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Glandular odontogenic cyst: an updated analysis of 169 cases reported in the literature

Running title: Glandular odontogenic cyst: review

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ABSTRACT

Objective. To integrate the available data published on glandular odontogenic cyst (GOC) into a comprehensive analysis of its clinical/radiologic and histopathological features.

Methods. An electronic search was undertaken in May/2017. Eligibility criteria included publications having enough clinical/radiological/histological information to confirm the diagnosis.

Results. 58 publications (169 GOCs) were included. The lesion was slightly more prevalent in men than in women. There was a high prevalence in the fifty/sixth decades of life, in the anterior regions, and in mandibles. Lesions were commonly associated with bone expansion (73%) and unilocular radiological appearance (61.5%). GOC was found to be associated with tooth displacement or an unerupted tooth (30.9%), cortical bone perforation (26%), presence of clinical symptoms (24.3%), root resorption (13.9%). Microscopic parameters most commonly observed in GOCs - in at least 95% of the lesions: presence of hobnail cells, intraepithelial microcysts, epithelial lining with variable thickness. The presence of apocrine snouting was the microscopic parameter less often found (40.4%).

Conclusions. Although the recurrence rate of GOCs is not as high as previously believed, it is a relevant phenomenon (21.6%). Adjunctive procedures after enucleation should be considered. None of the clinical/radiologic and histopathological features evaluated had a statistically significant effect on the recurrence rate.

INTRODUCTION

The glandular odontogenic cyst (GOC) was first described by Padayachee and Van Wyk (1987). The authors described two cases presenting features of both botryoid odontogenic cyst and central mucoepidermoid tumor, coining the term sialo-odontogenic cyst for the lesions. One year later Gardner et al. (1988) reported eight additional cases of lesion and proposed the term “glandular odontogenic cyst”, which is still used until this day. According to the most recent classification of head and neck tumors by the WHO (Speight et al., 2017), the GOC is a development cyst with epithelial features that simulate salivary gland or glandular differentiation.

GOC is considered to be a rare lesion. And because of that, there are limited details in the literature regarding their clinical and radiologic features. The epidemiological study of such rare lesions is of great importance because provides information that can improve the

diagnostic accuracy and will allow pathologists and surgeons to make informed decisions and refine the treatment plan to optimize the clinical outcome (Chrcanovic and Gomez, 2016, 2017a). The aim of the present study was to integrate the available data published in the literature on GOC into an updated comprehensive comparative analysis of their clinical, radiologic and histopathological features, as well as to investigate the probability of recurrence of the tumor for different variables and treatment approaches.

MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines (Moher et al., 2009).

Search strategies

An electronic search without time restrictions was undertaken in May 2017 in the following databases: PubMed/Medline, Web of Science, and Science Direct. The following terms were used in the search strategies:

(glandular odontogenic cyst) OR (sialo-odontogenic cyst)

Moreover, Google Scholar was also checked. A manual search of related journals, including *Acta Odontologica Scandinavica*, *Acta Oto-Laryngologica*, *Annals of Otolaryngology and Rhinology*, *British Journal of Oral and Maxillofacial Surgery*, *Cancer, Head & Neck*, *Head and Neck Pathology*, *International Journal of Oral and Maxillofacial Surgery*, *Japanese Journal of Oral and Maxillofacial Surgery*, *Journal of Dental Research*, *Journal of Craniofacial Surgery*, *Journal of Cranio-Maxillofacial Surgery*, *Journal of Japanese Society of Oral Oncology*, *Journal of the Japanese Stomatological Society*, *Journal of Laryngology and Otolaryngology*, *Journal of Maxillofacial and Oral Surgery*, *Journal of Nihon University School of Dentistry*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Oral Pathology and Medicine*, *Journal of the Stomatological Society*, *Laryngoscope*, *Oral Diseases*, *Oral Oncology*, *Oral Surgery Oral Medicine Oral Pathology Oral Radiology*, *Otolaryngology -- Head and Neck Surgery*, and *Quintessence International*, was performed. The reference list of the identified studies and the relevant reviews on the subject were also scanned for possible additional studies. Publications with lesions identified by other authors as being GOC, even not having the term “glandular odontogenic cyst” in the title of the article, were also re-evaluated by an author of the present study.

Inclusion and Exclusion Criteria

Eligibility criteria included publications reporting cases of GOC. The studies needed to have enough clinical, radiological and histological information to confirm the diagnosis. Fowler et al. (2011) listed the 10 microscopic parameters for the lesion, based on and adapted from previously reported microscopic features for GOC:

1. Surface eosinophilic cuboidal cells, also called “hobnail cells”;
2. Intraepithelial microcysts or duct-like spaces lined by a single layer of cuboidal to columnar cells similar to surface cells;
3. Apocrine snouting of hobnail cells;
4. Clear or vacuolated cells;
5. Epithelial lining with variable thickness;
6. Epithelium with papillary projections or “tufting” into the cyst lumen;
7. Mucous goblet cells;
8. Plaque like-thickenings or epithelial spheres;
9. Cilia;
10. Multiple cystic spaces.

As Fowler et al. (2011) showed that the presence of 5 or less microscopic parameters was highly predictive of a non-GOC diagnosis, the authors of the present study selected only the published cases which the pictures and/or histopathological description showed at least 6 microscopic parameters.

In order to have a clear and proper understanding and identification of the microscopic parameters described in the text, articles were included when only published in the languages that the authors were fluent (English, Spanish or Portuguese). Randomized and controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports were included.

Exclusion criteria were immunohistochemical studies, histomorphometric studies, radiological studies, genetic expression studies, histopathological studies, cytological studies, cell proliferation/apoptosis studies, *in vitro* studies, and review papers, unless any of these publication categories had reported any cases with enough clinical, radiological and histological information. Hybrid tumors containing parts of GOC were not considered for this study, as they may behave differently from non-hybrid GOC.

Study selection

The titles and abstracts of all reports identified through the electronic searches were read independently by the authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were solved by discussion between the authors. The clinical and radiological aspects, as well as the histological description of the lesions reported by the publications were thoroughly assessed by one of the authors of the present study, who is expert in oral pathology (R.S.G.), in order to confirm the diagnosis of GOC.

Data extraction

The authors independently extracted data using specially designed data extraction forms. Any disagreements were solved by discussion. For each of the identified studies included, the following data were then extracted on a standard form, when available: year of publication, number of patients, patient's sex, age and race, follow-up period, duration of the lesion previously to treatment, lesion location (maxilla/mandible), anterior/posterior location (three categories: [a] anterior: lesions in the incisors/canine region; [b] premolar region; [c] posterior: lesions in the molars/retromolar region), recurrence, recurrence period, lesion size, perforation of cortical bone, locularity radiological appearance (unilocular/multilocular), association of the lesion with a tooth (the tooth can either be erupted with the entire root(s) encompassed by the lesion or unerupted encompassing the entire tooth), tooth displacement and/or tooth root resorption due to lesion's growth, expansion of osseous region adjacent to the tumor, presence of clinical symptoms, and treatment performed (curettage/excision, enucleation, partial resection, resection with continuity). The lesion size was determined according to the largest diameter reported in the publications. Contact with authors for possible missing data was performed.

Analyses

The mean, standard deviation (SD), and percentages were presented as descriptive statistics. Kolmogorov–Smirnov test was performed to evaluate the normal distribution of the variables, and Levene's test evaluated homoscedasticity. The performed tests for two independent groups were Student's t-test or Mann-Whitney test, depending on the normality. Pearson's chi-squared or Fisher's exact tests were used for categorical variables,

depending on the expected count of events in a 2x2 contingency table. The degree of statistical significance was considered $p < 0.05$. All data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Literature search

The study selection process is summarized in Figure 1. The search strategy in the databases resulted in 1,086 papers. Search in Google Scholar resulted in 29 eligible papers not found in the three main databases. A number of 211 articles were cited in more than one database (duplicates). The reviewers independently screened the abstracts for those articles related to the focus question. Of the resulted 904 studies, 753 were excluded for not being related to the topic. Additional hand-searching of journals and of the reference lists of selected studies yielded 16 additional papers. The full-text reports of the remaining 167 articles led to the exclusion of 91 because did not have enough clinical, radiological and histological information to confirm the diagnosis of GOC and to the exclusion of an additional 18 papers did not meet the language inclusion criteria (see *Supplemental Appendix*). Thus, a total of 58 publications were included in the review.

Description of the Studies and Analyses

Fifty-eight publications reporting 169 GOCs were included in the present review (see *Supplemental Appendix*). Table 1 presents demographic and clinical features of the cysts. The lesion was discreetly more prevalent in men than in women, at a 1.15:1 proportion. The mean age $\pm$ SD of the patients was 48.1 ± 13.1 (min-max, 12-90). Figure 2 shows the distribution of the lesions according to age, with highest prevalence in the fifth and sixth decades of life. The lesions were more prevalent in the mandible in comparison to the maxilla (2.73:1), and at the anterior region in comparison to the posterior region (Figure 3). About 26% of the lesions showed signs of cortical bone perforation, 73% presented bone expansion, 24.3% of the patients presented symptoms, and about 62% of the lesions had a radiological unilocular appearance. Radiopacities in the lesion were observed in only one

case (Ramer et al., 1997). Approximately 31% of the lesions were associated with tooth displacement or an unerupted tooth. Nearly 14% of the lesions presented root resorption of teeth adjacent to the lesion.

The microscopic parameters most commonly observed in GOCs were the presence of hobnail cells, intraepithelial microcysts, and epithelial lining with variable thickness, all seen in at least 95% of the lesions. The presence of apocrine snouting was the microscopic parameter less often found in the lesions (40.4%).

Treatment of the lesions was known in 122 cases, of which 108 consisted of conservative surgery (27 curettages, 81 enucleations) and 12 cases were treated by marginal or segmental resection. There was information about recurrence for 97 lesions, of which 21 (21.6%) recurred (4 curettages, 16 enucleations, and 1 marginal resection). Two of the enucleated cases were previously submitted to marsupialization (Cano et al., 2012, Motooka et al., 2015), both with no recurrences, and were here considered under the category 'enucleation'. Five cases were previously submitted to Carnoy's solution (Bhat et al., 2014, Qin et al., 2005) before curettage or enucleation, all with no recurrences, and were here considered under the categories 'curettage' or 'enucleation'. Three cases were submitted to peripheral osteotomy (Lee et al., 2014, Lin et al., 2000, Reyes et al., 2008) after enucleation, one case with no recurrence and the other two cases with no follow-up information. The interval from initial treatment to the recurrence ranged from 6 to 96 months, with a mean $\pm$ SD interval of 62.3 $\pm$ 34.5 months. Time of follow-up was informed for 83 lesions, with a mean $\pm$ SD of 55.7 $\pm$ 48.0 months (min-max, 1-240). Patients referring to 16 lesions were followed up only up to 1 year after lesion excision, and 33 only up to 2 years. The race of the patient was reported in 106 cases. Forty-five cases (42.5%) were diagnosed in whites, 33 in Asians, 9 in Indians, 9 in blacks, 3 in Hispanics, 3 in Arabs, 2 in Turks, and 2 in Persians. Table 2 shows the recurrence rate for GOCs according to different factors. No factor showed to have a statistically significant effect on the recurrence rate.

DISCUSSION

In the present review of the literature on GOC many publications were excluded because they did not meet the criteria. This is not to say that all of them were not GOC, but the authors of the present review followed the criteria recommended by Fowler et al. (2011). This suggests that the authors need to better describe the findings and that many

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reviews included cases that may have this diagnosis questioned. For instance, some authors diagnose a GOC when they encounter ciliated and mucosecretory cells. Even though this is found in lesions in the jaws, the phenomenon of prosoplasia is described in odontogenic lesions. Some of the features described for GOCs may be seen in dentigerous cysts, botryoid odontogenic cysts, radicular cysts, and surgical ciliated cysts (Fowler et al., 2011). This may make it difficult to discern whether a particular cyst might represent a true GOC or another cyst with GOC-like features (Fowler et al., 2011). As previous reviews did not apply more strict criteria for inclusion, other lesions were mistakenly included in the survey, which undoubtedly undermined the analysis of the epidemiological data reported over the years on the disease. Kaplan et al. (2005, 2008) listed 5 major (must be present for the diagnosis) and 4 minor criteria (support the diagnosis, but are not mandatory) to help in the correct diagnosis of GOC. More recently Fowler et al. (2011) listed 10 microscopic criteria for the diagnosis, and determined from their series that the presence of 5 or less microscopic parameters was highly predictive of a diagnosis of non-GOC. As such, the authors of the present study decided to classify as a GOC only when the described lesion presented 6 or more of these microscopic features. It is interesting to note that none of the microscopic parameters used to select GOC cases were associated with the recurrence rate.

Some features of the GOC are highlighted, such as the fact that the cyst was never reported in individuals in the first decade of life (the youngest person with the lesion was a 12 years-old boy), a clear preference for the mandible, with 73.2% of the cases, bone expansion (73%), and the radiolucent radiological appearance. These results confirm major part of the results of Macdonald-Jankowski (2010). The only case with presence of radiopaque areas (Ramer et al., 1997) exhibited an unusual microscopic finding for the lesion, including ghost cells and dystrophic mineralizations. This unusual microscopic finding may be related to this rare radiographic finding. It has been stated that GOC has a high incidence of cortical perforation (Kaplan et al., 2008), but this was not observed in the present review (26%), which includes more cases than Kaplan et al. (Kaplan et al., 2008). However, Kaplan et al. (2008) also took into consideration thinning of the cortical plates, not the case for the present review. And this number can be underestimated, as this information was not available for almost 40% of the lesions reviewed here.

Fowler et al. (2011) reported a 50% recurrence rate for the lesions in their study that were follow-up (9 recurrences in 18 cases). All their cases were treated conservatively (enucleation, curettage, cystectomy, excision). According to the review of Kaplan et al. (2008), the recurrence rate is of about 30%. Although the recurrence rate of GOCs observed in the present review was not as high as previously believed, it is a relevant phenomenon (21.6%). However, this figure is most probably an underestimation of the true recurrence rate, because for only 83 lesions (out of 169) here reviewed there was information about follow-up, and 33 lesions were followed up only up to 2 years. Comparing different types of treatment, more conservative surgical procedures (curettage or enucleation) presented a higher recurrence rate than resection, but the difference in recurrence rate was not statistically significant. However, there were far less cases treated by more invasive surgical procedures, and a greater number of cases treated by resection would result in a fairer comparison. Simple enucleation is related to a considerable recurrence rate for a benign lesion such as GOC, very similar to that observed in keratocystic odontogenic tumors (Chrcanovic and Gomez, 2017b). Thus, treatment of this lesion might involve adjunctive therapy after enucleation, such as cryotherapy, Carnoy's solution, or peripheral ostectomy. Future prospective studies are necessary to prove this assumption.

Although our survey is the largest one on GOC in the literature, the results have to be interpreted with caution because of its limitations. First, all included studies were retrospective reports, which inherently results in flaws, manifested by the gaps in information and incomplete records. Second, some publications do not report whether the patients were followed up or not, and therefore there is no information about recurrence. Of those publications that provide this information, some cases have a short follow-up, which could have led to an underestimation of the actual recurrence rate, because a longer follow-up period can lead to an increase in the recurrence rate. However, it is hard to define what it would be considered a short follow-up period to evaluate the recurrence of GOC. Third, the great majority of the cases described were published as isolated case reports or small case series.

CONCLUSIONS

Considering the high recurrence rate for a benign cyst (21.6%), adjunctive procedures after enucleation should be considered in the treatment of the GOC. It is suggested that no factor have a statistically significant effect on the recurrence rate.

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Authors' individual contribution:

Bruno R. Chrcanovic: conception and design, acquisition of data, statistical analysis, interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the version to be published

Ricardo S. Gomez: conception and design, interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published

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TABLES

Table 1. Demographic and clinical features of glandular odontogenic cysts (n = 169) described in the literature.

Variables	
Age (years), mean±SD (min-max)	48.1±13.1 (12-90) ^b
Men	42.7±15.9 (12-69; n = 47) ^b
Women	53.5±17.2 (14-90; n = 44) ^b
p value ^a	0.005
Gender, n (%)	
Men	90 (53.6)
Women	78 (46.4)
Unknown	1
Jaw, n (%)	
Maxilla	45 (26.8)
Mandible	123 (73.2)
Unknown	1
Bone expansion, n (%)	
Yes	103 (73)
No	38 (27)
Unknown	28
Symptomatic, n (%)	
Yes	34 (24.3)
No	106 (75.7)
Unknown	29
Cortical bone perforation, n (%)	
Yes	27 (26)
No	77 (74)
Unknown	65
Locularity, n (%)	
Unilocular	88 (61.5)
Multilocular	55 (38.5)
Unknown	26
Tooth displacement/unerupted, n (%)	
Yes	42 (30.9)
No	94 (69.1)
Unknown	33
Tooth root resorption, n (%)	
Yes	19 (13.9)
No	118 (86.1)

Unknown	33
Treatment, n (%)	
None	2 (1.6)
Curettage	27 (22.1)
Enucleation	81 (66.4)
Marginal resection	9 (7.4)
Segmental resection ^c	3 (2.5)
Unknown	47
Recurrence, n (%)	
Yes	21 (21.6)
No	76 (78.4)
Unknown	72
Follow-up time (months), mean±SD (min-max)	55.7±48.0 (1-240; n = 83)
Lesion size (cm), mean±SD (min-max)	4.2±2.6 (0.5-14.0; n = 70)
Microscopic parameters, n (% of the total ^d)	
Hobnail cells	153 (95)
Intraepithelial microcysts	157 (97.5)
Apocrine snouting	65 (40.4)
Clear cells	73 (45.3)
Variable thickness	155 (96.3)
Papillary projections	125 (77.6)
Mucous goblet cells	116 (72)
Epithelial spheres	117 (72.7)
Cilia	99 (61.5)
Multiple cystic spaces	113 (70.2)

SD – standard deviation

^a Comparison of the mean age between men and women (Mann-Whitney test)

^b The mean age (min-max) of the cases of Pires et al. (2004), Kaplan et al. (2005), Shen et al. (2006), Fowler et al. (2011) were included for the calculation of the global mean age, but not separately for “men” and “women”, as the information of age for each patient was not provided for these studies

^c Resection with continuity defect

^d Number of lesions presenting the microscopic parameter. Only papers detailing this information for each individual case was included (n=161). The 8 lesions reported by Gardner et al. (1988) are not included here

Table 2. Recurrence rate for glandular odontogenic cysts according to different factors – for the lesions with available information about both recurrence and the factors here included.

Factor	Recurrence/total (% recurrence)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
<i>Treatment</i>				
Curettage	4/24 (16.7)			
Enucleation	16/63 (25.4)	0.387 ^{a,d}	1.702 (0.505, 5.732) ^g	0.391
Marginal resection	1/8 (12.5)	0.535 ^{b,e}	0.556 (0.054, 5.700) ^h	0.621
Segmental resection ^c	0/2 (0)	0.265 ^{b,f}	0.326 (0.038, 2.781) ⁱ	0.306
<i>Jaw</i>				
Maxilla	3/23 (13)		1	
Mandible	9/56 (16.1)	0.516 ^b	1.277 (0.312, 5.216)	0.734
<i>Bone expansion</i>				

No	1/12 (8.3)		1	
Yes	9/62 (14.5)	0.489 ^b	1.868 (0.214, 16.289)	0.572
<i>Cortical bone perforation</i>				
No	5/31 (16.1)		1	
Yes	5/17 (29.4)	0.235 ^b	2.167 (0.526, 8.926)	0.284
<i>Locularity</i>				
Unilocular	7/50 (14)		1	
Multilocular	5/29 (17.2)	0.467 ^b	1.280 (0.366, 4.474)	0.699
<i>Microscopic parameters</i>				
Hobnail cells				
No	1/6 (16.7)		1	
Yes	9/67 (13.4)	0.601 ^b	0.776 (0.081, 7.427)	0.826
Intraepithelial microcysts				
No	1/2 (50)		1	
Yes	9/71 (12.7)	0.257 ^b	0.145 (0.008, 2.531)	0.186
Apocrine snouting				
No	9/53 (17)		1	
Yes	1/20 (5)	0.174 ^b	0.257 (0.030, 2.176)	0.213
Clear cells				
No	8/54 (14.8)		1	
Yes	2/19 (10.5)	0.487 ^b	0.676 (0.130, 3.509)	0.642
Variable thickness				
No	1/1 (100)			
Yes	9/72 (12.5)	0.137 ^b	-	
Papillary projections				
No	2/17 (11.8)		1	
Yes	8/56 (14.3)	0.576 ^b	1.250 (0.239, 6.537)	0.792
Mucous goblet cells				
No	1/28 (3.6)		1	
Yes	9/45 (20)	0.045 ^b	6.750 (0.806, 56.539)	0.078
Epithelial spheres				
No	4/23 (17.4)		1	
Yes	6/50 (12)	0.387 ^b	0.648 (0.164, 2.561)	0.536
Cilia				
No	2/25 (8)		1	
Yes	8/48 (16.7)	0.260 ^b	2.300 (0.450, 11.764)	0.317
Multiple cystic spaces				
No	6/54 (11.1)		1	
Yes	4/19 (21.1)	0.236 ^b	2.133 (0.530, 8.579)	0.286

CI - confidence interval

^a Pearson's chi-squared test

^b Fisher's exact test

^c Resection with continuity defect

^d Significance of the difference of the recurrence rate between curettage and enucleation

^e Significance of the difference of the recurrence rate between curettage and resection (marginal + segmental)

^f Significance of the difference of the recurrence rate between enucleation and resection (marginal + segmental)

^g Odds ratio of the recurrence probability of enucleation in relation to curettage

^h Odds ratio of the recurrence probability of resection (marginal + segmental) in relation to curettage

ⁱ Odds ratio of the recurrence probability of resection (marginal + segmental) in relation to enucleation

FIGURE LEGENDS

Figure 1. Study screening process.

Figure 2. Distribution of GOCs according to age (for the cases which the patients' age were informed, n=90). The studies of Pires et al. (2004), Kaplan et al. (2005), Shen et al. (2006), and Fowler et al. (2011) (total of 79 lesions) reported the mean age (min-max) of the their cases, and not the age separately for each patient.

Figure 3. Topographical distribution of the known precise locations (n=88) of GOCs. Cases involving multiple regions (or an entire quadrant) are indicated between arrows. Numbers at the top and bottom of the lines indicate cases involving both adjoining regions: anterior/premolar, premolar/molar. One asterisk (*) indicates the number of lesions from the mandibular body that reached the angle and/or ramus. For the rest of the lesions (n=81), the location was the 'maxilla' (n=8), 'anterior maxilla' (n=9), 'posterior maxilla' (n=1), 'mandible' (n= 10), 'anterior mandible' (n=29), 'posterior mandible (n=23), and unknown (n=1).