types of dental cysts (5, 13). From the remnants of Serres takes origin the periodontal cyst, and the orthokeratocyst, that is a more aggressive type of cyst with a neoplastic variant5. From the residues of Malassez originates the inflammatory radicular cyst (9). For this last type of cyst, an infectious and/or inflammatory stimulus acting on a genetic predisposition has been proposed as the first pathogenic event causing the proliferation of cellular odontogenic remnants (11-14).

Cytokeratins (CKs) are epithelium-specific markers of differentiation and have been proposed as ideal markers for differential diagnosis of these cysts, being involved in physiological odontogenesis (14-23). In detail, CKs 5 and 14 are expressed in the basal cell layer of both the keratinized and non-keratinized epithelia, with a reduction in the upper layers; CKs 1 and 10 are specific to the spinous layer; CK 19 is present in the basal stratum of the non-keratinized epithelia; CKs 4 and 13 are specific for supra-basal cells of the tongue epithelium; K2p is present in the supra-basal epithelial cells of the hard palate and gingiva. During odontogenesis CKs have a peculiar pattern of expression: CK7 is expressed in the “stellatum reticulum” at the early bell stages along with CK14; these two CKs, together with CK 19, are also expressed in the cells of the enamel epithelium;

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Table I. *Cysts and pseudocysts of the oral cavity.*

1) CYSTS AND PSEUDOCYSTS OF ORAL BONE TISSUE AND PERIODONTAL
a) Odontogenic cysts
- "Inflammatory origin"
  Radicular-necrotic cyst
  Collateral inflammatory cyst (Paradental cyst, Juvenile paradental cyst)
- "Development origin" DC (dentigerous cysts): follicular, germinal, eruptive cysts
- Periodontal tissue (parodontal cysts)/BOC
- Gingival cysts of infants (newborn gingival cysts, dental lamina cysts, Bohn's nodules)

b) Non-odontogenic cysts
- Mid-palatal-raphe non-odontogenic cysts of infants (Epstein's pearls)
- Nasopalatine duct/midline palatine cyst

c) Cysts of so-called "Globulo-maxillary area"
d) Cysts with malignant variants and misdiagnosis
OOC (orthokeratinized odontogenic cyst)
COC (calcifying odontogenic cyst)
Glandular cysts (GOC: glandular odontogenic cyst; sialo-odontogenic cyst)
e) Cysts and pseudocysts of the maxillary sinus
f) Pseudocysts of the bone basis of the oral cavity: SBP (Solitary bone pseudo-cysts); ABP (aneurysmal bone cysts)

2) SOFT TISSUE NON-ODONTOGENIC CYSTS
- Cysts related to the lymphatic tissue (cystic hygroma; lymphoepithelial cysts), thyroglossal duct cyst
- Salivary cysts and pseudo-cysts
- Nasolabial cyst (synonyms: nasoalveolar cyst, Klestadt's cyst)
- DEC (dermoid and epidermoid congenital cysts)

CK14 is present at early "bell stage" and replaced by CK19 in differentiated ameloblasts; CKs 7 and 13 are found in the "rests of Serres" (16-18). It has been reported that the structure of CKs, as well as, their expression within the cells may be altered depending on environmental conditions (*e.g.* inflammation) (15, 19-21) and on changes in cellular function. Therefore, the detection of an altered expression is useful for the differential diagnosis of various diseases such as cysts and tumors. Indeed, CKs 5 and 6 are present in all layers of the odontogenic cysts, CK13 is expressed in the supra-basal cell layer of all odontogenic cysts, while CK20 is negative in all odontogenic cysts (18).

In this article, we propose a new classification for the cysts of the oral cavity. Briefly, we divide the different types of cysts in two major groups: 1) Cysts of oral bone tissue and periodontal, and 2) Soft tissue non-odontogenic cysts. Each group is, then, composed of different sub-groups, based on the established relationship with anatomical area, histological origin and clinical behavior (frequency, rate of recurrence, malignant potential). Table I depicts this classification with all the sub-groups. Following is a comprehensive description and discussion on this classification.

Cysts and Pseudocysts of Oral Bone Tissue and Periodontal

a) Odontogenic cysts of "inflammatory origin". Radicular-necrotic cyst. The most common cyst of the oral cavity is due to the loss of the biological barrier (the pulp of the tooth) that follows from carious lesions or dental trauma (6, 13, 14) with pulp necrosis and derives from the cellular remnants of the "Malassez". They can lead to the formation of an inflammatory radicular-necrotic cyst (RC), that can be periapical or peri-radicular. First event is the formation of a granuloma, that subsequently gives rise to a cyst, whose epithelium expresses a specific odontogenic CK such as 19 in the superficial cell layers (24-26) and co-expresses CK5 in the cyst lining (18). A peculiar variant of RC is considered the Residual Radicular Cysts that develop from apical granulomas or residual fragments of RC (5, 6).

Collateral inflammatory cyst (Paradental cyst, Juvenile paradental cyst). These cysts have overlapping histological features with RCs and their etiology is also considered inflammatory or meta-traumatic (3-5, 27). The inflammatory collateral cyst is located on the lateral side of a vital tooth and is the result of an inflammatory chronic process in the periodontal pocket (24-26). The juvenile paradental cyst of the lower molars (first-second) is located in the root area of the affected teeth of a young patient or distally to a lower wisdom tooth in adults (with appearance of pericoronitis) (27-29). These lesions are considered the same entity, regardless of localization (30). The histological features of these cysts are indistinguishable from those of the inflammatory RCs and this appearance emphasizes the origin from the remains of the Mallasez (14, 30-33).

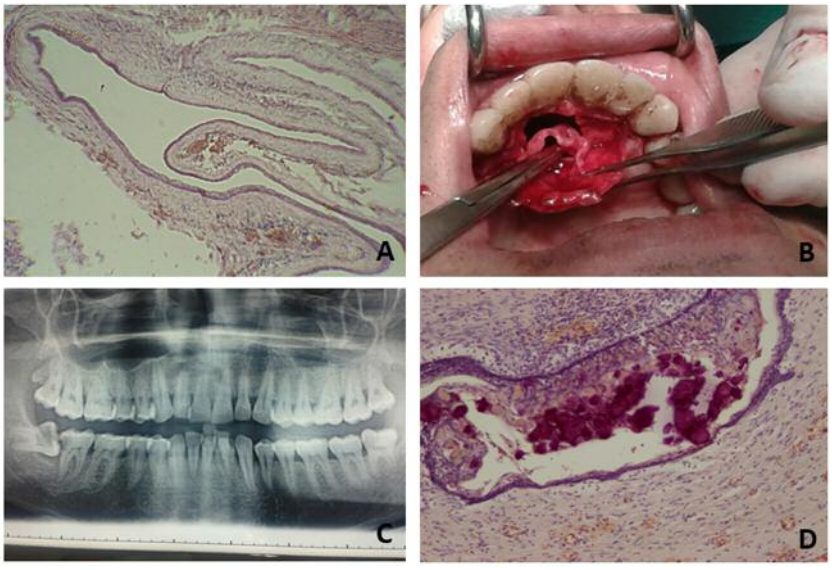

Figure 1. *Examples of different cysts of the oral cavity. A: Dentigerous cyst-Follicular cyst: cystic lumen is lining by stratified squamous epithelium B: Nasopalatine duct cyst: an intraoperative phase is depicted. C: Cyst of the globule-maxillary area (arrow): characteristic imaging that not presents always the same histological features at microscopic observations. D: Calcifying Odontogenic Cyst: histological feature of ghost cells identified as deep blue-purple areas.*

It is important to differentiate these cysts from other radiolucent jaw lesions, such as unicystic ameloblastoma, keratocystic odontogenic tumor (KCOT), dentigerous cysts (DC), LPC. CKs expression can aid to make a differential diagnosis through a combination of immunohistochemical markers such as CK10, CK13, CK17, perlecan, PCNA and UEA, to discriminate between RC and the other pathological conditions (31-33).

b) Odontogenic cysts of "development origin". Dentigerous cysts (DC). These cysts surround the crown of a tooth that has not migrated into the oral cavity and are named follicular, germinal, or eruptive cysts (Figure 1A) (7). The "primary event" is an accumulation of pathological fluid in the layer of the reduced enamel epithelium or between it and the crown of an un-erupted tooth. In this type of cysts, CK 5, 6, 19 are expressed, while CK7 is absent (18).

Periodontal tissue (parodontal cysts; Botryoid cyst). Because they are of dental origin and the periodontal tissue is contiguous to the teeth and bone, they form a single nosological-group, such as "cysts of the periodontal tissues". The "cyst of the newborn" is its particular form discussed separately later. The cysts which affect the periodontal tissue are gingival cysts (frequently of the adults) (34) and periodontal cysts (lateral parodontal cyst: LPC; its variant: botryoid cyst) (4, 31, 34-37) are unicystic (with differential diagnosis *versus* ameloblastoma cystic and "essential bone defects") (36). There are two or three layers of flattened cells mimicking a squamous epithelium; with a careful search, it is possible to find areas of nodular type thickening and clear cells rich in glycogen (13). The LPC may have a variant, multilocular, defined as "botryoid cyst". It can arise either from the remnants of Serres incorporated into the periodontal tissue, or, on the basis of an alternative hypothesis, from the reduced enamel epithelium of the follicle which expands to occupy a space in the periodontal ligament during the eruptive phase producing a parodontal cyst (38), while a portion of this may remain in the gum after the eruption forming a gingival cyst (39-42). LPCs are positive for CK13 and CK17 in the surface layers and perlecan and Ulex European Agglutinin (UEA) on the cell border of the whole layer, negative for CK10 (26). These cysts are made in relation to "remains of Malassez", causing confusion: ERM expresses CK19 and periapical granuloma is positive for CK 4/13, while RC are positive for CK13 and 19 (8, 18, 24, 25, 29).

Botryoid odontogenic cyst (BOC). BOC is a rare pathological multilocular cyst (43, 44) with or without proximity to a root of tooth, considered a variant of the LPC (44-46), derived from more groups of converging cellular debris of Serres. However, because of the presence of mucous cells and of the columnar cells (metaplastic type) (16, 20, 45-47), it has been also considered to represent a variant of glandular odontogenic cyst (GOC) (3). CK 18, 13, specific for "rests of Serres", show the origin from the odontogenic tissues (16,

37, 48). Differential diagnosis to ameloblastoma can be made by CD56 and calreatin which are negative in BOC (45).

Gingival cysts of infants (newborn gingival cysts, dental lamina cysts, Bohn's nodules). They are present in newborns with developmental origin from the remains of the dental lamina (4, 49-52). The epithelium lining is squamous with areas of parakeratosis, keratin fills the cavity (53).

c) Non-odontogenic cysts. Mid-palatal-raphe non-odontogenic cysts of infants (Epstein's pearls). These lesions present similar histological/ clinical features to gingival cysts (50, 54-56). Mid-palatal-raphe cysts arise from non-odontogenic epithelial remnants (52) after median palatal fusion.

Nasopalatine duct/ midline palatine cysts. The nasopalatine duct (NPD; Figure 1B) (54-57) represents the connection between the vomero-nasal organ and the nasal and oral cavities in many mammals, thus connecting the olfactory and the taste functions. Epithelial cells, organized in clusters or cords, may be present in the incisive canal of the maxilla. Unknown causes could stimulate the proliferation of these epithelial remnants, causing the formation of a cyst with a squamous or, more rarely, cylindrical and ciliated epithelium layer.

d) Cysts of the so-called "globulomaxillary area"
The cysts in this anatomical area (Figure 1C) frequently constitute a diagnostic and clinical problem (58). Globule-maxillary cysts were included in a group of cysts arising from an altered development, defined as "fissural cysts", but this pathogenesis is not accepted any more (59-64). These cysts display constant radiological and clinical features (58, 62-64), however they do not present always the same histological features: stratified squamous (odontogenic), parakeratinic (ortokeratocystic) or cylindrical respiratory (non-odontogenic) epithelium has been described in these cysts (65, 66). Indeed, in this group of cysts, we can include intraosseous cysts that develop between the roots of the lateral incisor and the canine teeth, causing their divergence (so-called globule-maxillary properly). Furthermore, cysts originating from the respiratory epithelium remained trapped in the globule-maxillary site and parodontal cyst. It is important to underline the fact that in this site it is possible to find also neoplastic cysts (67, 68).

e) Cysts with malignant variants and misdiagnosis. Some oral cysts present neoplastic variants (3). In our opinion, it seems more useful to consider in the classification a specific group of cysts designed as "cysts with tumor variants and possible misdiagnosis", such as the calcifying odontogenic cysts (69-71), the orthokeratinized odontogenic cyst (72-75), and the glandular odontogenic cyst (71, 72).

Orthokeratinized odontogenic cyst (OOC). OOC, is a cyst characterized by keratinized lining epithelium. When the epithelium displays significant parakeratosis or orthokeratosis, the term keratocystic odontogenic tumor (KCOT) is preferred, because this cyst is clinically more aggressive with a tendency to recur (74-76). Interestingly, these two cysts show a different pattern of expression for CKs: OOC expresses CK 1, 2, 10, and loricrin, while KCOT expresses CK 4, 10, 13, 16 and 17, and 19, similarly to the dental lamina (18-23, 50, 75-79). Very importantly, from the clinical point of view, is the possibility to distinguish these cysts from ameloblastoma, taking advantage from the differential immunohistochemical expression of CD-56, CD-105 and calreatin (36, 71, 74).

Calcifying Odontogenic Cyst (COC). We can distinguish three entities: simple intra-osseous COC, extra-osseous peripheral COC and the malignant form Calcifying Cystic Odontogenic Tumor (CCOT) (21, 23, 70-72, 79-81). COCs radiologically show a cystic imaging with small scattered areas of calcification, often resembling an odontoma (82). COCs (Figure 1D) have a peculiar histological pattern with an epithelial lining with a basal layer of columnar cells and an overlying epithelium, thick and vacuolated. Moreover, groups of eosinophilic cells with not stainable cellular structures are visible in the epithelial lining or in the connective tissue capsule or in both. These cells are named "ghost cells" and are considered dystrophic cells with aberrant keratinization or apoptotic cells with intracellular calcification (82-85). Ghost cells are present in different pathological entities, such as craniopharyngioma, odontoma, pilomatrixoma, ameloblastic fibroma and some visceral tumors (71). They accumulate some substances during the differentiation process, losing the cytoskeletal components and becoming CK10/13 negative (18). CKs 10/13 are, on the contrary, present in the upper layer of the cyst and CK14 is expressed in the basal layer. P63 expression seems evident in all layers of COC examined (85).

Glandular cysts (Glandular odontogenic cyst: GOC; sialo-odontogenic cyst). GOC present epithelial cells arranged in glandular structures, with groups of acidophilic cuboidal or columnar cells, sometimes with papillary growth and projections into the cyst-like spaces (86-93). These cysts are in differential diagnosis with the central mucoepidermoid carcinoma (90). This differential diagnosis is based on the diverse immunohistochemical expression of MASPIN (mammary serine protease inhibitor) and of the tumor-markers Ki67 and p63 (88-93). The location within the bone or in the soft tissue has an important role in determining the more appropriate surgical protocol (87, 91, 93).

f) Cysts and pseudocysts of the maxillary sinus. We think that it is important to report in this classification also cysts and

pseudo-cysts primitive of this anatomical region (94-103). The primary cysts of the maxillary sinus are of three types: a) true cysts, due to an occlusion of the excretory ducts of the sinus mucous glands; b) mucoceles, formed from the non-external drainage of normal mucous; c) secondary mucoceles, that result from post radical sinus surgery, probably due to residues of sinus mucosa forming a new mucocele in a closed compartment. The pseudocysts are formed between the inner surface of the bone wall and the connective tissue layer, the sinus mucosa remaining on the outside. Their etiology remains unknown, although allergies, inflammation of the maxillary sinus, and mucosal odontogenic inflammation have been considered (94, 99). Sometimes, the secondary odontogenic cysts (mostly follicular and radicular-necrotic), can develop in the bone base of the upper jaw and invade the maxillary sinus. These cysts are named "intrusive sinus oral cysts".

g) Pseudocysts of the bone basis of the oral cavity (Solitary bone pseudo-cysts: SBP; aneurysmal bone cysts: ABP). SBPs are devoid of any epithelium lining and are considered of traumatic origin (36, 104). They are also known as bone pseudo-cysts or bone traumatic pseudo-cysts. ABPs are blood-filled sinusoidal or cavernous spaces without cystic epithelium (105, 106). The pathogenesis of these cysts is very similar to that of SBPs: a trauma can cause a bone hemorrhage and the clot may not be re-canalized leaving a cavity devoid of content (bone pseudo-cyst) or may present continuous micro-hemorrhages that may lead to the local reaction of macrophages (giant cell granuloma), or a vascular dilatation. Recently ABPs have been related to a ubiquitous protease USP-6 mapped on cromosoma16q22, that may be used as a diagnostic tool (107).

Soft Tissue Non-Odontogenic Cysts

In this group we consider: cysts related to the lymphatic tissue (cystic hygroma and lymphoepithelial cysts), and thyroglossal duct cyst (108-110).

Salivary cysts and pseudo-cysts. They should be referred to as salivary duct cysts and pseudo-cysts (111, 112). These cysts may be surrounded by salivary tissue and, thus, considered as retention cysts with an epithelial lining composed of one or two layers of flat or cuboidal epithelial cells. Alternatively, they may represent an extra-vasation of mucous in the peri-glandular connective tissue and, thus, considered pseudo-cysts by a rupture of the salivary duct with a partial epithelial lining, or mucous extra-vasation cysts.

The salivary retention cyst should be considered as a pseudo-cyst but this condition is the evolution of a process that begins with the formation of a retention cyst, and therefore it is considered as a "primary cause" of the salivary accumulation. Histologically, it may present oncocyte-like cells, a pseudo-stratified columnar epithelium or a stratified squamous epithelium. Ranula represents a mucocele of the floor of the mouth due to salivary accumulation in sublingual or submaxillary followed by its rupture and extravasation of saliva in the surrounding connective tissue. Since this happens frequently and prematurely, most of the ranulas do not have epithelial coatings. Ranulas can be located above the mylohyoid muscle (the simple type) or can grow downwards assuming an" hourglass shape" (the complex type or pluningranula) (110-112).

Nasolabial cyst (synonyms: naso-alveolar cyst, Klestadt's cyst). The concept that it is a fissural cyst, because it is related to the globule-maxillary cyst as its peripheral form is no longer valid, because there is no evidence of epithelial interruption of the interactions of his three embryological processes (56, 113-116). Histologically it consists of a cyst lined by a bi-layered epithelium with a cuboidal basal layer, sometimes pseudo-stratified, with goblet cells and areas of squamous metaplasia. CKs 5 and 6 are expressed in the basal layer cells, while CKs 7 and 19 are positive in all layers. The mucin in the goblet cells is MUC-2 and MUC-5AC positive similarly to the human lacrimal organs (113, 116). It is possible to speculate that it is a developmental non-odontogenic cyst of the soft tissue originating from the lower portion of the naso-lacrimal duct (116).

Dermoid and epidermoid congenital cysts (DEC). They (CK10 positive) derive from embryonic pluripotential cells trapped during the early weeks of intrauterine life; they, subsequently, develop into one or into all three ectoderm, mesoderm and endoderm tissues. The term "dermoid cyst" often refers to all types of these lesions (117-119). DEC are ubiquitous in the human body in sites where the embryonic parts fuse together. In the oral cavity they are classified as non-odontogenic cystic lesions of the soft tissue of the midline sites: the floor of the mouth (sublingual or submental), the tongue, cheek, parotid gland, mandibula (30, 112, 118).

Conclusion

A precise classification of cysts will always be subject to continuous revisions based on continuous scientific updates, however, it should be essentially based on the histological and clinical features of these diseases. The proposed classification takes into account the site of the primary growth, the histological origin, the frequency, the recurrences, and the potential malignancy, so drawing attention to those cysts that may present uncertainty concerning their immediate diagnosis. The use of new technologies such as the confocal laser microscope and new acquisitions on biology and genetic alterations in odontogenic lesions (120, 121) will be able to

add new data to the classification of the individual types of cysts. It is plausible to assume that in the future it will be possible to compile specific modules for each type of dental cysts with its peculiar structural and molecular features. This will allow a quick and very efficient comparison between the different types of cysts with a fast and safe diagnosis also *versus* tumors of the oral cavity.

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