Factors influencing the recurrence of keratocysts: monocentric study

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Abstract – Introduction: The purpose of the study was to retrospectively analyse the recurrence rate of odontogenic keratocysts and to identify eventual features of the lesions that may influence recurrence. Material and methods: This was a retrospective study carried out for a period of 3 years. The medical records of patients treated in our institution were analysed to identify all the cases of odontogenic keratocysts. Results: A total of 16 odontogenic keratocysts were recorded. These lesions were treated with simple enucleation with or without adjuvant Carnoy’s solution. The relapse occurred in 4 patients treated with simple enucleation and in none of the patients that underwent enucleation and Carnoy’s solution application. The kind of treatment appeared not to influence recurrence rate at statistical analysis. Conclusions: Odontogenic keratocyst is a lesion with a locally aggressive behavior and a high tendency to relapse. This tendency of recurrence may be greater with syndromic presentation of odontogenic keratocyst, with soft tissue involvement, and with teeth proximity to the lesion. The application of Carnoy’s solution may be useful to minimize recurrence rate in those odontogenic keratocysts with an aggressive clinical behavior and secondly may be used for all the other lesions treated with simple enucleation that experienced relapse.

Introduction

Odontogenic keratocysts (OKCs) are frequent cysts of the jaw that originate either from the dental lamina or from the primordial odontogenic epithelium. These lesions have been described with a locally aggressive behavior and a high tendency to recurrence after treatment [1].

According to the fourth edition of the WHO classification of head and neck tumours, the term keratocystic odontogenic tumour was removed and the definition of odontogenic keratocyst has been reinstated [2].

The OKCs represent the 11% of all the jaw lesions of a similar kind and are frequently associated with Gorlin Goltz syndrome (or nevoid basal cell carcinoma syndrome) [3,4].

This lesions have male predilection and two peaks of presentation, the first during the second to third decades of life and the second during the sixth to seventh ones [5].

OKCs may present as single or multiple lesions that radiologically appear as unilocular or multilocular areas of radiolucency with well-defined borders [6].

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At histopathological analysis OKCs are characterized by five to eight layers of parakeratinized epithelial lining and may present with areas of squamous metaplasia if inflammation in the capsule occurs [7]. Moreover, the epithelium may present budding of the basal layer into the underlying connective tissue with formation of detached microcysts, named daughter cysts [8].

During the years many conservative and aggressive treatments have been proposed to minimize the high rate of recurrence, but none of them has been recognized as the gold standard for this entity [9,10].

The surgical treatment may consist on simple enucleation with or without curettage or marsupialization/decompression, with or without second therapeutic measures, peripheral ostectomy, chemical curettage with Carnoy’s solution, cryotherapy, electrocautery, or resection en bloc or marginal [11].

The recurrence rate described in literature ranges between 5% and 62% [12]; this discrepancy may be related to characteristics of the lesion and the kind of treatment performed.

The aim of the present study was to report and critically analyse our experience about the recurrence rate of odontogenic keratocysts. The specific purpose of this study was
to compare the recurrence rate of OKC treated with 2 different protocols and to identify the characteristics of the lesions that might influence the recurrence.

**Materials and methods**

This retrospective study was conducted to investigate the recurrence rate of odontogenic keratocyst after different surgical treatments.

The population was composed of patients with history of odontogenic keratocyst treated in the Maxillofacial Surgery Unit of the Hospital Santa Maria della Misericordia of Perugia between January 2016 and December 2018.

Inclusion criteria were a history of odontogenic keratocyst, surgical treatment for the disease, availability of preoperative radiological exams, postoperative radiological exams and at least a follow-up period of 6 months. Both syndromic and sporadic odontogenic keratocyst were included in this study. Exclusion criteria were inadequate follow-up period and missing data before or after surgery.

Data regarding age, sex, location of the lesion, syndromic or sporadic presentation, surgical treatment, complications after surgery, follow-up period and recurrence were collected. The clinical and radiological presentations of the OKCs were also analysed. The soft tissue involvement detected by palpation, the vitality test of teeth included into the lesion, the presentation of the cyst in a Gorlin Goltz patient and the anamnesis positive for previous OKCs surgery in the same area were analysed during the clinical exam. At the radiological analysis, the uniloculated or multiloculated presentation, the single or multiple presentation, the cortical bone perforation, the teeth involvement and the localization of the lesion were collected.

All the patients admitted with the preoperative diagnosis of jaw neoformation underwent enucleation of the lesion with curettage. Patients affected by Gorlin-Goltz syndrome or those with a preoperative diagnosis of OKC were treated with lesion enucleation, curettage and Carnoy’s solution. The Carnoy’s solution was applied for 3 minutes using ribbon gauzes in the bone cavity while taking care to protect the adjacent soft tissues. The teeth involved into the lesion were extracted or conserved performing an endodontic treatment followed by apical root resection during the cyst’s surgery. Clinical follow-up every 3 months and radiological follow-up with every 6 months of all the OKCs was performed to early detect the recurrence. The first radiological follow-up consisted in the orthopanoramic exam, while the computerized tomography was used only with the suspect of recurrence.

Statistical analysis was performed using SPSS Statistics® 23 (IBM, Armonk, NY, USA). Descriptive statistics was used to summarize demographic and clinical data. The Fisher’s Exact test was used to investigate the correlation between type of surgical treatment and presence of recurrence. Clinical and radiological factors influencing recurrence were also analysed using the Fisher’s Exact test. Recurrence rate was calculated using the Kaplan-Meier method, from the date of surgery until recurrence or the end of data collection. A \( p \)-value of 0.05 or less was considered statistically significant.

**Results**

This retrospective study included 14 patients treated for 16 (8.2%) odontogenic keratocysts of the 196 cysts treated in our institution between January 2016 and December 2018. None of the cases were excluded according to inclusion and exclusion criteria.

Most of the patients were male \((n = 10; 71.4\%)\) and affected by sporadic OKC \((n = 10; 71.4\%)\). Instead, 4 patients were affected by Gorlin Goltz syndrome and 2 of them was treated 2 times for the multiple occurrence of 2 OKC in 2 different periods of time (Fig. 1) The mean age of patients at first surgical treatment was 58.3 years (ranged from 33 to 74 years); patients with syndromic OKC were considerably younger than those with sporadic OKC with a mean age of 34 and 68 years, respectively (Tab. 1).

All the OKC were described in the mandible, with the posterior right side the most affected (Figs. 2 and 3). 14 of the included lesions presented tooth involvement and proximity to the inferior alveolar nerve. Furthermore, the cortical bone perforation was observed in the 62.5% \((n = 10)\) of OKC at clinical and radiological analyses (Tab. 1).
Most of the patients \((n = 13; 92.9\%)\) received their primary surgical treatment in our unit, while a single patient affected by Gorlin Goltz syndrome referred other 3 surgical treatment performed in another place for the presence of other OKCs in different sites.

A total of 10 OKCs with the preoperative diagnosis of jaw neoformation were treated with simple enucleation and curettage, while 6 OKCs in 4 Gorlin Goltz patients were also treated with Carnoy’s solution.

The concomitant apical root resection of 12 teeth proximal to the OKC was performed, while 28 teeth involved into the lesions were extracted. None of the patients developed postoperative infections and 2 patients treated with enucleation and application of Carnoy’s solution experienced hypoesthesia of the inferior alveolar nerve (Tab. I).

During follow-up, a recurrence rate of 25% was revealed \((n = 4)\) in the group of patients treated with simple enucleation (Tab. I).

The mean time of recurrence were 17.7 months (ranged from 12 to 26 months).

All the patients with lesion recurrence were treated again and Carnoy’s solution was applied. No recurrence of these 4 lesions were observed at 6 months follow-up.

All the recurred lesion presented tooth involvement, proximity to the inferior alveolar nerve and cortical bone perforation, while none of the cases without bone perforation performed in another place for the presence of other OKCs in different sites.

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showed signs of recurrence (Fig. 4; Tab. II). The 2 cases with the OKC next to the resected teeth recurred after 6 and 12 months.

No statistical difference was detected in the OKC recurrence between patients treated with simple enucleation and those dial with Carnoy’s solution \((p = 0.234)\). Moreover, none of the clinical and radiological factors seemed to influence recurrence. Also, the Kaplan-Meier analysis performed to evaluate the recurrence rate between the 2 groups of patients treated with or without Carnoy’s solution did not demonstrate a statistically significant difference \((p = 0.104)\) (Fig. 5).

**Discussion**

The objective of this study was to describe our experience on odontogenic keratocysts and to analyse either the clinical and radiological characteristics of the lesions or the surgical treatments that may influence their recurrence. About surgical treatment, in our experience the use of Carnoy’s solution seems not to influence the recurrence rate with results not statistically significant at Fisher’s Exact test and Kaplan-Meyer analysis. This solution is a chemical cauterization agent used at first as fixative and it is composed by chloroform, absolute ethanol, glacial acetic acid and ferric chloride in different concentrations. The Carnoy’s solution was widely described in literature and proposed as adjuvant treatment after enucleation to reduce the lesion relapse [4,6]. It should promote chemical necrosis of up to 1.5 mm eliminating the epithelial remnants and possible daughter cysts [13]. Some studies favour the careful use of Carnoy’s solution in the areas adjacent to neurovascular bundles because of the risk of neuropathic complications to the inferior alveolar nerve and the lingual nerve. However, these studies lack to descriptive information about the degree of neuropathy and its statistical correlation with surgery. So further clinical studies are required to establish this correlation. In our study, Carnoy’s solution was used only in patients with Gorlin Goltz syndrome in which a preoperative diagnosis of odontogenic keratocyst has been done. This syndrome is an autosomal dominant inherited condition that exhibit many specific features including multiple OKCs [12]. Noy et al. described the recurrence rate of syndromic OKCs compared with sporadic OKCs and observed that there was a 3.4 times increased risk of developing recurrence in patients affected by Gorlin Goltz syndrome independently from the kind of treatment performed [12]. This increased tendency to relapse in syndromic lesions may represent a bias of this study influencing the results. In fact, the efficacy of Carnoy’s solution was tested only in syndromic patients with the preoperative diagnosis of odontogenic keratocyst has been done. This syndrome is an autosomal dominant inherited condition that exhibit many specific features including multiple OKCs [12].

| Clinical factors                  | No. of cases/ tot | No. of cases/ tot recurrence | p-value |
|----------------------------------|-------------------|-----------------------------|---------|
| Soft tissue involvement          | 10/16             | 4/4                         | 0.234   |
| Positive vitality test of teeth  | 32/40             | 4/4                         | 1.000   |
| Gorlin Goltz syndrome            | 4/14              | 0/4                         | 0.234   |
| Previous surgical treatment      | 1/14              | 0/4                         | 1.000   |

| Radiological factors             | No. of cases/ tot | No. of cases/ tot recurrence | p-value |
|----------------------------------|-------------------|-----------------------------|---------|
| Uniloculated lesion              | 10/16             | 2/4                         | 0.604   |
| Single presentation              | 16/16             | 4/4                         | -       |
| Cortical bone perforation        | 10/16             | 4/4                         | 0.234   |
| Teeth involvement                | 14/16             | 4/4                         | 1.000   |

Fig. 4. Bar chart showing the correlation between cortical bone perforation and lesions recurrence.
pattern of recurrence of nonsyndromic OKCs and observed that relapse appeared earlier and frequently for those lesions with bone perforation [14]. A similar finding was earlier described for other aggressive lesion such as ameloblastoma [15] and the authors proposed to resect adjacent soft tissue to prevent recurrence. The rationale for this approach is based on the locally aggressive behaviour of the OKCs in which the epithelium of the cyst can overcomes the basal layer to reach the underlying connective tissue with formation of daughter microcysts [8]. As a type of connective tissue, the periosteum may be reached by the epithelium of the OKCs and predispose to lesion recurrence. The resection of the adjacent periosteum and soft tissues may be proposed for those OKCs with cortical bone perforation [16]. The gingival and mucosal defects may be subsequently fill with a local flap such as a Rehrmann flap or a myomucosal flap for major defects. Also, the use of vascularized osteocutaneous free flaps was described in literature to reconstruct defects occurring after mandibular resection for extensive OKC [17].

In this study a single patient diagnosed with jaw neoformation underwent enucleation of the lesion and apical root resection of the teeth involved into the neoformation; after 12 months the patients presented relapse of the OKC. Cunha et al. observed that OKCs with tooth involvement recurred more frequently and speculated that the epithelium of the cystic capsule may insinuate between the dental roots causing relapse of the lesions [18]. For this reason, apical root resection might be avoided with a preoperative diagnosis of OKCs to minimize recurrence of the lesions due to the involvement of dental roots by the epithelium of the cysts and tooth extraction may be preferred [19].

Due to the high recurrence rate is really important to obtain a precise preoperative diagnosis of OKC to establish an appropriate surgical plan. When possible, the association between clinical and radiographic features to cytological and immunohistochemical ones may permit a more accurate diagnosis before surgical treatment. Cytological and immunohistochemical exams are little-used in the diagnosis of deep intrabony lesions, but these techniques can be useful in the preoperative diagnosis of superficial lesions with cortical bone thinning or perforation. Few studies have employed fine needle aspiration biopsy (FNAB) in the preoperative diagnosis of OKC and this technique is still rarely used [5,20]. August et al. described a modified FNAB technique by establishing contact between the needle bevel and the bony wall of the cystic lesion in tangential fashion to improve the sampling of lining epithelial cells and increase the diagnostic accuracy of FNAB [20]. Also, the incisional biopsy may be used to obtain a pretreatment diagnosis for intraosseous lesion such as odontogenic keratocysts. However, some authors affirmed that this exam may be not accurate when areas of inflammation occurs in which the epithelial lining displayed a squamous-type metaplasia that precluded the diagnosis of OKCs if that was the only area of epithelium sampled [21,22]. At last, some authors recently described the use of the cell block technique to diagnose OKCs [23,24]. This technique is able to facilitate an

Fig. 5. Kaplan-Meyer test for the recurrence of OKCs with simple enucleation or enucleation with Carnoy’s solution application.
accurate diagnosis by allowing the identification of the cellular details preserving cell morphology and tissue organization [23] (Fig. 6).

Conclusions

Despite efforts to find a surgical treatment able to minimize recurrence rate of OKCs, this represents an unsolved problem yet. Factors such as the cortical bone erosion with soft tissue involvement, the teeth involvement and the syndromic presentation of the OKCs may influence the recurrence, but more studies are requested to confirm this trend. For this reason, an accurate diagnosis with the screening of Gorlin Goltz syndrome, the execution of complete clinical and radiological exams, and if indicated cytological and immunohistochemical analysis are mandatory to plan the best surgical treatment for each single case. The use of FNAB, incisional biopsy and cell block technique may be really helpful to early diagnose OKCs and to perform more conservative treatment for those lesions without teeth involvement and cortical bone perforation, or more aggressive surgical plan for OKCs with periosteum involvement, up to justify jaw resection for recurred lesions with high aggressiveness. The use of Carnoy’s solution may be an adjuvant treatment act to reduce OKC relapse for those lesions preoperatively diagnosed or for OKCs treated with simple enucleation that experienced recurrence.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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