Scripta Scientifica Medicinae Dentalis, 2023;9(2):11-19
DOI: 10.14748/ssmd.v9i2.9089

ISSN 2367-7236 (Print)
ISSN 2367-7244 (Online)

REVIEWS

GLANDULAR ODONTOGENIC CYST—A REVIEW OF CHARACTERISTIC FEATURES, TREATMENT, AND RECURRENCE

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ABSTRACT

INTRODUCTION: The glandular odontogenic cyst is classified as a developmental epithelial odontogenic cyst and defined as "arising in the tooth-bearing areas of the jaws and characterized by an epithelial lining with cuboidal or columnar cells both at the surface and lining crypts or cyst-like spaces within the thickness of the epithelium".

AIM: This review outlines the epidemiology, clinical and radiological presentation, histological characteristics, additional markers aiding in the correct diagnosis, treatment modalities, and recurrence rates of glandular odontogenic cysts.

MATERIALS AND METHODS: For the purpose of this review, literature reviews and case reports with included literature reviews from the Scopus, PubMed, and ScienceDirect databases were used. The bibliography of the selected articles was additionally analyzed.

RESULTS: The glandular odontogenic cyst is a relatively rare entity, clinically and radiographically nonspecific. It is often misdiagnosed because of its overlapping histopathological features with other odontogenic cysts such as lateral periodontal or botryoid cyst, dentigerous and radicular cysts with mucous metaplasia, and central mucoepidermoid carcinoma. Regarding the treatment, both conservative and radical methods may be applied. These cysts have a high propensity for recurrence and display an aggressive behavior.

CONCLUSION: Clinically and radiographically glandular odontogenic cysts can resemble several other lesions of the jaws, which denotes the importance of a precise histopathological diagnosis. The choice of treatment should be based on the degree of aggressive behavior of the cyst. Meticulous examination, appropriate treatment planning, and sufficient follow-up periods are key to a successful outcome.

Keywords: *glandular odontogenic cyst, odontogenic cyst*

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Received: August 2, 2023
Accepted: September 17, 2023

INTRODUCTION

The glandular odontogenic cyst (GOC) was initially described by Padayachee and Van Wyk (1) in 1987 as *sialo-odontogenic* as the authors assumed its origin to be sialogenic. The following year Gardner et al. (2) observed 8 similar cases, which led to the suggestion that the lesion would be called *glandular odontogenic cyst* due to its histological characteristics. In 1992, the World Health Organization (3)

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classified it as a developmental epithelial odontogenic cyst and gave its definition as follows: "arising in the tooth-bearing areas of the jaws and characterized by an epithelial lining with cuboidal or columnar cells both at the surface and lining crypts or cyst-like spaces within the thickness of the epithelium". This lesion poses a diagnostic challenge due to its overlapping features with other entities, among which are botryoid odontogenic cysts, radicular or dentigerous cysts with mucous metaplasia, and especially low-grade central mucoepidermoid carcinoma (4).

AIM

The purpose of this review is to outline the epidemiology, clinical and radiological presentation, histological characteristics, additional markers aiding in the correct diagnosis, treatment modalities and recurrence rates of glandular odontogenic cysts.

MATERIALS AND METHODS

For the purpose of this review article, literature reviews and case reports with included literature reviews from the Scopus, PubMed, and ScienceDirect databases were used. The bibliography of the selected articles was additionally analyzed.

RESULTS

1. Epidemiology

The glandular odontogenic cyst is considered to be an infrequent entity, with a prevalence of 0.012% (5) to 1.3% (6) among jaw cysts. It usually presents in the 5th decade of life. In accordance with Robinson et al. (7) the average age of presentation was 46 years and lesions of the upper jaw occurred at a younger age. Fowler et al. (8) found that the average age at which the cyst was diagnosed was 51 years (ranging from 20 to 82), although Faisal et al. (9) described a histologically confirmed GOC case in an 11-year-old patient. In a systematic review (10), MacDonald-Jankowski compared the features of GOCs among 4 global groups (Western, sub-Saharan African, Latin American, and East Asian) and found differences in the age of first presentation—44 years in the Western group and nearly a decade younger in the East Asian and sub-Saharan African. The cyst seems to be slightly more prevalent in men than women with a ratio of 1.15:1 (11) to 1.50:1 (12).

2. Clinical and radiological features

Different authors have established a predilection for mandibular localization (approximately 3:1 mandible to maxilla ratio), particularly in the anterior region (7–9,11–14). In 3 cases by Noffke and Raubenheimer where the maxilla was involved, the globulomaxillary region tended to be affected (15).

Although the lesion typically occurs as a painless swelling, it can sometimes be symptomatic, causing pain, discomfort or paresthesia, as described by Manor et al. (16). Pain and paresthesia were recorded in 24.3% of cases analyzed by Chrcanovic and Gomez (11). In one of their 5 cases, Anchlia et al. (4) presented a patient with all of the symptoms mentioned above and who also reported a history of traumatic injuries in the affected area fifteen years prior.

According to MacDonald-Jankowski's review (10), tooth displacement was seen in 50% of the cases and association with unerupted teeth—in only 11% of cases. Fowler et al. (8) analyzed 46 cases and 8 of them were associated with unerupted teeth, which surprised the authors because only 6 had previously been reported in the literature (12,17–20). More et al. (21) published a case of a glandular odontogenic cyst in a 21-year-old male in association with an impacted 3rd molar, which was first diagnosed as a follicular cyst. Ferreira et al. (22) also presented a case of the aforementioned cyst in a dentigerous relationship—a lesion associated with an impacted third molar. The authors found 22 similar cases previously described in the literature. One of them, reported by Ide et al. (17), was an atypical case of the lesion appearing as a follicular cyst that contained hyaline bodies in its epithelial lining. The lesion was associated with a horizontally impacted mandibular canine. After enucleation, the pathological diagnosis was GOC. In addition to glandular structures, a focal area of hyaline bodies was seen. According to the authors, the presence of hyaline bodies, exclusively seen in odontogenic lesions, affirms the origin of the cyst.

Localization in edentulous or partially edentulous areas has also been described in 7 cases (14).

The radiological manifestation of glandular odontogenic cysts has been various and is not pathognomonic (23).

In 2003, Manor et al. (16) published a review of the literature regarding the radiographic attributes of GOCs. Most cases were studied with panoramic or periapical projections. Computed tomography (CT) was performed in 5 cases. The lesions were either unilocular (52%) or multilocular (48%), and well-defined in 94.5% of the cases. On average the dimensions of the unilocular lesions were 3.9 cm x 2.8 cm, and of the multilocular—6.3 cm x 3.0 cm. The cortical plate was expanded in 33 (87%) of the 38 lesions for which such data was present. In the 24 cases where the integrity of the cortical plate was studied, 50% showed perforation. Resorption of the dental roots was described in 22% of cases and displacement of teeth—in 24.4%. These findings point to the aggressive behavior of GOCs.

Chrcanovic and Gomez (11) did an extensive analysis of 169 GOC cases. Their findings included 73% bone expansion, 26% cortical bone perforation, 31% associated with tooth displacement or unerupted teeth, and 14% root resorption. Unilocular appearance was recorded in 61.5% of the cases, slightly more prevalent than the multilocular variant.

According to Robinson et al. (7) in their review of 92 cases, the majority of cysts presented as unilocular (53%) and uniformly radiolucent (97%), with well-defined borders (93%). Scalloping between the dental roots was seen in 36% of the x-rays. Expansion of the cortical bone (62%), as well as loss of integrity of the latter (71%), and infiltration of the maxillary sinus (67%) and nasal cavity (72%) were often seen. In the mandible, 40% of glandular cysts showed displacement of the mandibular canal.

Noffke and Raubenheimer (15) presented 9 cases of GOCs, 2 of which were multilocular. Both were seen in the mandible and they measured 16.5 cm and 9 cm horizontally, which led the authors to believe that there could be a correlation between size and mutilocularity.

Silva et al. (24) described a case of an initially unilocular lesion, which upon recurrence presented with a multilocular radiological appearance. This was also noted by Robinson et al. – three of their reviewed lesions displayed progression of unilocular to multilocular radiolucencies.

When appearing in the anterior region as a multilocular expansile lesion, radiographically, the cyst resembles both the central giant cell carcinoma and the solid type of ameloblastoma (10). When located in the posterior mandible, the GOC must also be differentiated from an odontogenic keratocyst (23). Other differential diagnoses include odontogenic myxomas and simple bone cysts (24).

3. Histopathology

In 2005, Kaplan et al. (25) reviewed 29 articles from 1987 to 2004 regarding the histopathological characteristics of GOCs. Based on their results and literature review, the authors proposed major and minor histological criteria and indicated that all major ones must be present in order to establish a definite diagnosis of GOC (Fig. 1).

Fowler et al. (8) disagreed with Kaplan and his team's statement that all major criteria should be evident for diagnosing the lesion as GOC. According to them, a combination of particular microscopic features, which do not essentially correlate with the pro-

Major criteria	Minor criteria
1. Squamous epithelial lining, flat interface. 2. Variations in thickness of the lining with or without epithelial ''spheres'' or ''whorls'' or focal luminal proliferation; no palisades. 3. Cuboidal eosinophilic cells or ''hob-nail'' cells, present on the surface of the cyst lining. 4. Mucous (goblet) cells with intraepithelial mucous pools with or without crypts lined by mucous-producing cells. 5. Intraepithelial glandular microcystic or duct-like structures.	1. Papillary proliferation ("tufting" into the cyst lumen). 2. Ciliated cells. 3. Multicystic or multiluminal architecture. 4. Clear or vacuolated cells in basal or spinous layer.

Fig. 1. Major and minor histologic criteria for diagnosing GOC, proposed by Kaplan et al. (2005).

posed criteria, is necessary to reliably diagnose a lesion as GOC. The authors also included a 10th criterion, *apocrine snouting of hobnail cells*, and stated that a lesion presenting with 7 or more parameters fits the description of GOC; if they are less than 5 the entity is likely to be non-GOC.

According to the authors, eosinophilic cuboidal (hobnail) cells, as well as mucous cells, are observed in both glandular cysts and non-GOCs, such as metaplastic, botryoid odontogenic, radicular and surgical ciliated cysts. A difficult differential diagnosis of GOC is a follicular cyst displaying metaplasia. The appearance of microcysts, epithelial spheres, clear cells, variable thickness of the cyst lining, and multiple compartments can be useful in differentiating glandular cysts from their mimickers. Multiple compartments and clear cells are considered important in combination with the presence of microcysts, whereas epithelial spheres are independent of the microcysts. This differentiation is helpful when GOCs histologically resemble dentigerous cysts with metaplastic changes.

Regarding the histological differentiation between GOCs and low-grade mucoepidermoid carcinoma (LGMEC), the authors concluded that LGMECs do not typically include hobnail cells, epithelial spheres, ciliated cells, and intraepithelial microcysts.

According to Noffke and Raubenheimer (15), the cystic cavities of both lesions are lined with squamous, cylindrical, and cuboidal epithelium, and contain cells that produce mucus, arranged in papillary folds. Also seen are gland-like structures or crypts that contain mucus. Unlike LGMEC, epithelial plaques are sometimes present in the GOC, similar to those seen in lateral periodontal cysts. Because of the many similarities, the authors conclude that GOCs and LGMECs could represent a spectrum of the same lesion. This finding is supported by Waldron and Koh (26), who acknowledge the possibility of previous GOC cases being misdiagnosed as LGMEC.

4. Immunohistochemistry

Kaplan et al. (25) investigated the use of immunohistochemical markers such as p53, Ki67 and proliferating cell nuclear antigen (PCNA) in order to identify GOC and compared their expression in GOCs, LGMECs and radicular cysts with mucous metaplasia (RCM). P53 was increased in GOCs and LGMECs compared to radicular cysts, while Ki67 was higher in GOCs and RCM.

Pires et al. (27) compared the cytokeratin (CK) expression in salivary gland mucoepidermoid carcinoma and odontogenic cysts and tumors. They studied 85 lesions, among which 6 central mucoepidermoid carcinomas, 23 salivary gland mucoepidermoid carcinomas (MECs), 10 glandular odontogenic cysts, 34 odontogenic cysts, and 12 ameloblastomas. Eleven monoclonal anti-CK antibodies were used for the immunohistochemical analysis. Cytokeratin profiles of central MEC (CMEC) and MEC of salivary origin were similar. Those of GOCs showed overlapping with odontogenic lesions, as well as with MECs. The authors found higher levels of CK18 in CMECs and CK19 in GOCs, concluding that these findings could aid in the differential diagnosis.

Mammary serine protease inhibitor (MASPIN), which has been shown to have tumor suppressor qualities, is found in many glandular and epithelial benign and malignant lesions. Vered et al. (28) compared its levels in low-grade mucoepidermoid carcinoma (LGMEC), GOC, and odontogenic cysts with mucous metaplasia and discovered they were higher in the epithelial mucous cells in LGMEC than in the other two groups. They concluded that the carcinoma and the glandular cyst could not be conclusively differentiated, but the more frequent immunopositivity of epithelial mucous cells is suggestive of LGMEC.

Montague et al. (29) compared the bcl-2 expression in GOCs and non-GOCs with similar attributes. The studied cases diagnosed as GOC were strongly bcl-2 positive upon staining in the basal and suprabasal layers of the epithelium, while the non-GOC cysts were minimally to focally positive for bcl-2. These findings suggested that bcl-2 staining could be useful for differentiating GOCs from other entities when limited clinical data is present or when histological characteristics overlap.

5. Treatment and recurrence

Both conservative and radical methods have been proposed for the management of glandular cysts. Conservative options, such as enucleation, marsupialization, curettage with or without periph-

eral ostectomy, curettage with adjuvant Carnoy's solution, and cryotherapy, have been applied. More aggressive approaches, namely marginal or partial jaw resections, have been described (23).

Faisal et al. (9) concluded in their review that the treatment of choice was mostly conservative (in 157 of the 177 reported cases) and it encompassed enucleation with or without curettage, peripheral ostectomy, and cryotherapy. Radical treatment, such as marginal jaw resection, segmental mandibulectomy, etc., was conducted in 20 cases. The average follow-up period was 2.2 years, with a recurrence rate of 35.8%.

Fowler et al. (8) reviewed 46 cases and all were conservatively treated (enucleation, curettage, excision, cystectomy, and peripheral ostectomy). Eighteen out of 46 cases were followed up, 50% of which recurred. The mean follow-up period was 8.75 years. Second and third recurrences were also noted.

In 2005 Kaplan et al. (12) analyzed 49 cases from the literature and presented 7 newly discovered cases of glandular cysts. A total of 85% of the patients were treated conservatively and 14.5%—radically. Recurrent disease was linked to conservative treatment options such as enucleation and curettage. Cases managed with peripheral ostectomy, marginal bone resection, or partial jaw resection did not recur. In the recurrence group, multilocular lesions were more frequently seen than in the group without recurrence (64.3% vs. 41.2%), as well as loss of cortical integrity (71.4% vs. 47.1%). Cortical integrity was measured radiologically and clinically (crepitus or lesion extending into the soft tissue). The authors classified the lesions as small if they encompassed fewer than two adjacent teeth and were limited to the alveolar bone. Large lesions encompassed more than the abovementioned and expanded past the alveolar bone or into the ramus of the mandible, maxillary sinus, or nasal cavity. The authors believed that large lesions should be biopsied prior to treatment and concluded that small unilocular lesions may be enucleated, but larger ones required more radical treatment—enucleation with peripheral osteotomy for unilocular and jaw resection (could be marginal or partial) for multilocular cysts. Marsupialization and a following second stage surgery could be useful for cysts in close proximity to vital structures. The period before the second surgery depended on the rate of reduction of the cyst dimensions. For the second surgery, curettage and peripheral ostectomy were recommended. In the cases with cortical perforation, the authors suggested that resection of the overlying mucosa should be considered, similar to the treatment of odontogenic keratocysts. They also proposed a minimum follow-up period of 3 years

In Chrcanovic and Gomez's review (11) of 169 cases, treatment was known in 122, in 108 of which a conservative approach was chosen (27 curettages, 81 enucleations) and 12 had been managed by bone resection (marginal or segmental). Data on recurrence was present for ninety-seven cases, of which twenty-one (21.6%) recurred (4 curettages, 16 enucleations, and 1 marginal resection). Three different patients were submitted to peripheral osteotomy post enucleation, one of whom without recurrence and the other two lacked follow-up data. The period between the initial treatment and the recurrence varied from 6 to 96 months, with a mean ±SD interval of 62.3±34.5 months. Follow-up periods were available for 83 patients, with a mean ±SD of 55.7±48.0 months. Sixteen patients were followed up for just a year after the operation, and thirty-three—for two years.

Koppang et al. (30) reviewed 45 literature cases and presented 2 new ones. Information regarding the recurrence was available in 38 of them, 8 of which recurred after 2–8 years. Two of the cysts recurred twice, with the second recurrence at 5 years, which led the authors to believe that the minimum follow-up period should be 5 years, not the previously proposed 3 years.

Bhatt (31) presented a case report and proposed marsupialization as a treatment modality. Two other cases by Cano et al. (32) and Motooka et al. (33) were treated with marsupialization as a first stage surgery and later enucleated. Both showed no recurrences.

Stoelinga (34) advocated for enucleation as treatment of choice for unilocular odontogenic cysts, including GOCs. Adjunctive therapy with Carnoy's solution (60% ethanol, 30% chloroform, and 10% acetic acid) was also described by the author, as well as Ficarra et al. (35). Qin et al. (18) successfully used it as a treatment modality after curettage. Silva et al. (24) also applied the solution for 3 minutes following enucleation of a recurrent cyst and no further re-

currence was seen 1 year postoperatively. Akkas et al. (36) described a bilateral occurrence of GOC in the mandible. Both lesions were unilocular and treated with peripheral ostectomy and application of Carnoy's solution. The patient showed no signs of recurrent disease in the following 36 months.

In multilocular lesions Stoelinga (34) suggested performing a biopsy prior to treatment in order to exclude other lesions like ameloblastoma, central giant cell granuloma, or myxoma.

While most authors advocate for the conservative approaches such as excision, enucleation, curettage, complete extirpation, and cryotherapy, Hussain et al. (37) recommended local en bloc excision with primary reconstruction. This treatment approach was also undertaken by Boffano et al. (23) in one of their patients where they used a 2.4 mm mandibular plate for the reconstruction. The patient showed no recurrence in the following 6 years. Thor et al. (38) treated a recurrent case (7 previous extirpations) of GOC with marginal resection, followed by reconstruction of the alveolar ridge with a particulated iliac crest autogenous bone graft, mixed with platelet-rich plasma. Five months later, a vertical osteodistraction device was placed. After 3 months, six dental implants were placed and prosthetic treatment was carried out in the following months.

DISCUSSION

The glandular odontogenic cyst is an uncommon lesion, comprising up to 1.3% of all jaw cysts. It is most often seen in the 5th decade of life, slightly more often in males. It has shown some ethnic differences in the age of first presentation (10). The most commonly reported localization of the lesion is the anterior mandible. It is usually described as a painless swelling, although symptomatic presentation including pain and paresthesia have also been mentioned.

Radiologically, conventional radiographs are most commonly used, however CT and cone-beam computed tomography (CBCT) can be more valuable for diagnosis, planning of the surgery, and follow-up. Radiographically, the lesion presents as a well-defined, uni- or multilocular radiolucency. Cortical integrity loss and root resorption may occur (39) and occasionally the cyst can be associated with an impacted tooth (22). Based on these findings, differential diagnoses taken into account are radicular cysts, keratocysts, dentigerous cysts, ameloblastomas, odontogenic myxomas, and simple bone cysts.

Microscopically, glandular cysts could share resemblance with lateral periodontal cysts, botryoid odontogenic cysts, dentigerous and radicular cysts with mucous metaplasia and, more importantly, mucoepidermoid carcinomas (39). Histological major and minor criteria for diagnosis have been proposed by Kaplan et al. (25). and they have been widely accepted. However, as Fowler et al. (8) stated that not all major criteria are necessary for an accurate diagnosis, but rather a combination of specific microscopic features. Overall, diagnosis should be based on clinical, radiological, and histological features interpreted as a whole. Additional immunohistochemical markers, such as p53, Ki67, PCNA, cytokeratins 18 and 19, MASPIN, and bcl-2, could aid in the differential diagnosis.

Treatment options range from conservative (enucleation, marsupialization, curettage with and without peripheral ostectomy) to radical (marginal and partial jaw resection). The choice depends on the degree of aggressive behavior, indicated by the loss of cortical integrity, size, and locularity of the cyst. Kaplan et al. (12) stated that large lesions should be biopsied prior to treatment and concluded that smaller unilocular lesions may be managed by enucleation, but larger ones require more radical treatment—enucleation with peripheral osteotomy for unilocular and marginal or partial jaw resection for multilocular cysts. Marsupialization with enucleation as a second stage surgery is a viable alternative for cysts in close proximity to vital structures.

Recurrence rates seem to have a correlation with the chosen treatment method. According to Kaplan et al. (12), in glandular cysts managed by extensive surgical procedures (marginal or partial jaw resection) no recurrences were reported, unlike the conservative approaches often associated with such. In addition to the treatment method, the recurrence rate is proportionally associated with the size and the locularity of the cyst. According to Thor et al. (38) the majority of patients with recurrent disease had large multilocular lesions with cortical perforations, while smaller unilocular ones appeared to be manageable with curettage and peripheral ostectomy, with few-

er incidences of recurrence. Consequently, the radicality of surgical approach should be dependent on the behavior of the lesion. The high propensity for recurrence of glandular cysts could also be attributed to incomplete removal of the lesion because of its multicystic configuration (23), the thin nature of its wall, and the presence of microcysts (38). In lesions where perforation of the cortical plate is present, resection of the overlying mucosa has been suggested (12). Recurrent disease is at a rate of 29% to 55%, usually within 0.5 to 7 years, with an average of 2.9 years (38). After analyzing previous reports, Thor et al. (38) concluded that follow-up periods were largely insufficient—the mean follow-up period was 2 years or less. Therefore, the follow-up period should be adequate and, according to Kaplan et al. (12), it needs to be extended to at least 3 years and up to 7 years where features indicating high risk of recurrence are present (size, multilocularity, and cortical plate erosion.) Based on their acquired data, Koppang et al. (30) proposed a longer follow-up period of at least 5 years.

In light of the increased recurrence associated with conservative approaches and where indications are present, radical approaches seem to be a viable and definitive treatment option.

Adjunctive therapies, such as fixation with Carnoy's solution, have been proposed in order to preserve bone whenever possible, considering future rehabilitation with dental implants (24).

CONCLUSION

The glandular odontogenic cyst, which has been recently described, can be locally aggressive and has a propensity for recurrence. Clinically and radiographically it could resemble several other lesions of the jaws, which denotes the importance of a precise histopathological diagnosis. Treatment options vary from conservative to radical and should be based on the degree of aggressive behavior of the cyst. Meticulous examination, proper treatment planning, and sufficient follow-up periods are key to a successful outcome.

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