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Non-Syndromic Multiple Odontogenic Keratocysts and Odontogenic Cysts: A Case Report

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ABSTRACT

Odontogenic kerato Cyst (OKC) is a developmental odontogenic cyst with specific histopathologic features and clinical behavior. Several investigators suggested that OKCs should be considered benign cystic neoplasms rather than cysts. OKCs are locally aggressive benign tumors with a high recurrence rate. Usually, multiple OKCs are observed in nevoid basal cell carcinoma syndrome (NBCCS) but about 5% of OKC have multiple cysts without an accompanying syndrome.

Mutation in the human homolog of the Drosophila segment polarity gene, "patched" ((PTCH) gene) is seen. Multiple recurrent OKCs without associated systemic findings are related to the partial expression of the gene. However, few cases of non-syndromic multiple keratocystic odontogenic tumors have been reported in the literature. This case report presents a rare case of an 11-year-old boy with multiple OKCs without any syndromic association. The patient underwent surgery for multiple and recurrent cysts in the jaws over 5 years. The patient was screened for syndromic diseases and no signs or symptoms of the syndrome were found.

Keywords: Odontogenic Cysts, Gorlin Syndrome, Neoplasms.

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Introduction

Odontogenic kerato cyst (OKC) is known as a developmental odontogenic cyst with certain clinical behaviors and histopathologic features. [1] It is a special type of developmental odontogenic cyst that deserves specific attention because of its specific histopathologic features and clinical behavior. There is general agreement that OKC arises from cellular remnants of the dental lamina. This cyst has a different growth mechanism and biological behavior than the more common dentigerous and radicular cysts. Its growth could be related to genetic factors inherent to the

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epithelium itself or enzymatic activity in the fibrous wall. Several investigators suggested that OKCs should be considered benign cystic neoplasms rather than cysts. [2] They are characterized by aggressive behavior with a relatively high recurrence rate. [3] It is the third most common cystic lesion of the oral cavity [4, 5], usually occurring in the second to fourth decade of life and slightly more common in males. [1] It occurs more frequently in the mandible than in the maxilla. The molars and ramus are the most common sites in the mandible, while the anterior region in the maxilla is the most common site for OKC, followed by the third molar region. The periapical region of the teeth or the lateral region and the dental crown may be associated with OKC. [6]

Histologically, OKCs arise from the dental lamina and consist of a cystic cavity containing desquamated keratin. The cyst is lined with a uniform parakeratinized or orthokeratinized squamous epithelium of 6–10 cell layers thick, with a distinct high columnar basal cell layer of palisaded arrangement with hyperchromatic nuclei, whose nuclei tend to be vertically oriented. Infiltrative growth with adjacent connective tissue is usually shallow, with the possibility of budding of the basal layer and the formation of small satellite or daughter cysts. Mitotic activity in OKC is higher than in other cysts of odontogenic origin. [3] OKCs are characterized by their potentially local aggressive behavior with invasion of adjacent structures, especially bone, and their high recurrence rate (up to 60%) after treatment (depending on the course of treatment), which led to their classification as odontogenic tumors between 2005 and 2007. However, since 2017, keratocystic odontogenic tumors have been reclassified as odontogenic cysts due to their pathogenic cystic process and are therefore no longer classified as benign odontogenic tumors. In the WHO classification, keratocystic odontogenic tumor (KCOT) and OKC are considered synonyms. [7] Usually, multiple OKCs are associated with nevoid basal cell carcinoma syndrome (NBCCS), but rarely may they occur without concomitant syndromic manifestations. Nevoid basal cell carcinoma syndrome is associated with a triad of multiple OKCs, multiple basal nevi, and skeletal abnormalities. This triad of symptoms may be associated with other manifestations that include skeletal, craniofacial, neurologic, skin, sexual, ophthalmic, and cardiac abnormalities. [8] In non-syndromic patients, these criteria are not observed.

Case Report

This study was approved by the Ethics Committee of Babol University of Medical Sciences (NO. IR.MUBABOL.REC.1401.172). An 11-year-old boy was referred to Babol Faculty of Dentistry with pain and swelling of the left mandibular second molar (2020.04.29).

His general medical history was unremarkable and there were no clinical symptoms of syndromal disease. He had undergone testicular surgery at the age of 2 years. After an intraoral and radiographic examination, A radiolucent lesion was found on the left side of mandible, pericoronal to the impacted third molar and extending from the distal first molar to the vicinity of the ascending ramus (figure 1a). Radiographs showed the lesion with a corticated margin and perforation of the mandibular plate of the ramus and alveolar ridge (figure. 1b).

On aspiration, a yellowish and cheesy fluid was observed, supporting the cystic nature of the lesion. An incisional biopsy was taken from this area and referred to the pathology department. Histopathologic examination revealed that the cystic lining of the lesion was a corrugated, parakeratinized epithelium with a uniform thickness of 5–6 cells and a palisaded basal cell layer without rete ridge (H&E stain 10x). Several strands and islands of activated odontogenic epithelium with ameloblastic changes were seen in the fibrotic cyst wall. The result was a keratocystic odontogenic tumor (figure. 2). Surgery with marsupialization was performed.

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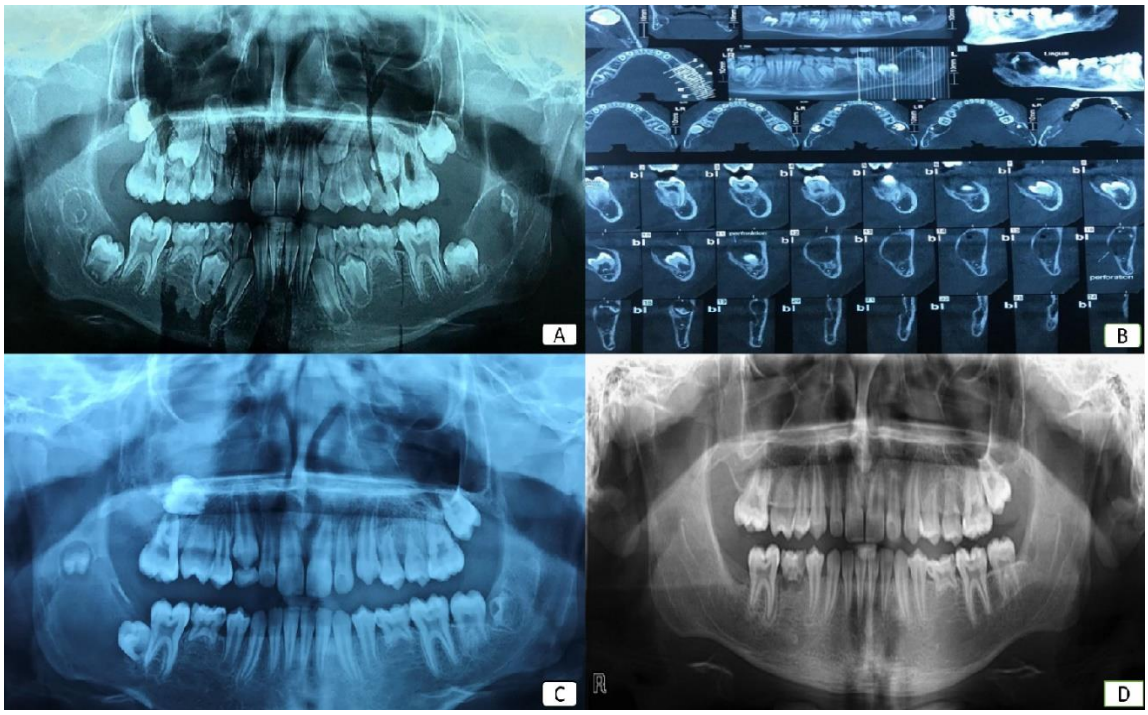

Figure 1. A) Radiolucent lesion on the left side of the mandible is pericoronal to the impacted third molar and extended from the distal of first molar to near the ascending ramus. B) Lesion with a cortical margin and perforation of the mandibular plate of the ramus and alveolar ridge. C) Radiolucencies with impacted and displaced right maxillary second molar and displaced bud of the right mandibular third molar and impacted right mandibular second molar. D) Follow up radiograph; note the radiolucent lesion in the distal region of the second molar

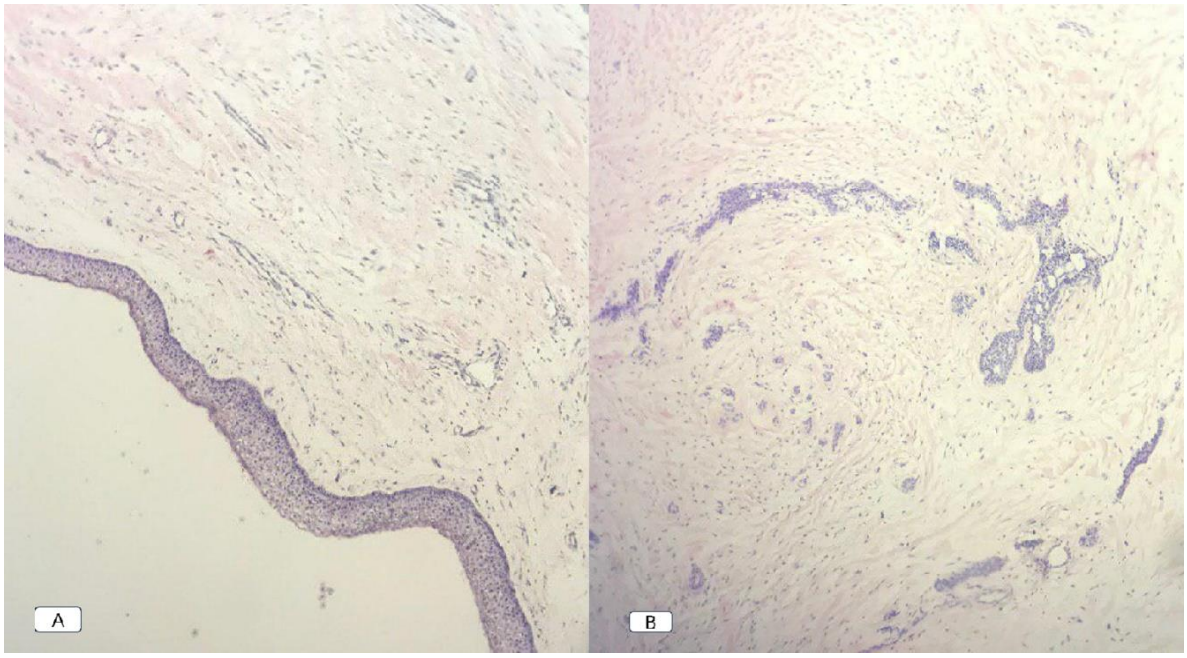

Figure 2. A) This section shows a fibrocollagenous cyst wall lined by a fairly thin and flat stratified squamous epithelium without rete ridges. (Hematoxylin-Eosin, 100X Magnification B) This section shows ameloblastic proliferation in the cyst wall (Hematoxylin-Eosin, 100X Magnification).

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During subsequent visit (11 April 2021), panoramic radiograph were obtained showing radiolucencies with impacted and displaced right maxillary second molar and the displaced bud of the right mandibular third molar and impacted right mandibular second molar (figure. 1C). After the lesion on the left side of the mandible shrank, a surgical procedure was performed and the bud of the third molar was removed with the residual lesion. The specimen contained some cream to brown parietal particles with a diameter of 1.6×1.6×0.8 centimeters and the third molar bud (germ).

Finding was a keratocystic odontogenic tumor. During the last surgery, (9 April 2022), the lesion in the distal region of the second molar of the right side of the mandible was removed together Histopathologic examination of the mandibular lesion revealed a cystic lesion with nonkeratinized stratified squamous epithelium indicating hyperplasia and arcuate epithelium in some areas. Spongiosis and exocytosis were noted. Chronic inflammation was observed in the cyst wall. The pathological result was an inflamed dentigerous cyst. After five weeks (22 May 2021), an incisional biopsy was performed for the lesions of the right side of the maxilla and mandible with the affected buds (germs) of the impacted tooth, histopathological examination was subsequently indicated as OKC for the lesion in the mandible and dentigerous cyst for the lesion in the maxilla.

Two weeks later (15 June 2021), an excisional biopsy was performed for a lesion on the right side of the maxilla (sinus lesion), and the pathologic result was reported to be consistent with an OKC. Approximately one year later (April 9, 2022), an excisional biopsy of the lesion of the second molar on the right side of the mandible was performed and the pathological with the impacted second molar. Histopathologic examination revealed that the cystic lining of the lesion was a corrugated, parakeratinized epithelium with a uniform thickness of 5-6 cells and a palisaded basal cell layer without rete ridge (H & E Stain. 100x) (figure. 3A). The cyst wall was composed of fibrous connective tissue with strong lymphoplasmacytic infiltration with angiogenesis in some areas that lacked the typical characteristic features of an OKC (figure. 3B). A daughter cyst was seen in the cyst wall. All these features confirmed the diagnosis of OKC for the mandibular lesion. The patient's most recent radiograph, taken in September 2022, revealed a radiolucent lesion in the distal region of the second molar (figure. 1D). Therefore, we called the patient again 6 months later and continued to observe him.

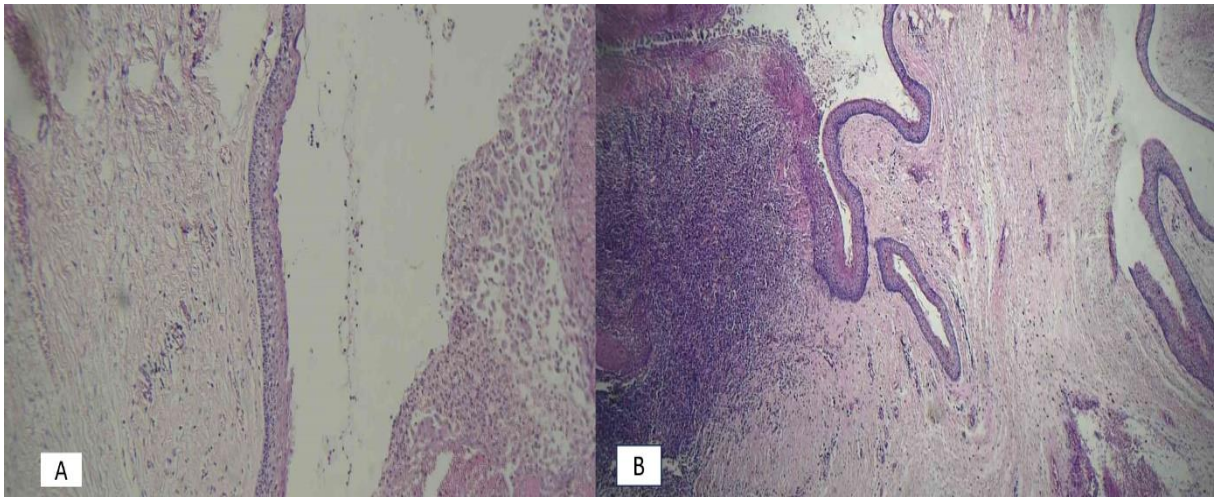

Figure 3. A) Cystic lining of the lesion was a corrugated, parakeratinized epithelium with a uniform thickness of 5-6 cells and a palisaded basal cell layer without rete ridge; the basal layer is cuboidal with hyperchromatic nuclei.b; Cyst wall with strong lymphoplasmacytic infiltration and angiogenesis and disappearing the typical characteristic features of an OKC.

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Discussion

Cystic lesions of the jaw may be odontogenic or non-odontogenic, epithelial or non-epithelial, developmental or inflammatory in origin. OKC was first described by Mikulicz and introduced by Philipsen in 1956. It is a developmental odontogenic cyst arising from either remnants of the dental lamina or basal cells of the overlying oral epithelium. The lesion commonly occurs in the maxilla and mandible and can become quite large due to its potential for significant extension into adjacent tissues, and rapid growth. [10] Most cases occur in the mandible, especially in the ramus and posterior segments of the body. They typically present as large unilocular radiolucencies with displacement of the adjacent teeth. [11]

OKCs can affect any age, with the highest prevalence between 10 and 40 years of age.[1] Recurrence rates vary, ranging from 2.5% to 62.5%. [10] In cases associated with an impacted tooth, the radiograph may resemble a dentigerous cyst. In our case, the radiographic findings of the mandibular lesion showed cortical margin and perforation of the mandibular plate of the ramus and alveolar ridge were seen. Panoramic radiographs were obtained showing radiolucencies with impacted and displaced right maxillary second molar and displaced nuclei of the right mandibular third molar and impacted right mandibular second molar.Microscopically, the parakeratinized epithelium without a rete ridge and with a corrugated luminal surface and a prominent cuboidal basal layer is a characteristic feature that allows recognition and diagnosis. [2]

Occasionally, smaller “satellite” or “daughter” cysts are seen in the underlying stroma sometimes detached from the basal layer. [11] If we see secondary inflammation, these diagnostic features may become unrecognizable and nonspecific. [2]In this case, microscopic evaluation of the left mandibular lesion showed characteristic features of KCOT, which produced a corrugated, parakeratinized stratified squamous layer with palisaded basal cell layer without rete ridge formation and ameloblastic proliferation. The right maxillary lesion in the excisional biopsy showed histopathologic features of an OKC. The right mandibular lesion showed histopathologic features of an OKC.

Multiple OKCs are usually considered components of Gorlin-Goltz syndrome or NBCCS [4], Ehlers-Danlos syndrome, orofacial finger syndrome [1], Noonan syndrome [4], or other syndromes. Single OKCs usually occur in elderly patients, in contrast to multiple OKCs, which occur in either syndromal or non-syndromal patients. Small OKCs are often asymptomatic, whereas larger cysts may be painful, swollen, or discharge. [4] Kimonis et al. described the diagnostic criteria for Gorlin-Colts syndrome (GCS). There are major and minor criteria. Diagnosis requires two major criteria or one major and two minor criteria.

However, apart from the presence of OKCs and odontogenic cysts, our patient was healthy on clinical examination, and suggestive features of these syndromes such as skeletal or orofacial defects, basal cell carcinoma, hemorrhage diathesis, stunted growth, hypermobile joints, hyperextensible skin, and other features were not present.Multiple OKCs may be the first and only manifestation of NBCCS without other features associated with the syndrome, but in this case, we found no syndromal symptoms. However, other symptoms may appear in later decades of life. [1]

Therefore, follow-up of these patients is necessary. Cases similar to the current case have been described in a few published English articles. Auluck et al. reported a 22-year-old patient with multiple recurrent KCOTs in all four quadrants who complained of pus discharge in the previous week, without pain or swelling in the face. The patient had no other features associated with NBCCS. [1]Sholapurkur et al. presented a 24-year-old case with multiple nonsyndromal KCOTs in both jaws with the chief complaint of slow-growing swelling for 3 years and drainage for 15 days. The swelling was associated with pain and gradually radiated into the head on the same side. The lesions were cyst-

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like radiolucencies associated with impacted teeth on a panoramic radiograph. [1] A similar treatment was prepared for our patient. In a 2022 retrospective study by Favia et al., the histopathological characteristics of syndromic and non-syndromic odontogenic keratocysts (OKCs) were comprehensively compared using conventional and Confocal Laser Scanning Microscopy (CLSM). The findings revealed distinct histopathological features in syndromic OKCs, including a thicker epithelium with a higher mitotic rate, more frequent epithelial detachment, and a higher prevalence of satellite cysts. Additionally, CLSM demonstrated a more complex and disorganized stromal architecture in syndromic OKCs. These findings suggest that syndromic OKCs exhibit a more aggressive biological behavior compared to non-syndromic OKCs, highlighting the importance of careful histopathological evaluation, including CLSM, for accurate diagnosis and management, particularly in patients with Nevoid Basal Cell Carcinoma Syndrome (NBCCS).[12]

Patients with multiple OKCs should always be evaluated to exclude the presence of Gorlin syndrome, even in those with late-onset cysts and no skin manifestations. These patients have an increased risk of developing additional OKCs during their lifetime. Therefore, close clinical follow-up is required for early detection. In addition, genetic counseling with or without genetic testing for family members should be considered. For the treatment of OKCs, a preoperative biopsy is required to make a definitive diagnosis. To prevent recurrence, all OKCs must be completely removed, and close clinical follow-up is required thereafter, similar to the same therapeutic actions that we performed for the relevant case.

Conclusion

Patients with multiple OKCs should always be evaluated to exclude the presence of Gorlin syndrome, even in those with late-onset cysts and no skin manifestations. These patients have an increased risk of developing additional OKCs during their lifetime. Children with unerupted permanent teeth should initially be treated conservatively, as aggressive interventions can have negative effects on tooth development and eruption. Among conservative treatments, marsupialization followed by enucleation of the cyst has the lowest recurrence rate. Therefore, close clinical follow-up is required for early detection. In addition, genetic counseling with or without genetic testing for family members should be considered. For the treatment of OKCs, a preoperative biopsy is required to make a definitive diagnosis. To prevent recurrence, all OKCs must be completely removed, and close clinical follow-up is required thereafter.

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Conflict of interest

All authors declare no conflict of interest.

Author's Contribution

Zahra Zolfaghari Saravi collected the data, wrote the histopathology report, drafted the manuscript, and edited the article. Maryam Seyedmajidi and Fatima Bijani collaborated on the histopathology diagnosis, Ehsan Moudi wrote the radiographic report, and Arezoo Javani performed the surgery.

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