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Non-Syndromic Multiple OdontogenicKeratocysts: A Rare Case Report and Review of Literature

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ABSTRACT: The odontogenickeratocyst (OKC) is one of the most common odontogenic cysts originating from the dental lamina and affects the oral and maxillofacial area. Multiple OKCs are typically observed in nevoid basal cell carcinoma syndrome (NBCCS), which has been linked to (human homolog of the drosophila segment polarity gene, "patched" (PTCH). Multiple recurrent OKC may solely develop as a result of partial gene expression with no concomitant systemic symptoms. In this report, we present a rare case of a 34-year old non-syndromic male patient with multiple OKCs located in the anterior regions of both jaws who was treated surgically with no obvious post-operative complications during the follow-up period.

Key words: Multiple OdontogenicKeratocyst; Non-Syndromic; Gorlin-Goltz Syndrome.

I. INTRODUCTION

Odontogenickeratocyst (OKC), accounts for around 10% of odontogenic cysts, is a locally aggressive cystic lesion that affects the maxilla or mandible and is capable of causing major destruction [1]. Due to these characteristics, in 2005 the WHO classified it as an odontogenickeratocysttumor [2]. However, in the most recent WHO classification, which was published in 2017, it was considered as a developmental odontogenic cyst again. Finally, the most recent classification of WHO in 2022 also considered it under the category of odontogenic cyst [3].

Prevalence and incidence OKCs represent 7.8% of whole jawbone cysts, and incidence varies between 4 and 16.5%. Men are more commonly affected than women, with most OKCs occurring in white populations [4]. Ages from 8 to 82 make up the large age range, with the second and third decades of life reporting the highest incidence rates [5]. OKCs occur in tooth-bearing regions. The mandible is more affected than the maxilla, and the posterior region of the mandible, especially the angle and ascending ramus region, is involved most commonly [6].

The etiopathogenesis of OKCs depends on the mechanism of intraluminal hyperosmolarity, on the active epithelial proliferation, on the collagenolytic activity of the wall of the cyst and on the synthesis of interleukin-1 and interleukin-6 by keratinocytes. In contrast to other cysts (such as dentigerous cysts), which only grow by intraluminal hyperosmolarity, this mechanism, especially in large lesions, requires a specific growth along the cancellous channels with a decreased cortical expansion. [7].

Clinically, OKC often manifests as asymptomatic lesion, usually with a medullary growth pattern, which result in a minimal expansion of the cortical bone, but sometimes it may be accompanied by pain and aggressive growth. It mainly affects posterior region of mandible with common involvement of mandibular angle and third molar [2,8]. Multiple OKCs are usually associated with cutaneous, skeletal, ocular and neurologic abnormalities as a component of nevoid basal cell carcinoma syndrome (NBCCS). The characteristics of this syndrome were first described by Gorlin and Goltz in 1960, so it is also known as Gorlin- Goltz syndrome [9]. NBCCS has typically been associated with multiple OKCs, however they are rarely seen without concomitant syndromic manifestations [10]. Patients with multiple OKCs had a higher recurrence rate (30%) than patients with solitary OKCs (which is 10%). Individuals with OKC need

to have annual panoramic radiography exams (OPG). To track early recurring lesions, magnetic resonance imaging (MRI) might be performed every two years. The period of follow-up should be lengthy—at least 10 years [2,11].

From a radiographic perspective, it displays a well-defined radiolucent area with border demarcation, which can be unilocular or multilocular. The multilocular form resembles ameloblastoma, especially when it affects the lower jaw. Also, it may or may not be related to an included tooth, which is commonly mistaken for dentigerous cyst [11].

Histologically, OKCs are characterised by a cystic wall with a uniform parakeratosis squamous epithelium that has a well-defined basal layer of palisaded columnar or cuboidal cells. Also, a flat epithelium-connective tissue interface with an unnoticeable rete ridge formation is noted. A history of local infection can affect the histological findings, and in this case, an inflammatory cell infiltrate was observed. The cystic wall has small satellite cysts, cords, or islands of odontogenic epithelium that can be found beneath the fibrous wall in the adjacent intramedullary spaces [7,10-11].

In this paper, we report a case of a young male patient who presented to our service with a mandibular and maxillary inflammatory cyst-like lesion that had an unexpected histopathological examination diagnosis of multiple OKCs without any syndromic manifestations.

II. CASE REPORT

A 34-year-old male patient presented to the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Cairo University, with the chief complaint of intraoral discharge in the lower and upper anterior region for the past 3 months. There was no history of any trauma or swelling. When asked for a personal history, there was no history of any deleterious habits such as smoking, using tobacco or drinking alcohol. Systemic signs and symptoms, past medical history, and hematologic tests were within normal ranges.

During the extraoral examination, there was no swelling or pus discharge **[Figure 1]. In a** panoramic radiograph, two unilocularradiolucencies with corticated borders were revealed around the unerupted mandibular left canine, and the roots of the left lateral and left 1st premolar were displaced. Other radiolucency was noted in anterior maxillary region extending from the mesial root of the left 1st molar to the root of the left maxillary central incisor. In addition, a badly decayed right maxillary lateral incisor with radiolucence and root resorption was observed [Figure 2].

Regarding the radiographic examination and the presence of unerupted teeth and their location, the initial differential diagnosis was dentigerous cyst and the second was adenmatoidodontogenic tumor. Other odontogenic cysts and tumours such as odontogenickeratocyst, calcifying epithelial odontogenic tumor, and unicysticameloblastoma were considered as other differential diagnoses **[Figure 2].**

Root canal treatment was done in both maxillary and mandibular anterior teeth, and after taking the informed consent of the patient, complete enucleation of the lesion was done under general anaesthesia with removal of the impacted tooth **[Figures 3 A, B, and C].** Then, peripheral ostectomy of the whole surgical bed was completed, followed by a single application of Carnoy's solution. The cystic lesions were sent for histopathologic examination **[Figures 3 D].** Finally, the wound closure was done with 3-0 silk suture **[Figures 3 E and F].**

The histopathologic examination revealed that the cystic lining of the lesion was lined by 6-10 layers of thin, uniform, parakeratinized stratified squamous epithelium. The basal cell layer consists of palisaded and polarized low columnar cells with hyperchromatic nuclei, giving off a "tombstone appearance. The supra-basal cells are polyhedral and show intercellular edema and intercellular bridges. The surface keratinization is corrugated and the parakeratin is noticeable and having nuclear remnants. The fibrous connective tissue that formed the cyst wall had no inflammatory properties. **[Figures 4A, B, and C].** Multiple sections were cut from the maxillary lesion with a definitive diagnosis of OKC in the mandibular lesion and the absence of any evidence of NBCCS in clinical examinations. These sections were obtained because of the probability of multiple non-syndromic OKCs.

The maxillary lesion showed a cystic cavity lined by thin, uniform, parakeratinized stratified squamous epithelium. The epithelium-connective tissue interface is flat with an absence of rete pegs and a potential for budding of the basal cell layers and the formation of satellite cysts. Due to the weak attachment between the epithelium and the connective tissue capsule, many areas of separation are seen at the interface **[Figures 5].**

The hematoxylin and eosin slides were evaluated carefully and, according to the entire histopathologic features, which were correlated with the clinical and radiographic findings, the diagnosis of multiple non-syndromic OKC was established.

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III. DISCUSSION

OKC is defined as the most common developmental odontogenic cyst, which represents about 10% to 14% of entire jaw cysts. Its distinctive microscopic characteristics are specified, including basilar nuclear palisading and surface keratinization (especially parakeratin). Depending on its probable aggressive nature and genetic abnormalities, there has been an argument about whether OKC should be categorised as a cyst or a neoplasm. Both terms (OKC and KCOT) are recently being used, although the most recent WHO 2022 classification system supports designation as a cyst [3,12].

OKC is a locally aggressive cyst which makes up approximately 10% of odontogenic cysts. It affects males twice as much as females and has a wide age distribution, occurring anywhere from the first decade to the eighth decade with two main peaks: the first peak is at 25-34 years and the second is at 55-64 years. OKCs are typically intraosseous, affecting the mandible more frequently than the maxilla, with only a few peripheral cases recorded. It is commonly asymptomatic despite its aggressive nature. In fact, 5.2 to 42.5% of cases are accidentally diagnosed during routine dental examinations. However, large lesions in the mandible may cause trismus, and those in the maxilla may expand into the maxillary sinus and cause ipsilateral nasal obstruction. In addition, slowly growing lesions stimulate bone apposition, causing bone expansion without cortical perforation. Spontaneous drainage of cyst fluids, paresthesia, and pain are other rare manifestations that can occur.The main symptoms include swelling and pain -infection-discharge-paresthesia of the lower lip or teeth-tooth displacement-nasal obstruction [13-15].

Radiographic features of OKC range from well-defined unilocular lesions to extensive multilocular lesions with ill-defined borders. The ratio of unilocular to multilocular radiolucency associated with OKC in the maxilla was 6:1, while in the mandible the ratio was 1.9:1. Moreover, the perforation rate was found to be 50.8%. The radiolucency is usually well demarcated and bound by a sclerotic margin. However, it may be diffuse in some areas. Displacement of adjacent teeth occurs more frequently than resorption, owing to the lesion's expansile nature. Especially in smaller unilocular lesions, the radiographic features of OKCs may not always indicate a specific diagnosis. An anterior sextant small unilocular OKC may mimic a radicular cyst, lateral periodontal cyst, or nasopalatine cyst. The multilocular form can also be challenging to identify since OKCs can have septation, closely resembling ameloblastomas. The most frequently employed radiographic techniques for diagnosing OKCs are conventional radiography, particularly panoramic radiography, computed tomography (CT), and magnetic resonance imaging (MRI) [16-18].

The main histopathological features defined in 2005 enable us to differentiate OKCs from jaw cysts with keratinization. The well-defined, often palisaded, basal layer of columnar or cuboidal cells, intense basophilic nuclei of the columnar basal cells with reversed polarization, parakeratotic layers with an often corrugated surface, and mitotic figures commonly found in the suprabasal layers [12]. The epithelium can show budding of the basal layer into the underlying connective tissue with the formation of detached microcysts, known as daughter cysts. Some studies have suggested that parakeratinization, intramural epithelial remnants, and satellite cysts are more commonly observed among OKCs associated with NBCCS. The fibrous cyst wall is relatively thin and usually devoid of inflammatory cell infiltration [19].

The epithelial lining occasionally displays characteristics of epithelial dysplasia, and malignant transformation into squamous cell carcinoma, though rare, has been reported. OKCs have a weak and discontinuous linear staining for laminin and collagen IV, suggesting interactions between the epithelium and the adjacent connective tissue. Furthermore, suprabasal staining with markers of proliferation, such as Ki-67 and proliferating cell nuclear antigen (PCNA), and more significant staining with p53 as compared to the other odontogenic cysts have been reported. Agaram et al claimed that the daughter cysts were associated with a higher frequency of allelic losses [20-22].

It is still debatable how the OKCs were treated. The two types of treatments are often categorised as conservative and aggressive. Simple enucleation, with or without curettage, or marsupialization are common examples of conservative treatments. Peripheral ostectomy, chemical curettage using Carnoy's solution, cryotherapy, or electrocautery and resection are examples of aggressive treatments. Ultrasonic debridement of the cystic cavity is a new method for eliminating epithelial remnants while preserving bone and adjacent tissues that are damaged by other methods [1,23-24].

This case shows multiple OKC without any other notable features, which are indicative of GorlinGoltz Syndrome. As such, the occurrence of multiple recurrent OKC's may be the first and only manifestation of GGS, indicating partial expression of the PTCH gene. Thus, it is imperative that patients having multiple OKCs should be examined to see if any syndromes are present. However,

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multiple OKCs may occur without the syndrome and need not be because of gene mutation, probably as a result of the multifocal nature of OKCs.

From a differential diagnosis viewpoint, the OKC can mimic various other odontogenic cysts and tumors. Unilocular lesions in relation to impacted teeth can look like dentigerous cysts, which are seen most in young patients. As seen in our case (lower jaw lesion), OKCs are justifiably misdiagnosed as dentigerous cysts or adenomatoidodontogenic tumours. Unilocular radiolucency located beneath tooth roots can be mistaken for a radicular cyst (this was presented and described in upper jaw lesion). However, histopathological features of dentigerous cysts and adenomatoidodontogenic tumours do not exhibit the regular, palisaded arrangement of cuboidal/columnar basilar cells or the corrugated surface layer of parakeratin.

Histopathological differential diagnoses include orthokeratinizedodontogenic cysts (OOCs), glandular odontogenic cysts (GOCs), and unicysticameloblastomas (UA). OOCs also produce keratin; this keratin consists of orthokeratin associated with a subjacent granular cell layer. Besides, the basilar layer of OOCs does not exhibit nuclear palisading. The diagnosis of GOC had to be based on the mandatory presence of the five major criteria. These are squamous epithelium of varying thickness, cuboidal eosinophilic (‘‘hobnail’’) cells, mucous (goblet) cells, and intraepithelial glandular or duct-like structures. In addition to minor criteria, papillary proliferation of the lining epithelium, ciliated cells, multicystic or multiluminal architecture, and clear or vacuolated cells in the basal or spinous layers Unicysticameloblastomas demonstrate a palisaded layer of columnar basal cells that could mimic an OKC. However, the ameloblastoma's basilar cells are usually more hyperchromatic and demonstrate areas with reverse polarization, in which the nuclei are pulled away from the basement membrane. What is more, the upper epithelial layers of cystic ameloblastoma are loosely arranged, reminiscent of the stellate reticulum of the enamel organ [12,25-27]. The definite diagnosis of our case fulfilled the histopathological criteria for multiple OKCs without syndromic association (Table 1).

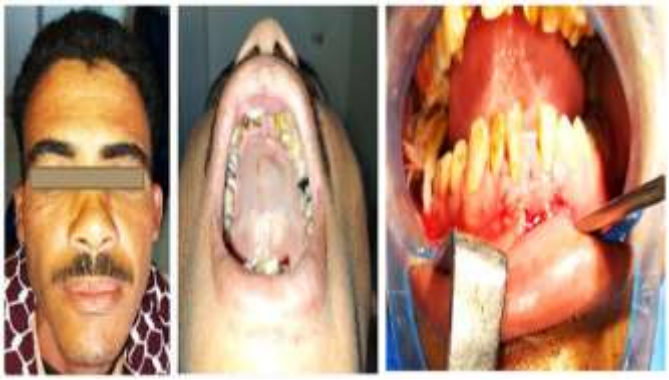

Figure 1. Extraoral and intraoral photograph without any remarkable swelling.

Figure 2.A. Panoramic radiograph showing multiple radiolucencies in the upper and lower jaws, and there is evidence of an impacted lower left canine within the osteolytic area. B. Computed tomography (CT) shows buccolingual expansion of the left side anterior area.

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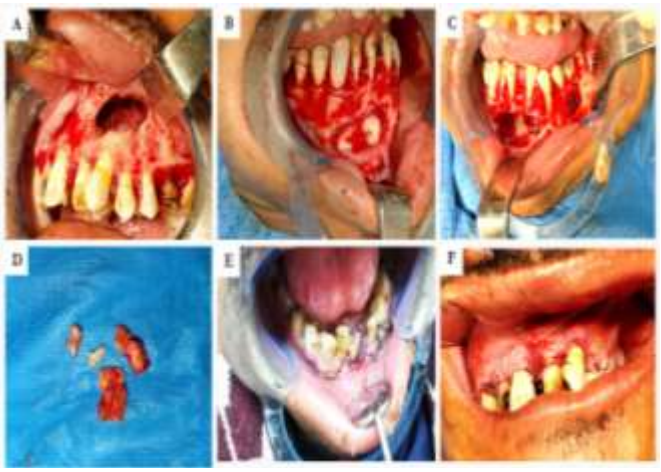

Figure 3. A, B, and C. Photographs showing mandibular and maxillary enucleation of the lesion. D. Showing the pathological specimen and the extracted impacted canine. E and F. Showing suturing and wound closure.

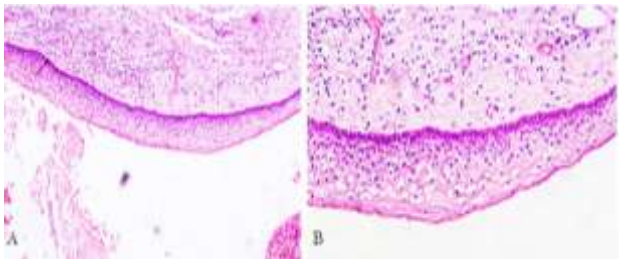

Figure 4. Odontogenickeratocyst photomicrographs of a mandibular lesion stained with Hematoxylin and Eosin (H&E). A and B. Cystic cavity lined by layers of thin, uniform, parakeratinized stratified squamous epithelium, palisade layer of low columnar basal cells with hyperchromatic nuclei, giving the appearance of a tombstone. The supra-basal cells are polyhedral and show intercellular edema and intercellular bridges (x 50) (x 100).

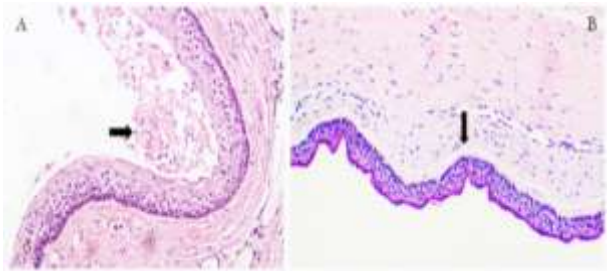

Figure 5. Maxillary lesion photomicrograph, Hematoxylin and eosin (H&E) staining. Showing cyst lined by thin, uniform, corrugated parakeratinized stratified squamous epithelium without rete pegs (arrow) (x100). B. Separation between epithelium and connective tissue (arrow) (x100).

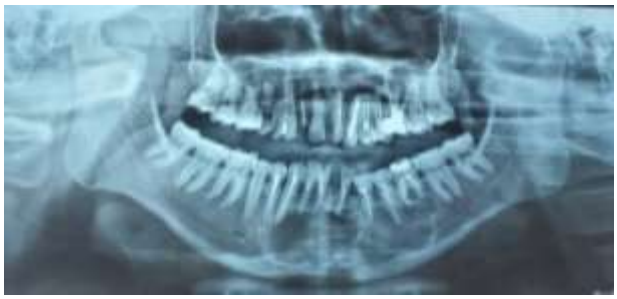

Figure 6. A. Post-operative panoramic radiograph of a three weeks follow-up.

IV. CONCLUSION

Multiple cysts (MC) affecting the jaw are quite uncommon. When multiple, it is generally linked with a syndrome. It is extremely rare for MC to occur without syndromic association. This illustrates how crucial it is to correlate the clinical, radiographic, and histopathologic components for a full closure and the determination of the pathology's suitable therapy.

Abbreviation:
OKCs: Odontogenickeratocysts; NBCCS: Nevoid Basal Cell Carcinoma Syndrome; OOCs: OrthokeratinizedOdontogenic Cysts; GOC: Glandular Odontogenic Cyst; UA: UnicysticAmeloblastomas; MC: Multiple cysts.

Authors' contributions
Writing and reviewing the paper: LA, MA. Surgical work: MA, MS, HS. Histopathological diagnosis: LA. Critical revision: LA. Final approval: All authors.

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Availability of data and material
The data used during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Not applicable.

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

Competing interests
The authors declare that they have no competing interests.

Table 1. Odontogenickeratocyst in comparison to orthokeratinizedodontogenic cysts, glandular odontogenic cysts, and unicysticameloblastomas according to WHO.

	OKC	OOC	GOC	UA
Surface keratinization	Keratin consists parakeratin (having nuclear remnants)	Keratin consists of orthokeratin (without nuclear remnants)	Not seen	Not seen
Surface corrugation	Always seen	Not seen	Not seen	Not seen
Basal cell palisading	Always seen	Not seen	Not seen	Always seenwith reverse polarization
Recurrence rate (%)	25%	Less than 2%	30-50%	--

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