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HOT TOPIC

Glandular odontogenic cyst: a challenge in diagnosis and treatment

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The present review analyzes the accumulated data from all cases of glandular odontogenic cyst (GOC) reported in the English language literature. In the 20 years since it was first described, 111 cases have been reported, an incidence of 0.2% of odontogenic cysts. The age range is 14–75, mean 45.7, with a M/F ratio of 1.3:1. GOC has a predilection for the mandible (70%), affecting both anterior and posterior areas. It is typically radiolucent, well defined, either unilocular (53.8%) or multilocular (46.2%). Frequent perforation (61%) and of thinning of cortical plates (24.4%) indicate aggressiveness. Sufficient follow-up indicates that 30% of cases can recur. Treatment by enucleation or curettage carries the highest risk for recurrence, especially in large and multilocular lesions. Peripheral osteoectomy or marginal resection can eliminate the risk. Defined criteria for microscopic diagnosis are described, which in addition to Ki67 and p53 can help in differentiating GOC from lesions with histological similarities (cysts with mucous metaplasia, botryoid and surgical ciliated cysts, low-grade mucoepidermoid carcinoma). Definite diagnosis may not be possible in small incisional biopsies due to the focal presentation of characteristic features required for diagnosis. There is now evidence to support an odontogenic rather than a sialogenic origin.

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Introduction

Glandular odontogenic cyst (GOC) is a relatively rare cystic lesion of the jaws, which poses a diagnostic challenge as well as a challenge in treatment.

The first reports used the term sialodontogenic cyst, based on the microscopic resemblance to salivary gland tissue, (Padayachee and Van Wyk, 1987). The name had been replaced with GOC by the World Health Organization (WHO), since at that time there seemed to be no evidence for salivary gland origin (Kramer *et al*, 1992). In the following years, the issue of the origin of GOC has not been completely resolved, although there now seems to be more evidence to support an odontogenic rather than sialogenic origin. Several cases of hybrid lesions of GOC with other odontogenic tumors are an indicator of odontogenic origin, whereas the minimal or lack of expression of markers such as epithelial membrane antigen (EMA) and mammary serine protease inhibitor (MASPIN) do not support a sialogenic origin (Gardner *et al*, 1988; Koppang *et al*, 1998; Hisatomi *et al*, 2000; Yoon *et al*, 2006; Vered *et al*, 2007).

Although it is relatively rare, correct diagnosis is of major clinical importance, since GOC has an aggressive potential, a high incidence of cortical perforation and a relatively high rate of recurrence, especially in cases treated with a conservative approach (Kaplan *et al*, 2005a).

However, due to similarities in microscopic characteristics between GOC and lesions such as botryoid cyst, radicular or dentigerous cysts with mucous metaplasia and most importantly low-grade mucoepidermoid carcinoma (MEPCa), a definitive diagnosis can be difficult to make. To help with diagnosis, a clear definition of criteria is necessary, as well as a search for specific markers that would support the diagnosis.

The aim of the present review was to analyze the accumulated data from all cases of GOC reported in the English language literature. The clinical, radiographic and pathologic features as well as the differential diagnosis and aids for diagnosis will be addressed. The analysis will also refer to the biological behavior and treatment requirements, and finally will touch upon the debate regarding the origin of GOC.

Incidence and prevalence

To date, a total of 111 cases of GOC have been reported in 48 articles in the English language literature, approximately half of these in the last 7 years (Padayachee and Van Wyk, 1987; Gardner *et al*, 1988; Ficarra *et al*, 1990;

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Lindh and Larsson, 1990 ; Patron *et al*, 1991; Sadeghi *et al*, 1991; Van Heerden *et al*, 1992; Gardner and Morency, 1993; De Carvalho *et al*, 1994; Semba *et al*, 1994; Takeda, 1994 ; Toida *et al*, 1994; Economopoulou and Patrikiou, 1995 ; Hussain *et al*, 1995; High *et al*, 1996; Ide *et al*, 1996; Savage *et al*, 1996; Baliga *et al*, 1997; Machade de Sousa *et al*, 1997; Magnusson *et al*, 1997; Manojlovic *et al*, 1997; Ramer *et al*, 1997; Koppang *et al*, 1998; Chavez and Richter, 1999 ; Damm and Fantasia, 2000 ; Jose *et al*, 2000; Lin *et al*, 2000; Tosios *et al*, 2000; Barreto *et al*, 2001; Bhatt *et al*, 2001; Babburi *et al*, 2003; Ertas *et al*, 2003; Geist *et al*, 2003; Manor *et al*, 2003; Ferreira *et al*, 2004; Pires *et al*, 2004; Tran *et al*, 2004; Abu-Id *et al*, 2005; Demetriades *et al*, 2005; Kaplan *et al*, 2005a; Lo Muzio *et al*, 2005; Qin *et al*, 2005; Velez, 2006; Kasaboglu *et al*, 2006; Shen *et al*, 2006; Sittitavornwong *et al*, 2006).

Three of the cases (2.7%) described hybrid lesions of GOC with other odontogenic tumors such as ameloblastoma (Gardner *et al*, 1988; Hisatomi *et al*, 2000) and keratocystic odontogenic tumor (KOC) (Yoon *et al*, 2006). These three cases have been excluded from the quantitative analysis of the clinical and radiographic characteristics for the present review, to avoid any possible bias in evaluation of the typical behavior of GOC.

While there is insufficient data to accurately asses the incidence of GOC, it has been estimated to be $<1\%$ of odontogenic cysts. In a recent epidemiologic study of 7121 odontogenic cysts from the UK population, GOC represented 0.2% of all cases (Jones *et al*, 2006).

Gender and age

A total of 57% of the cases have been reported in males and 43% in females, (1.3:1, M:F ratio). The majority of cases were reported in patients older than 30 years, with a mean of 45.7 years (Figure 1). GOC can occur within a wide age range of 14–75 years, but has never been reported in children <10 years of age.

Location

Glandular odontogenic cyst has a clear preference for the mandible, with 70% of cases located in the mandible and 30% in the maxilla. When dividing the jaws into anterior (incisors and canines) and posterior (premolar, molar, body of mandible and ramus) areas 50.6% of cases involved both the anterior and posterior areas, the remaining cases were distributed in almost equal proportions between anterior (24.1%) and posterior locations (25.3%). Thus, although earlier reports suggested a predilection for the anterior areas of the jaws, the present analysis of the literature does not support this (Figure 2).

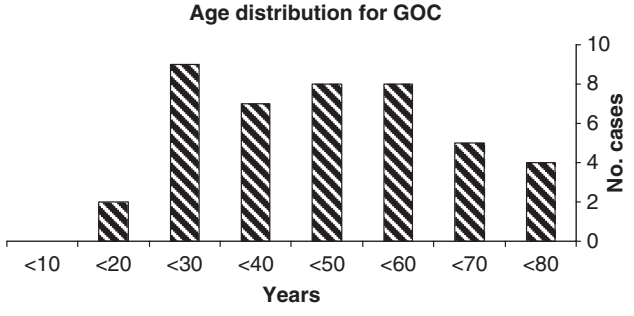

Figure 1 Age distribution for glandular odontogenic cyst showing a wide distribution, with the majority of cases in patients over 30 years

Radiographic characteristics

Glandular odontogenic cyst typically presents as a radiolucent lesion, except in one case which reported some calcifications in an otherwise radiolucent lesion. The lesions can be unilocular (53.8%) or multilocular (46.2%), with well defined borders in 95% of cases. Scalloped borders were described in 13% of cases.

Size

Glandular odontogenic cyst can present a spectrum of dimensions ranging between 0.5–12 cm, (mean 4.9 cm). The multilocular lesions are generally larger (Manor *et al*, 2003). For a semi-quantitative evaluation of the size in GOC, in a previous article lesions were classified as 'large' if they involved an area of bone larger than the space occupied by 2 teeth, and 'small' when the area involved was <2 teeth (Kaplan *et al*, 2005a). Using these criteria, 79.4% of all cases was large and 20.6% small, a ratio of approximately 4:1 in favor of large size lesions. This semi-quantitative evaluation of size is important because size was found to be one of the features with correlation to the aggressiveness and recurrence tendency of GOC: 86.5% of recurrent cases was classified as large at first presentation, 64.3% of these were both large and multilocular (Kaplan *et al*, 2005a).

Clinical presentation

Lesions tend to cause expansion in most cases (88.5%). Other features such as root resorption or tooth displacement were present in 22–24%, of cases.

Cortical plate integrity

Cortical plate integrity is frequently compromised. Of the 41 cases in which information was available, perforation was reported in 61% of the cases, and thinning of the plates in additional 24.4% of the cases. Thus, 85.4% of GOC cases encroach upon the cortical plates. This feature is an indication for the aggressive potential of GOC.

Treatment

Details of treatment are not uniformly available in the cases reviewed, and there is inconsistent terminology

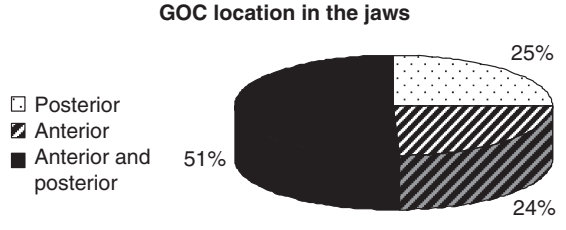

Figure 2 Anterior–Posterior distribution of the lesions within the jaws

used to describe the surgical procedures. Minor procedures such as enucleation or curettage were the most frequent types of treatment, reported in 83.5% of cases, while marsupialization was used in only 2.7%. Major procedures such as marginal resection or partial jaw resection account for the remaining cases. Adjuvant methods to treat the margins were not frequent: marginal osteoectomy (4%), fixation by Carnoy solution (4%) and cryosurgery (2.7%).

Considering its rarity, it is understandable why controlled studies comparing different treatment schemes in GOC have not been conducted. However, from the available data, it is evident that in cases treated by major surgical procedures there were no recurrent cases reported, while in cases treated by minor surgery 35.9% recurred.

Recurrence

Glandular odontogenic cyst has been reported to recur after treatment in 13.8% cases reviewed; however, this figure is most probably an under-estimation of the true recurrence rate. In many of the reported cases, there is no follow-up information, or a very short follow-up, ranging between 3 months and 2 years, while in the cases that have recurred the time for recurrence ranged between 6 months and 7 years, with a mean of 2.7 years. Thus, GOC cases need a long follow-up period for the true recurrence rate to be evaluated. When only cases with follow-up information were included in the analysis, the recurrence rate climbed to 30%, a high rate which is comparable to KOC (Blanas *et al*, 2000).

As stated earlier, the recurrence rate is directly related with the size of the lesion, 14.4% of the small lesions recur in contrast to 85.6% of the large lesions (Kaplan *et al*, 2005b). Therefore, large lesions should be treated more aggressively and followed for long periods.

Locularity is also a significant factor in relation to the tendency to recur, approximately 2/3 of the recurrent cases being multilocular, and only 1/3 unilocular (Figure 3).

Multiple recurrences have also been described in some cases. Three cases, which represent 20% of recurrent cases, have recurred several times. In one case the lesion recurred eight times over a 20-year period (High *et al*, 1996; Thor *et al*, 2006).

Acknowledging the fact that the biologic nature of the lesion is not the only factor responsible for the tendency to recur, the correlation between treatment modality and recurrence has been investigated in a previous study (Kaplan *et al*, 2005a). The results demonstrated that enucleation or curettage are the treatment modalities with the highest risk of recurrence, especially in large and multilocular lesions, while use of adjuvant methods such as peripheral osteoectomy or marginal resection is associated with a significant reduction in the risk for recurrent disease.

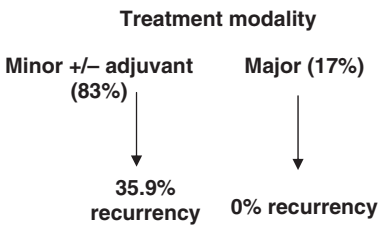

Figure 3 Correlations between initial treatment modality and tendency to recurr. *Adapted from Kaplan *et al*, 2005a

The role of adjuvant methods to treat the bony cavity such as cryosurgery or fixation solution in reducing recurrent lesions is yet undetermined, because of the small number of cases reported to date (Figure 3).

Microscopic characteristics

The histological diagnosis of GOC had been considered difficult because the exact criteria for the diagnosis have not been clearly defined. Many different features have been described in the cases reviewed: the lining is composed of non-keratinized stratified squamous epithelium, with variations in thickness along the lining, which can take the form of focal luminal proliferation, epithelial whorls, or spheres. The epithelial – connective tissue interface is flat and lacks palisading of the basal cells. Within the lining, superficial cuboidal eosinophilic cells or 'hob-nail' cells are a frequent finding. Mucous cells in the superficial layers, pools of mucicarmine or Periodic Acid Schiff (PAS) positive material or clefts lined by mucous cells may be found within the epithelial lining, as well as intra-epithelial duct-like or microcystic structures. Less frequently, papillary configurations, cilia, vacuolated cells and daughter cysts were documented. Some of the cases were multi-cystic or multi-luminal.

Each individual lesion usually presents some but not all of the many different features described, often exhibited only focally within the cyst lining. In addition some of these individual features may be found in other lesions such as botryoid cyst, radicular or dentigerous cysts with mucous metaplasia, surgical ciliated cysts and low-grade MEPCa.

These problems have been addressed in a previous study (Kaplan *et al*, 2005b). Based on the frequency of each parameter in the cases reviewed from the literature, a set of criteria for histological diagnosis has been proposed. These were divided into major and minor criteria, where we suggest that at least focal presence of each of the major ones is mandatory for diagnosis, while the minor criteria can support the diagnosis but are not mandatory.

The major criteria include:

- Squamous epithelial lining, with a flat interface with the connective tissue wall, lacking basal palisading.
- Epithelium exhibiting variations in thickness along the cystic lining with or without epithelial 'spheres' or 'whorls' or focal luminal proliferation.
- Cuboidal eosinophilic cells or 'hob-nail' cells.
- Mucous (goblet) cells with intraepithelial mucous pools, with or without crypts lined by mucous-producing cells.
- Intraepithelial glandular, microcystic or duct-like structures.

The minor criteria include:

- Papillary proliferation of the lining epithelium.
- Ciliated cells.
- Multicystic or multiluminal architecture.
- Clear or vacuolated cells in the basal or spinous layers.

Applying this set of criteria will help narrow down the list of differential diagnosis (Figure 4).

For example, a case reported as a botryoid cyst (Ucok *et al*, 2005), was considered to have features consistent with the diagnosis of GOC (Slater, 2006). This case fulfils the criteria presented here, and is probably an example of the under-diagnosis of GOC.

Botryoid cysts are characterized by multiple cystic spaces, as well as variations in the lining thickness, with epithelial protrusions into the lumen (Gurol *et al*, 1995). Glycogen-containing clear cells may also be present, but not by any of the other major criteria: they lack mucus-producing cells, mucous pools, crypts, intraepithelial microcysts, duct-like structures or 'hob-nail' cells. The same reasoning would be true for lateral periodontal cysts, which are essentially botryoid cysts with a single space (Kerezoudis *et al*, 2000).

Surgical ciliated cysts are characterized by a thin lining, usually a single layer of ciliated cells (Sugar *et al*, 1990). Mucous cells may also be present but mucous pools or crypts have not been described, neither duct-like structures nor variation in lining thickness are typical for surgical ciliated cysts.

Mucous metaplasia of the epithelial lining has been described in radicular, dentigerous and primordial cysts in a total incidence of 20.8%, and ciliated cells in 11.4% (Takeda *et al*, 2005). Incidental findings of intra-epithelial gland-like structures have also been described; however, the exact incidence has not been given (Takeda *et al*, 2005). In fact, although the details in the article do not allow a precise diagnosis, it is possible that at least some of the cases included by the authors would meet the criteria for GOC.

As the presence of at least five major signs is considered mandatory for the diagnosis of GOC, the separation of GOC from other odontogenic cysts should not prove difficult in most cases, providing that the biopsy material submitted contains a large and representative sample. The most important differential diagnosis is low grade MEPCa, in which multiple cyst-like structures lined by mucus-producing cells are typically found, in addition to epidermoid and intermediate cell populations. Clear cells may also be a feature of MEPCa (Speight and Barrett, 2002). To help in the differentiation from MEPCa, the lesion should be screened for presence of hobnail or cuboidal eosinophilic cells in the superficial layer of the lining epithelium, and for small intra-epithelial glandular micro-cysts or duct-like structures which are not typical for MEPCa. The epidermoid component in MEPCa is usually seen at the periphery of the cystic spaces, and not as epithelial spherules or whorls protruding into the lumen which is characteristic of

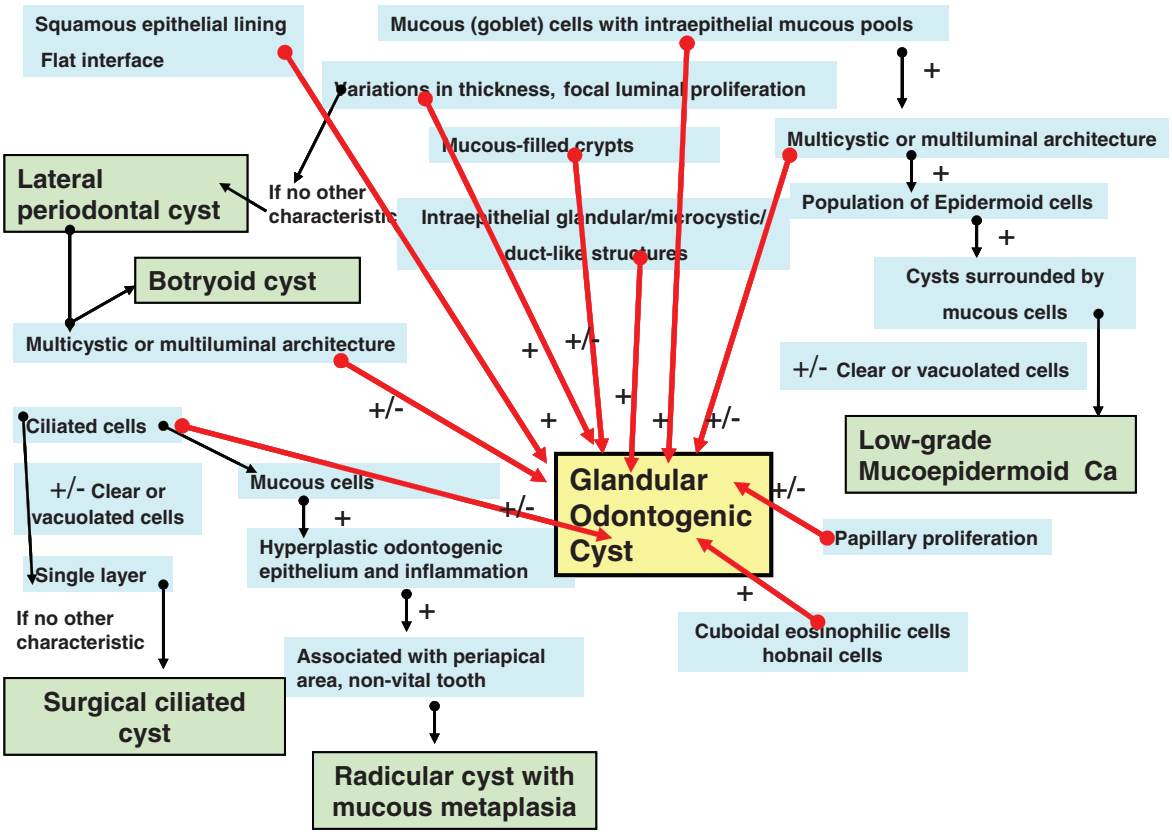

Figure 4 An aid for microscopic differential diagnosis in GOC.

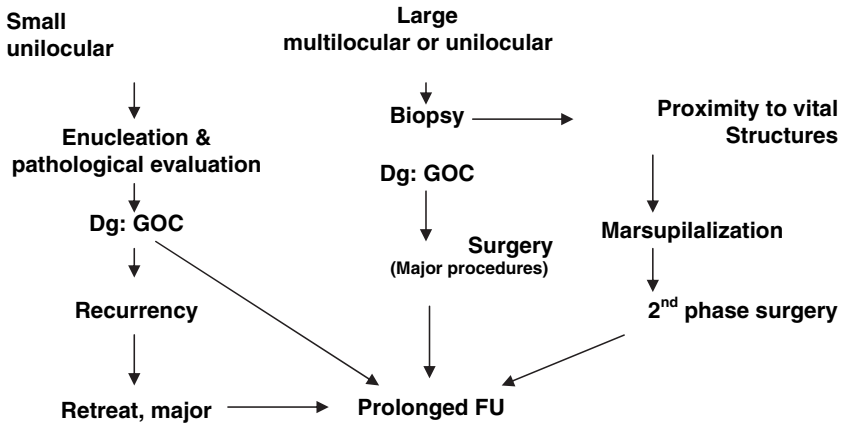

Figure 5 Treatment scheme for glandular odontogenic cyst cases. *Adapted from Kaplan *et al*, 2005a

GOC. Attention to these details should help in separating low-grade MEPCa from GOC.

In view of the overlapping features between GOC, low grade MEPCa, and other odontogenic cysts with mucous metaplasia, there have been several attempts to use molecular markers as an aid in diagnosis.

When comparing GOC, low-grade MEPCa and radicular cysts with mucous metaplasia (RC) by immunohistochemistry for p53, the mean labeling indices (LI) were 3%, 4.9% and 0.4% respectively, indicating that this marker can help separate RC from GOC and low grade MEPCa, both of which show significantly higher LI for p53 than RC. Ki67 mean LI was found to be 4.4% in GOC, 0.7% in low grade MEPCa and 3.7% in RC. Although low grade MEPCa is a malignancy, its proliferation index turned out to be significantly lower than GOC, indicating that Ki67 could be used as an aid to distinguish between GOC and low grade MEPCa (Kaplan *et al*, 2005b).

The profile of cytokeratin (CK) expression was found significantly different in GOC, low grade MEPCa and odontogenic cysts. From the many CK examined, CK's 18 and 19 seem to be of some value in this context, with CK 18 expressed by 100% of low grade MEPCa, 30% of GOC and only 7% of odontogenic cysts, while CK 19 expressed by 100% of low grade MEPCa and 50% of GOC (Pires *et al*, 2004). Although these differences were statistically significant, the role of CK's in everyday practice is probably still of limited value because of the large overlap in expression between low grade MEPCa and GOC.

Mammary serine protease inhibitor, which was originally described in breast myoepithelial cells, had been later identified in other normal and neoplastic glandular tissues, including in salivary glands. A recent study found significantly higher expression of both cytoplasmic and nuclear MASPIN in the mucous cells in low grade MEPCa (16.5% cytoplasmic, 1.7% nuclear) as compared with GOC (1.5% and 0.3%) or odontogenic cysts with mucous metaplasia (1% and 0.4%), (Vered *et al*, 2007). Further studies are probably needed to establish the role of MASPIN in the context of the differential diagnosis of GOC.

In the 20 years that have passed since it was first described, the bulk of information that has accumulated is adequate to establish the 'profile' of GOC.

It is a relatively aggressive cystic lesion, which in both its radiologic presentation (unilocular or multilocular, well defined borders) and biologic behavior (high prevalence of cortical perforation, tendency to recur) is similar to the more common KOC. Like KOC it tends to recur more often when treated by enucleation alone, while adjuvant modalities such as peripheral osteoectomy or marginal resection can reduce or eliminate the recurrence rate.

Unlike KOC in which microscopic diagnosis is relatively simple in most cases, the microscopic diagnosis of GOC can be complicated by the overlap with features of both the less aggressive but far more frequent radicular or dentigerous cysts with mucous metaplasia, as well as with central low-grade MEPCa, which is probably even less frequent than GOC, but as a malignancy is potentially more dangerous.

The question of origin is still unresolved. Although there clearly is a morphologic resemblance to salivary gland in the cystic lining, which was the reason it was first termed sialodontogenic cyst, there seems to be more evidence in favor of an odontogenic origin.

In three cases GOC has been associated with other odontogenic tumors such as KOC (Yoon *et al*, 2006), and ameloblastoma (Gardner *et al*, 1988; Hisatomi *et al*, 2000). Other cases had features such as osteodentin (Koppang *et al*, 1998) and ghost cells (Ramer *et al*, 1997), all of which support an odontogenic origin.

Immunohistochemical studies have also attempted to clarify the lesion's origin. EMA was negative in the glandular structures, an indication against a true glandular epithelial origin (Koppang *et al*, 1998).

The minimal expression of MASPIN in GOC, as opposed to the significantly higher expression in MEPCa is an additional indication against a true glandular origin, in spite of the morphologic resemblance.

Investigation of the cytokeratin profile failed to provide support for either an odontogenic or a sialogenic origin since there were many similarities between

GOC, odontogenic cysts and MEPCa, (Pires *et al*, 2004). The bulk of existing evidence is mostly in favor of an odontogenic origin.

Conclusions and recommendations

In terms of establishing a diagnosis of GOC, it is necessary for the level of awareness to the characteristics of this rare lesion to be raised among oral surgeons, oral and general pathologists.

The proposed detailed microscopic criteria in addition to use of p53 and Ki67 should help the pathologist to arrive at a definitive diagnosis of GOC with a high level of confidence. However, this may not be possible in incisional biopsy material, because of the focal nature of individual microscopic feature within the lining epithelium.

It is recommended that in cases where not all criteria for diagnosis are met in an incisional biopsy, the resemblance to GOC be clearly indicated in the report, and the surgeons be advised to consider this possibility in the plan for the final surgical procedure.

Treatment by enucleation or curettage alone, especially in large and multilocular lesions, carries the highest risk for recurrence. Therefore, more extensive surgical procedure such as peripheral osteoectomy or marginal resection is recommended. Other options such as marsupialization, use of fixation solution or cryosurgery to treat the bony cavity could be introduced, although there is not yet enough evidence of their efficacy to reduce the risk for recurrent disease, mostly since there are only a small number of cases treated this way in the literature.

It is also important that patients diagnosed with GOC be entered in a follow-up regimen, which should last for a minimum of 3 years, preferably for 7 years (Figure 5).

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