MAXILLOFACIAL SURGERY

ODONTOGENIC KERATOCYST OF THE MANDIBLE: A COMBINED INTRA/EXTRA- ORAL APPROACH

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Introduction: An odontogenic keratocyst (OKC) of the mandible is a benign intraosseus lesion of odontogenic origin characterized by a high recurrence rate. In this case report, we highlight the challenging diagnosis and propose a potential treatment for an extensive OKC with lingual expansion.

Case presentation: A 26-year-old male with an OKC in the ramus of the right mandible near the second and third molars was treated by a combined intra/ extra- oral approach. A reconstruction plate was adapted and fixed by extra-oral submandibular access, followed by intra/extra-orally executed enucleation.

Discussion: The adaptation and fixation of the reconstruction plate aims to avoid pathological fractures of the mandible when executing enucleation. No Carnoy's solution or other additional techniques were applied to restrict recurrence.

Conclusion: Future research and rigorous follow-up are necessary to determine whether this technique has an acceptable recurrence rate while guaranteeing mandibular continuity.

Keywords: Odontogenic keratocyst, mandible, WHO classification, treatment, intra/extra-oral approach

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1. Introduction

Odontogenic keratocysts (OKCs) of the mandible have been of interest since first presented by Philipsen in 1956 [1,17]. OKCs are considered to be benign intraosseous lesions of odontogenic origin that arise from dental lamina remnants. The lesions are characterized by a tendency to invade adjacent tissues and a relatively high recurrence rate. The potential aggressiveness of OKCs is reflected by their potential to extend into soft tissues and bone. In contrast to ameloblastomas, OKCs cause bone destruction but do not invade through an intact periosteum [1,33]. This was questioned by Stoelinga, who described a few rare instances of keratocysts with soft tissue penetrance [2].

OKCs exhibit characteristics of both cysts and benign tumors and were reclassified as odontogenic tumors by the World Health Organization (WHO) in their 2005 Classification of Head and Neck Tumors. In the 2017 classification, the WHO re- categorized the keratocystic odontogenic tumor into the "cyst" category, and the term "odontogenic keratocyst" has been used since. According to the WHO, OKCs are not necessarily neoplastic and there is not enough evidence for using the term keratocystic odontogenic tumor. Furthermore, OKCs do not cause metastases or lymph node invasion, and do not form tumoral masses [3]. The reclassification could lead to confusion and decreased alertness concerning this lesion. According to Stoelinga, this reclassification to OKC denies the potential of this benign but aggressive tumor [3, 36]. When consulting the literature, one must be aware of the different appellations. OKC has a broad age predominance, with a peak incidence in the 2nd-3th decades. In addition, the incidence is higher in male patients, with a male to female ratio of 3:1 [4]. Presentation occurs twice as often in the mandible (70-75%) as in the maxilla. The posterior body and ascending ramus of the mandible are typical locations. However, OKCs can also occur in the dentate area of the mandible or maxilla, mimicking ordinary odontogenic cysts. Signs and symptoms can be subtle, but the typical presentation is pain, swelling, infection, and cellulitis [1,4,6,12]. OKCs are often asymptomatic, probably because they grow in the mesiodistal direction into the intramedullary space, with little cortical expansion [9, 21]. A third of the cases will be related



Figure 1. Panoramic radiograph of the lower jaw depicting a large cystic mass in the right mandible.

to an unerupted tooth; the relationship between OKCs and impacted third molars is 10-15%. In addition, growing OKCs can push away associated teeth [23,24]. OKCs represent approximately 10% of all cysts of the jaw. They are frequently discovered incidentally by radiographic examination. Gorlin Goltz syndrome has to be considered if a patient presents with multiple OKCs. This is an autosomal dominant multisystem disease that leads to multiple OKCs, as well as several nevoid basal cell carcinomas, palmar or plantar pits, calcification of falx cerebri, and skeletal abnormalities. Gorlin Goltz syndrome is associated with mutations in the PTCH gene situated on 9q22.3-q31, with described mutation rates of 80-90%. This PTCH gene is crucial in the Hedgehog pathway, which is the key regulator of embryonic development, controlling cell proliferation. Multiple authors suggest that the PTCH gene is also involved in non-syndromal OKC pathogenesis. With advances in molecular and genetic research, the pathogenesis of OKC is being elucidated [1,7,8,16,19,20].

On radiography, the OKC presents itself as a welldefined radiolucent area and may be unilocular or multilocular [6,9]. Specific clinical and radiographic characteristics that point to a certain diagnosis pre-operatively are lacking. Histologically, an OKC is characterized by a lining of parakeratinizedstratified squamous epithelium, 6-10 layers lacking rete ridges [7,8]. The best treatment for an OKC of the mandible is still a matter of debate, as diagnosis is not straightforward. With this case report, we demonstrate the ambiguity in diagnosis and existing treatment modalities and propose treatment for a large OKC in the right mandible with lingual expansion.

2. Case presentation

A 26-year-old Caucasian male consulted the dentist for an aggravating pain in the right mandible region

that started 1 week prior. He did not experience swelling, but over a few days he experienced a bad taste. He had no relevant medical history. A panoramic radiograph (Fig. 1) showed a large radiolucent lesion in the ramus of the right mandible. The patient was referred to the Department of Oral and Maxillofacial Surgery for further investigation.

Clinical examination did not reveal abnormalities. No regional lymph nodes were palpable and intra-oral examination revealed no swelling. Cone beam computed tomography (Fig. 2) showed an expansive, well-demarcated, unilocular cystic lesion longitudinally in the right mandible near the second molar and closely adhering to the third unerupted molar. The lesion had a sclerotic rim but caused thinning of the lingual cortex of the mandible with destruction of the cortex at the medial and caudal edge of the mandible. Peri-apical resorption was apparent lateral and posterior to the apex of the second mandibular molar with destruction of the two roots. Neither calcification nor a periosteal reaction were identifiable.

The differential diagnosis consisted of OKC, ameloblastoma, dentigerous cyst, or radicular cyst. Clinically, these lesions can be indistinguishable, but on imaging they each have typical characteristics. An OKC can be a unilocular or multilocular lesion with few septa and minimal buccolingual expansion. An ameloblastoma typically presents as a multilocular lesion with root resorption and high tendency for buccolingual expansion. A dentigerous cyst will present as a unilocular cyst around the crown of an impacted tooth with possible buccolingual expansion and without septa. Lastly, a radicular/ inflammatory cyst will present as a unilocular lesion connected to the apex of a non-vital tooth. Additional MRI was considered necessary, as the literature has shown that it can narrow the proposed differential diagnosis [1,24].

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Figure 2. Cone beam computed tomography (a) and 3D volume rendering (b) of the right mandible showing a unilocular cystic mass (42 mm x 37 mm). The green line indicates the inferior alveolar nerve channel

On MRI (Fig. 3), the lesion had homogenous high signal intensity on T2-weighted imaging, low signal intensity on T1-weighted imaging, and homogenous enhancement of the cyst wall after administration of intravenous gadolinium. These characteristics were more suggestive of a benign odontogenic cyst rather than an OKC because of the lack of high intensity on T1-weighted imaging before contrast administration, correlating with ortho/parakeratin or hemorrhage in keratocysts. An ultrasound-guided fine needle biopsy was performed, which was suggestive of an inflammatory follicular or radicular cyst, rather than a keratocyst or ameloblastoma.

Based on the radiological findings, the history of the patient, the clinical findings, and the fine needle biopsy results, a provisional diagnosis of radicular/ inflammatory odontogenic cyst was determined. Two weeks later, surgery was performed under general anesthesia. First, a submandibular neck incision (10 cm) was made, followed by dissection and local excision of the enlarged submandibular lymph nodes. The periosteum was incised over the mandible inferior edge and the mental foramen located. A Martin 2.3 plate was adapted and fixated with 7-9 mm screws (Fig. 4). Subsequently, elements 47 and 48 were extracted after preparation of a buccolingual mucoperiosteal flap. Via combined intra/extra-oral access, the cystic mass was exposed. A local posterior gingival resection was performed by intra-oral access. The inferior alveolar nerve was released of extensive adhesions over 4 cm without causing a continuity defect. Local bone trepanation was performed to facilitate enucleation while safeguarding bony continuity of the lower border. The surgeons did not apply Carnoy's solution because of the location of the inferior alveolar nerve and the potential neurotoxicity. After flushing, achieving hemostasis, and applying a tetracycline suspension in the intramandibular cavity, intra-oral suturing was performed. The submandibular incision was closed

after placing a drain. A postoperative panoramic radiograph showed adequate positioning of the reconstruction plate at the lower border of the right mandible (Fig. 5).

One week after the procedure, the pathology analysis was complete. The microscopic characteristics of the H&E stained section showed Malpighian epithelium with marked peripheral palisading of the stratum basale. Parakeratosis and orthokeratosis were present with characteristic corrugations of the superficial layer. Some epithelial neutrophilic granulocytes were present and part of the cystic wall



Figure 3. Magnetic resonance imaging. (a) T2-weighted imaging showing homogenous high signal intensity.

(b) T1-weighted imaging before and

(c) after administration of gadolinium, showing low signal intensity and homogenous enhancement of the cyst wall.



Figure 4. Peri-operative images. (a) Removed cystic mass and (b) plate osteosynthesis of the right mandible.

was replaced by inflammatory granulation tissue (Fig. 6). Taken together, these findings confirmed the diagnosis of OKC.

Rigorous follow-up was organized with a panoramic radiograph, cephalometric X-ray, and cone beam computed tomography after 6 months, showing no recurrence. The cone beam computed tomography showed a favorable ossifying pattern (Fig. 7). Anamnesis and clinical examination indicated a favorable healing process (Fig. 8).

3. Discussion

The OKC is an expansive, solitary, mostly unilocular (approximately 80% of cases) jaw lesion thought to arise from remnants of the dental lamina. The active epithelial lining and high proliferation rate reflect a potentially aggressive growth pattern. There is a high recurrence rate, between 25 and 60%, linked to the dental lamina origin and its epithelial islands. Epithelial islands, or micro cysts, can be found in the overlying mucosa in almost 50% of cases. Research on recurrent OKCs has shown that epithelial islands or micro cysts are present in almost 100% of recurrent cases [37]. The high recurrence rate is

attributed to the parakeratotic character of OKCs [8-10]. Most cases of recurrence present within 5 years of treatment, but recurrence after more than 10 years has been described. Higher recurrence rates have been reported with multilocular lesions and in patients with Gorlin Goltz syndrome [8-10,14,18,25]. Our patient consulted with aggravating pain in the right mandible region and a bad taste. The bad taste was probably caused by a fistula between the lesion and the oral cavity, through which keratin could enter the mouth. Panoramic radiography is helpful in the preliminary assessment, as an OKC will present as a defined radiolucent lesion, mostly unilocular, with smooth and corticated margins [1,3]. Panoramic radiography will show the possible relationship with (impacted) teeth. Cone beam CT should be the next step, as it is considered superior to panoramic radiography in differentiating OKCs from other lesions and showing other features, such as extension, bony changes in the cortical plates, and internal density. It has a high spatial resolution but poor contrast resolution, which is not suitable for soft tissue discrimination [1]. Cortical expansion is not as frequent in OKCs and will occur more often



Figure 5. Postoperative panoramic radiograph after removal of the cystic mass and plate osteosynthesis at the lower border of the the right mandible.



Figure 6. Biopsy of the cystic mandibular mass. Note the wall of the keratocyst with notable palisading and slightly wavy surface.

lingually than buccally. Furthermore, root resorption is rare with OKCs, in contrast to ameloblastomas, with which root resorption is seen frequently. In our case, the radiolucent lesion caused thinning of the lingual cortex of the mandible and root resorption of the second molar. This highlights that a diagnosis of OKC cannot be made using imaging techniques only. When evaluating a cystic lesion of the mandible, MRI is a complementary technique to cone beam CT and applicable in select cases. MRI is superior in illuminating the soft tissue involvement, and a number of studies argue that MRI is crucial in discriminating ameloblastomas from OKCs [28,29]. As such, cone beam CT and MRI, in select cases, are crucial in the diagnosis of OKCs. Some lesions can be indistinguishable from other osteolytic jaw lesions on imaging; therefore, histopathology is always necessary for a definitive diagnosis. A prospective study of 82 OKCs reported that 40% were not suspected before surgery [1,22,24].

Fine needle aspiration biopsy can be considered a safe technique, offering a possibly valuable contribution to pre-operative diagnosis. However, it can be misleading due to inflammation in OKCs. In addition, a biopsy of an unrepresentative area of the lesion can be misleading. The result can be indicative, but a negative result can never rule out a possible diagnosis of OKC until investigation of the final resection specimen. Baykul et al. showed a correlation of 89.95% between cytological and histopathological diagnosis for cystic lesions in the maxillofacial region [22,29,30,31].

With this in mind, diagnosis and subsequent treatment of OKCs poses a challenge. The objective is to reduce the recurrence risk as much as possible, while minimizing morbidity. This delicate balance has led to heavy international debate, and no consensus on treatment has been reached.

Established treatment modalities can be divided into radical and conservative treatment options. Radical treatment consists of en bloc resection with negative margins of the segment and has been associated with a recurrence rate of approximately 0%. Knowing the benign nature of this lesion and the morbidity of en bloc resection, this technique has to be reserved for wide, extensive lesions.

A retrospective study showed that the main reasons for radical treatment are invasion of the pterygoid muscles and the presence of malignant change [5,12,13,34]. The conservative therapies consist of enucleation, but it is generally agreed upon that additional measures for enucleation are crucial to minimize recurrence.

The three main techniques are peripheral ostectomy, chemical curettage with application of Carnoy's solution, and cryotherapy. In the literature, there is immense variability in the use of additional techniques, and studies have shown a similar efficacy between peripheral ostectomy and Carnoy's solution. Superior outcomes of cryotherapy have not been described [6,12,13,21,26].

Lesions exceeding 3 cm are not fully suitable for enucleation. In these cases, decompression by marsupialization can reduce the lesion size. The literature has not shown an increased risk of



Figure 7. Follow-up 6 months after surgery. (a) Panoramic radiograph, (b) cephalometric X- ray, and (c) cone beam computed tomography.

recurrence after decompression [25-27]. It seems advisable to treat each cyst in the mandibular third molar region with possible extension into the ascending ramus by enucleation, with excision of the mucosa if possible. Subsequently, treatment with Carnoy's solution or liquid nitrogen has to be considered.

Targeted treatment of the OKC seems achievable, as multiple mutations have been elucidated. Mutations in the PTCH gene or the gene encoding smoothened protein that enhances sonic hedgehog signaling (SMO) can be drug targets. The antimetabolite 5-fluorouracil may affect the sonic hedgehog pathway and has shown lower postoperative morbidity in studies [25,32].

Postoperatively, rigorous follow-up is necessary because of the high recurrence rate. Clinical examination and radiographic monitoring is crucial in the first 5 years. After 5 years, radiographic followup every 2 years is advisable. This sequence has to be continued for at least 25 years [13-15,22]. However, in this case report, an adapted treatment was performed. Because of the size of the lesion and its lingual expansion, there was uncertainty about mandibular stability after enucleation. The location of the lesion with immediate connection to the deep neck soft tissues could not be neglected. The expanded resorption of the lingual cortex with broad fenestration could induce a pathological fracture after enucleation with bone trepanation for removal of elements 47 and 48.

Therefore, a combined intra/extra-oral technique was applied. By adapting and fixating a plate before performing the enucleation, we tried to avoid a pathological fracture. With this degree of extended osteolysis, we felt fixation of a plate was necessary. What if mandibular continuity resection is necessary peri-operatively?

Then, the mandibular bony contour would be guaranteed by using the reconstruction plate.

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Figure 8. Clinical pictures 6 months after surgery

As no clear arguments for OKC were present preoperatively and peri-operatively, the surgeons decided not to use Carnoy's solution to save the soft tissue as much as possible.

The described technique seems suitable for lesions of this size when pathological fractures are likely. It provides an elegant way to provide mandibular continuity while executing enucleation. We are aware that the short follow-up is a limitation of this case report.

4. Conclusion

With this case report, we tried to point out the difficult diagnosis of OKC and, by extension, all radiolucent lesions of the mandible. Although the lesion does not always present with its typical features, the possibility of OKC must be taken into account when setting up a treatment protocol. We suggest a combined intra/extra- oral approach for an OKC in the ramus of the right mandible near the second and third molars with lingual expansion, as adapting and fixating a reconstruction plate before executing enucleation could prevent pathological fractures.

More extensive clinical trials and longer follow-up will show whether this technique has an acceptable recurrence rate while guaranteeing the continuity of the mandible.

Conflicts of interest

None

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Ethical approval

Not applicable. The present study is not a research study.

Consent

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Author Contributions

MV: leading author of the manuscript. PD: critically revising the manuscript. SK: critically revising the manuscript. BL: giving more insight in radiologic aspect of the case report. CP: critically revising the manuscript.

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