Conservative Management of a Large Odontogenic Keratocyst: Report of a Case and Review of the Literature

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Case Presentation

A 30-year-old man was referred to the Dental Department because of a hard, tender swelling of the left cheek. The patient reported that the swelling had gradually increased in size over a period of 2 months but denied any neurosensory deficit associated with the left inferior alveolar nerve. His past medical history and his general physical examination were unremarkable: in particular, the patient did not present any skin lesions suggestive of basal cell nevus syndrome. Laboratory data on admission were within the normal limits. Head and neck examination showed left facial swelling along with an expanded and indurate mandibular left buccal vestibule. There was a small discharge of purulent fluid from an opening in the oral mucosa just behind the mandibular left second molar. The teeth on the left side of the mandible presented some carious lesions and the second left molar was necrotic with grade II mobility.

A panoramic radiograph showed a “soap-bubble” appearance of the mandible, extending from the neck of the condyle to the mandibular left first molar area (Fig 1).

A computed tomography (CT) scan showed the extension of the lesion that involved the ramus, angle, and body of the mandible. Perforation of lateral cortical plates and a thinning of the medial cortical plate were observed (Fig 2).

The patient was hospitalized and, under a short general anesthesia, the lesion was marsupialized via the buccal sulcus and the roof of the cyst was removed and sent out for histology. Meanwhile, the mandibular left second molar was extracted because it was mobile and necrotic. Amoxicillin (1 g twice a day) was prescribed for 7 days after the surgery. The first left molar, vital, received a single filling.

Histopathology revealed an odontogenic keratocyst (OKC) type 1 according to Forssell classification1 (Fig 3).

Review of Treatment Modalities and Treatment Recommendations

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The OKC has been the subject of great interest since Philipsen introduced the term in 1956.2 Investigations continue into the lesion’s pathologic classification, diagnosis, and biologic behavior. Considerable controversy exists regarding the proper management of these lesions. There are proponents of “conservative” or “aggressive” methods of treatment.

A number of clinicians favor “conservative” therapy, while others advocate more “aggressive” forms of treatment. Meiselman et al3 consider conservative therapies to include “enucleation, curettage, and marsupialization.” Williams et al4 define aggressive treatment as “that which is used in addition to enucleation, and includes curettage (mechanical, physical, and/or chemical) and/or resection with or without loss of jaw continuity.” The use of standardized surgical terminology for methods of excision of bony lesions is paramount to the discussion. Recommended terminology includes enucleation, curettage, decompression, marsupialization, resection with and without continuity defect, and disarticulation. The statement “one surgeon’s ‘aggressive’ may be another surgeon’s ‘conservative’” underscores the importance of abandoning the use of ill-defined terms.5

To enucleate is “to remove whole or clean, as a tumor from its envelope.”6 Curettage is defined as “the removal of growths or other material from the wall of a cavity . . . as with a curette.”6 Decompression is “a surgical operation for relief of pressure in a body compartment.”6 Marsupialization is “the cre-
ration of a pouch: applied especially to surgical exteriorization of a cyst by resection of the anterior wall and suturing of the cut edges of the remaining cyst to the adjacent edges of the skin, thereby establishing a pouch of what was formerly an enclosed cyst.6

Historically, the following modalities have been employed in the management of OKC: decompression alone, marsupialization alone, enucleation alone, enucleation with excision of overlying oral mucosa/soft tissue, enucleation with adjuvant therapies (mechanical curettage, chemical [Carnoy’s solution] curettage, cryosurgery), decompression followed by enucleation with or without curettage/adjuvant therapies, resection without continuity defect, resection with continuity defect, and resection with disarticulation.

Beginning with Pindborg and Hansen’s initial report in 1963,7 clinicians have documented a wide range of recurrence rates (0% to 62.5%) associated with the various treatment modalities.8-36 Confounding these results further may be variations in both sample size and length of follow-up. This was the finding of Blanas et al,37 who attempted to systematically evaluate the various treatment methods by applying specific inclusion criteria and standards to evaluate the scientific literature. The tremendous degree of variability among the studies (all retrospective case series) precluded any quantitative analysis, prompting a call for prospective studies.

The OKC is thought to recur by the following mechanisms:
1. Incomplete removal/residual cystic lesion gives rise to new cyst formation (microcysts [daughter-cysts] or epithelial islands in the wall of the original cyst remain in the surrounding bone or soft tissue).
2. New keratocysts develop from epithelial offshoots of the basal layer of the oral epithelium.56,58
3. Continuous formation of new cysts in patients with basal cell nevus syndrome.

Enucleation with and without various adjuncts has been utilized for many years. Given our knowledge of recurrence rates as high as 62.5%7 with simple enucleation or cystectomy, this is no longer an acceptable treatment modality. Many clinicians consider enucleation and curettage the minimal requirement. As was shown in the earliest studies,15,53,59 complete eradication of the cystic lesion is necessary to decrease or eliminate recurrences. Taking this a step further, Stoelinga40 advocated resection of overlying oral mucosa. Many clinicians have cited difficulty in the enucleation and curettage of keratocysts with or without cortical perforation as adherence of the keratocyst’s thin lining to adjacent bone or soft tissues may result in incomplete enucleation of the lesion.9,10,12,14,16,17,35,36,41,42 In such cases, several authors advise excision of soft tissue in continuity with the cystic lesion.35,56,40,41

Regarding curettage, clinicians have advocated mechanical techniques (hand, rotary) alone or in combination with a chemical solution (Carnoy’s)35,40 or cryosurgical agents (liquid nitrogen).20,43-45 While depth of mechanical curettage is difficult to quantify, Voorsmit35 has shown the mean depth of bone penetration of Carnoy’s solution with respect to length of application (1.54 mm after 5 minutes).

The techniques of decompression and marsupialization have appeared in the scientific literature for more than 30 years.14,22,25,29,37,46-48 The following distinction in terminology is well-stated by Tucker et al.48: “Decompression and marsupialization, although serving the same function and relying on the same basic principle of bone regeneration, are two entirely different techniques. Although both have the purpose of relieving the pressure within the cystic cavity and allowing new bone to fill the defect, marsupialization is a one-stage operation; decompression is a two-stage procedure.” Marsupialization is the creation of a pouch by suturing the cut edges of the cyst wall to the contiguous soft tissue. Decompression requires the placement of a drainage tube, followed by (delayed) enucleation of the residual cyst.

Decompression without subsequent enucleation is seldom indicated, except perhaps in cases of advanced patient age, compromised medical status, or desire for palliation only.35

Advocates of decompression and marsupialization22,25,29,46,48 argue that by relieving the pressure within the cystic cavity, one can achieve the following results: a decrease in lesion size, new bone fill behind as lesional size decreases, and minimization of extent of secondary surgery. Furthermore, it has been noted after decompression and marsupialization that the cyst lining undergoes histologic changes resulting in eventual replacement by oral epithelium.22 Several studies have addressed the favorable relationship between inflammation and the keratocyst.49-51 The presence of inflammation is thought to change the biologic behavior of the keratocyst to a less aggressive form. There is evidence that the keratocyst lining is transformed into nonkeratinizing epithelium. This is one theory proposed for the success of these modalities.

Another mechanism proposed for the success of decompression and marsupialization is the immunohistochemical finding of decreased interleukin 1α levels.52 Interleukin-1α is thought by some to play a crucial role in the expansion of keratocysts. Another may be the disappearance of cytokeratin-10 from the cyst epithelium.49 The expression of cytokeratin is thought to be of value in the diagnosis of OKC.49

Marsupialization, first described by Partsch in 1892,35 remains controversial. As with the other surgical modalities used, reports vary regarding the recurrence observed with this treatment option for this case.22,25,29,35,46,47 Published recurrence rates range from 0%29,35,46,47 to 100%.35 Several studies have found no difference in recurrence rates when comparing marsupialization to enucleation.7,10,50

One disadvantage of marsupialization is the compliance required of the patient for a prolonged period of time. Failure of the procedure to eradicate the lesion will require subsequent enucleation or resection.

Success of a given treatment requires the elimination of the lesion clinically and histologically. The benefit of histopathologic examination of an entire specimen rather than a single biopsy must not be underestimated. Multiple biopsies within a lesion at the time of presentation may reveal conflicting results. While thought to be rare, possible ameloblastomatous9,53,54 or malignant transformation53,55,73 may be present at the time of initial treatment and may progress undetected during the prolonged decompression or marsupialization period. Therefore, with either decompression or marsupialization, there may be a missed diagnosis at the time of initial treatment, resulting in a catastrophic outcome. The presence of infection may affect the accuracy of diagnosis. Inflammation may cloud histologic analysis. It is reasonable that incisal biopsies of large keratocysts be sam-
bled away from inflamed sites due to the risk of sampling non-diagnostic tissue.74

Enucleation/curettage has the advantage over marsupialization of providing a complete specimen for histopathologic analysis. The ability of the OKC to exhibit destructive growth and invade adjacent structures has been documented.75,76 The keratocyst frequently perforates adjacent cortical bone and may lie partially within soft tissue.10,27 Recurrences within soft tissue12,32,77,78 and bone grafts27,79 have been reported.

Marsupialization may be technically more difficult due to size and extent of the lesion. In order to properly decompress or marsupialize the OKC, it is necessary to surgically enter and join each cystic area. A large multilocular lesion of the ascending ramus may not only be difficult to fully access, but one or more small extensions may be missed, leading to persistence of residual lesion.

In analyzing case series of any of the proposed treatment modalities, several factors must be considered. Are the lesions unicellular or multilocular, and are they evaluated separately? Are the lesions recurrent? Is there evidence of cortical perforation and/or soft tissue involvement? Are lesions of basal cell nevus syndrome included? Are the follow-up periods long enough to establish a rate of recurrence?

Despite its classification as a benign cystic lesion,80 the aggressive nature of the OKC continues to generate discussion among clinicians and investigators. It has been suggested that the keratocyst is a benign neoplasm rather than a nonneoplastic cyst.27,75,81-85 Investigators cite evidence of high mitotic activity, high epithelial turnover rate,75,86 prostaglandin-induced bone resorption,34,87,88 and active collagenases in the fibrous tissue lining.89 Shear, who in 1960 and 1961 helped establish the histologic criteria for the keratocyst, initially stated that the keratocyst was “simple in behavior” and would not recur if enucleated.90 Subsequent clinical and laboratory research, however, has led to a different conclusion. In 2002, Shear published a 3-part series that offered support for the keratocyst to be designated a benign neoplasm.83-85 Upon further review of immunocytochemical (epidermal growth factor and transforming growth factor reactivity) and genetic studies (loss of tumor suppressor genes), Shear found additional support for such an idea.

While the debate continues, many clinicians agree that the goals of treatment should include eradication of the pathologic lesion, while minimizing risk of recurrence and patient morbidity. One must weigh the potential rate of recurrence of a particular therapy with the potential morbidity and functional outcome for the patient.

In the selection of the most appropriate treatment for OKC, one must take into consideration both patient factors and lesion characteristics. Patient factors include age and general medical condition. Coexistence of the nevoid basal cell carcinoma syndrome (first described in 1960 by Gorlin and Goltz) may affect one’s approach to treatment, as recurrence rates are noted to be higher than in nonsyndromic patients.25 Lesion characteristics include size, location, extent, presence of cortical perforation, and/or involvement of soft tissue and adjacent structures. The recurrent nature of a lesion may also alter the approach to its retreatment. Many advocate a more aggressive approach to a recurrent keratocyst.

Some investigators have found higher recurrence rates when using enucleation and curettage for lesions of the mandibular angle and ramus,24 especially multilocular lesions.15 This may be due to the difficult access in this region, and the inability to adequately instrument blindly. Still others have found that cyst location (body versus ramus) may have an effect on the success of marsupialization.25

In lesions of the mandibular symphysis, body, and third molar regions, enucleation and curettage would appear to be the most common method of treatment. Lesions of the ascending ramus, if extensive in size, may be more difficult to successfully treat in this manner. Likewise, posterior maxillary lesions of significant size can be problematic. Various techniques have been proposed to address this concern. Some clinicians29,46,47,91 have successfully utilized marsupialization or decompression to eliminate or significantly decrease the size of lesions prior to enucleation and curettage. The experience at this institution with marsupialization or decompression for the large multilocular/multicystic keratocyst has not been uniformly successful.

There continues to be controversy specifically regarding the management of the large, multilocular/multicystic keratocyst, with cortical perforation and extension into soft tissue.10,14

Upon initial evaluation, a thorough history and physical exam (including features of basal cell nevus syndrome) should be performed. Diagnostic imaging should include panoramic and periapical radiographs. The appearance of this large, multicystic mandibular lesion on the panoramic radiograph warrants further radiographic evaluation. CT (3-dimensional is preferred) scanning and/or magnetic resonance imaging (MRI) should be obtained to determine the hard and soft tissue extent of this lesion. Differential diagnosis should include OKC, dentigerous cyst, and ameloblastoma. Aspiration of the lesion followed by several incisional biopsies is appropriate for this case. The presence of infection may complicate the course of therapy. The biopsy procedure may be both diagno-
tic and therapeutic in terms of facilitating drainage of purulent material and aiding resolution of the concurrent infectious process. Of course, antibiotics should be initiated. After the establishment of a histologic diagnosis of OKC, a surgical treatment plan must be formulated.

This lesion appears to be a large, multilocular radiolucency of the left mandible involving the entire angle and ascending ramus (with obliteration of the coronoid process) and extending into the subcondylar/condylar region. There is radiographic evidence of inferior border perforation as well as lateral cortical perforation adjacent to the temporalis muscle and infratemporal fossa. The extent of the lesion within soft tissue is unclear given the single cut presented from the axial CT. A 3-dimensional CT representation and MRI are imperative in the treatment planning of this case.

Decompression with subsequent enucleation would require compliance of the patient for a period of more than a year due to the size of the lesion. With decompression, the surgeon is faced with difficult transoral access to the ascending ramus and subcondylar region in order to enter each cystic cavity. The strong possibility exists that not all bony septae/loculations will be successfully entered. One may not be able to sample tissue from as many locations as may be necessary for a full analysis. Such a lesion could contain areas of ameloblastoma, or areas displaying dysplasia or carcinoma. While either transformation is rare, it is a distinct possibility. In the event that this lesion exhibits malignant features, a delay in diagnosis or a lack of true diagnosis will result in a compromised outcome if decompression/enucleation is used.

What of the cortical perforations? Will there be residual lesion or daughter cysts adherent to soft tissue or periosteum at subsequent enucleation? The scientific literature to date has not examined the effects of marsupialization or decompression on those lesions extending outside the confines of cortical bone. Will these regress in the same fashion as those entirely within cortical bone? Pogrel et al describe 10 cases of keratocyst that responded to either decompression or marsupialization. The longest time to resolution was 19 months. Success was based on clinical and radiographic resolution of lesions. Immunohistochemical markers for keratin were inconclusive. The follow-up period was quite short. Given the wide range of resolution and recurrence rates, there does not appear to be a consensus regarding this treatment option. For these reasons, as well as the lack of a surgical specimen for histopathologic review, marsupialization is not advisable as a treatment option for this case. There is a need for prospective investigation of the large, multilocular keratocyst, with particular study of those involving cortical perforation. Long-term (>10 to 20 years) follow-up is essential for an adequate assessment the recurrence rates of keratocysts.

Given the clinical and radiographic extent of this lesion, the only realistic treatment option, given the imaging offered, is continuity resection with disarticulation and excision of adjacent soft tissue.

Due to this lesion’s size, multilocularity, and extension to adjacent tissue, a continuity resection to the left second bicuspid with condylar disarticulation is appropriate. After resolution of the acute inflammatory process, resection should be performed. A combined extraoral/transoral approach will provide good surgical access. The inferior alveolar nerve within the lesion will be resected with the specimen, and a sural nerve graft may be used for immediate reconstruction. Overlying soft tissue, including involved oral mucosa, temporalis, and masseter muscle, should be excised with the specimen. Soft tissue margins should be assessed with frozen section. A reconstruction plate with condylar prosthesis should be placed. The entire specimen should be histopathologically examined to confirm the diagnosis and exclude malignancy. Future reconstruction should be planned and carried out using an extraoral approach. The patient will continue in follow-up indefinitely to monitor for recurrence.

Not knowing the treatment method utilized in this case or the length of follow-up, one cannot accurately assess the success of therapy. Is the follow-up period for recurrence long enough to document a cure?

**Subsequent Course**

Iodoform gauze was packed and left inside the cavity for 8 days in order to epithelialize it. After the removal of this packing, the patient was instructed to wash out the cavity 4 times a day (after meals and before bedtime) with warm saline solution using a 30-mL syringe.

The cavity slowly decreased in size, and 4 months later, the panoramic radiograph showed bone remodeling toward a normal mandibular pattern (Fig 4).

Ten months after surgery, the patient was hospitalized for enucleation of the remaining cystic lining. In the operating theater, under general anesthesia, a mucoperiosteal flap was reflected and the cyst was completely removed. After a thorough cleanup of the cystic cavity with saline solution, the flap was repositioned and sutured. No drainage was necessary. The postoperative course was uneventful and the patient was discharged 2 days later. Again, amoxicillin (1 g twice a day) was prescribed for 7 days after the surgery. The histology revealed a stratified, nonkeratinized squamous epithelium (Fig 5).
After 6 years of follow-up, there is no evidence of recurrence and radiographs showed that the cystic area had totally recovered: the contours of the mandible are now almost symmetrical (Fig 6).

Discussion

The OKC was first identified by Philipsen in 1956 and was more recently defined in 1990 by the World Health Organization as a cyst "characterized by a thin fibrous capsule and a lining of keratinised stratified squamous epithelium, usually about five to eight cells in thickness and generally without rete pegs."2

Even if OKC cannot really be considered a malignancy, some of its characteristics make this pathology extremely serious. In fact, keratocysts tend to recur, can reach considerable dimensions, and can arise close to delicate and important anatomical structures (ie, alveolar nerve). All these characteristics had suggested, in the past, that an aggressive surgical approach should be followed in order to eradicate these cysts completely. Such radical behavior might result in severe mutilation, so, for this reason, it is not always advisable.92,93 Furthermore, its clinical and radiographic features rarely allow the making of a correct diagnosis, thus being a challenge for the oral surgeon.94

In the past decade, some conservative surgical approaches (lateral cystectomy, enucleation, cryosurgery, decompression, and marsupialization) have been proposed in order to reduce the negative effects of an aggressive surgery and, thus, respecting the delicate anatomical structure of the jaws, giving the patient a better quality of life.22,24

According to literature, OKCs have an incidence rate of about 12% to 14% of all odontogenic cysts with 2 peaks around the ages of 30 and 60 and seem to be more frequent in males (M/F 2:1). From 60% to 80% of reported cases occur in the mandible, mainly found in the molar, angle, and ramus area. Usually a localized asymptomatic swelling is the most common symptom; spontaneous drainage of the cyst into the oral cavity and teeth mobility are also common. Nasal obstruction, paresthesia, and root erosion are more rare symptoms. Some reports underline that OKCs can undergo malignant transformation.8,11,45,95,96
Radiographic appearance of OKCs is an unilocular or a multilocular radiolucency with scalloped and well-defined margins, mainly located in the aforementioned area of the mandible. Because OKC can be associated with the crown of an included tooth, the cyst must be distinguished from a dentigerous cyst. Other cystic and neoplastic diseases, such as traumatic bone cyst, lateral periodontal cyst, central giant cell granuloma, fissural cysts, minimally calcifying odontogenic cyst, radicular cyst, arteriovenous malformation, benign bone tumors, ameloblastoma, adenomatoid odontogenic tumor, ameloblastic fibroma and plasmacitoma, can present with the same radiologic features.23,97,98

Even if radiology, together with clinical features, is indicative of OKCs, a definite diagnosis cannot be made without histology. Recently, a study conducted on 18 OKCs showed that fine-needle aspiration biopsy (FNAB) together with immunocytochemistry for cytokeratin-10 could be a useful diagnostic tool.43

Many other biological markers, such as Ki-67, nucleolar organizer regions (AgNORs), proliferating cell nuclear antigen (PCNA), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), and p53, which are still being studied to clarify the pathogenesis (dental lamina seems to be involved) and the possible relation of OKC with benign tumors, might help to make a more reliable diagnosis and to identify the cysts that have a malignant behavior in order to perform an aggressive surgery and a more careful follow-up. Unfortunately, some of these markers may even be misleading if inflammation is present.50,83,85

Blanas et al, in reviewing the possible treatments of OKCs, point out 5 ways of treating OKCs: simple curettage, enucleation (intact shelling with or without the use of Carnoy’s solution or cryotherapy), radical enucleation, marsupialization, and resection (marginal or segmental).57

Based on the high rate of recurrence, most authors advocate radical enucleation for small unilocular keratocysts and suggest resection and bone grafting for very large lesions. But there is a general agreement that complete removal of large multilocular OKCs of the mandible ramus may be difficult because of the possibility that remnants of cystic tissue or that so-called satellite microcysts may be left behind. The involvement of the condylar process of the mandible may require even a disarticulation and then reconstruction with bone grafts causing aesthetic and functional damages that, especially among young patients, could give the patient a poor quality of life.25,45,95

It has also been suggested that the mucoperiosteal overlying areas of cortical perforation should be removed and that marsupialization should not be the treatment of choice for large multilocular OKCs because pathologic epithelium, which may contain developing microcysts, may be left in situ.1,8

Advocates of conservative management of large multilocular OKCs outline some technical difficulties in attempting the complete enucleation: the limited access to the depth of the mandible, the possibility that rapid bone healing over a residual keratinizing cyst lining may trap cells deep within the cavity leading to multiple recurrences, and severe aesthetic and functional impairments that can follow an aggressive surgery. It seems wise therefore, in such cases where enucleation of the lining is thought difficult, to allow natural healing of the cyst cavity. This will make the decompression push any residual fragments toward the bony surface, so that subsequent cystectomy could be easier, and should a recurrence occur, it is likely to be superficial.99

Some recent studies on conservative management of OKCs report that decompression of cysts followed by secondary enucleation yields results comparable to those obtained with more extensive surgery: no statistical differences in the recurrences were observed, no postoperative complications were noted and, in some cases, marsupialization caused the complete regression of the cyst. Furthermore, histology and biological changes happened after marsupialization: a nonkeratinized squamous epithelium was observed in many cases and a decrease in interleukin-1α and Ki-67 was detected that could be the biological cause of the decrease in volume of the marsupialized cysts and the diminished epithelial cell proliferation.52,24,52 In fact, interleukin-1α seems to be able to promote the bone resorption and the proliferation of epithelial cells.52

In line with the above-mentioned studies, we found, at the time of the subsequent cystectomy, a considerable decrease of the cyst dimensions, a thickening of the cyst wall, which made removal easier, and histology examination revealed a normal nonkeratinized epithelium.

In conclusion, in light of the previous clinical trials, this case report outlines that large multilocular keratocysts might be treated with a conservative approach, the only disadvantages being the extended therapeutic time and the frequent and recurrent medications.22,24 Extensive resection of the mandible with its attendant morbidity may be too radical for large OKCs and even an overtreatment. Radical surgery for OKCs should be, of course, reserved for those cysts that have undergone carcinomatous transformation. In any case, clinical and radiographic follow-up is mandatory for years after surgery, because recurrence of this lesion may occur even years later.
References

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