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Case Series

A series of six uncanny orthokeratinized odontogenic cysts: Revisiting the literature

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ABSTRACT

Introduction: Orthokeratinized odontogenic cyst is a rare odontogenic cyst which was considered to be a variant of odontogenic keratocyst, but has been recognized as a separate entity due to its varied behavior and histology. Commonly associated with an unerupted tooth in the posterior mandible, it mimics various lesions like dentigerous cyst, odontogenic keratocyst, unicystic ameloblastoma etc. Orthokeratinized odontogenic cyst was thought to be less destructive compared to odontogenic keratocyst. This case series highlights the clinically aggressive nature of Orthokeratinized odontogenic cyst.

Case Presentation: In this case series six cases of diagnosed Orthokeratinized Odontogenic cyst have been described along with one case of multiple Orthokeratinized odontogenic cysts in a female patient. The clinical, radiographic and histopathologic features have been described in great detail in order to correlate with the previous literature and highlight their clinically aggressive behavior.

Conclusions: Orthokeratinized odontogenic cyst can be deceptive and should be diagnosed appropriately to avoid aggressive treatment protocol. Most of these cysts are associated with inflammation which makes it harder to be diagnosed as the epithelium and connective tissue would have undergone structural changes. Differentiating the cystic lesions of the oral cavity is utmost important to devise appropriate treatment suitable for the patient and for assessing the prognosis, recurrence and rehabilitation to improve the quality of life.

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1. Introduction

Orthokeratinized odontogenic cyst (OOC) is a distinctive and rare cyst. It is defined as an odontogenic cyst that is entirely or predominantly lined by orthokeratinized stratified squamous epithelium (WHO 2017).[1] Initially it was thought to be an orthokeratinized variant of Odontogenic Keratocyst (OKC) due to similarities in location and origin.[2] American oral pathologist John M Wright in 1981 was the first to identify it as a separate entity due to its low recurrence and varied histology. Further studies have shown that it has low proliferating potential, is less aggressive and has a different protein expression compared to OKC.[3] Hence, for the first time OOC was included as a separate entity in the World Health Organization Classification of Head and Neck Tumors in 2017.[4] It shows peculiar features under the microscope like a thick orthokeratinized keratin layer due to the presence of keratohyaline granules, lack of surface corrugations, prominent granular cell layer and flat to cuboidal basal cell layer.[5] Even if there are multiple OOCs in a patient, it is not necessary that the patient should have Nevoid Basal Cell Carcinoma syndrome. Such cysts are termed as Sporadic OOCs. The diagnosis should be made after ruling out Nevoid Basal Cell Carcinoma syndrome according to the First International Colloquium on NBCCS held in

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2011.[3] Because of different treatment approach in OOC compared to OKC it has to be differentiated from the later. The treatment of OOC is conservative in contrast to OKC which has an aggressive treatment protocol. The prognosis, following enucleation is excellent with a recurrence rate of less than 2%. Whereas recurrence rate varies between 8 and 25% after enucleation for OKCs.[6]

In this paper a series of five simple OOC cases and one multiple OOC case has been described correlating clinical, radiographic and histopathological features.

2. Case Description and Results

2.1. Case 1: Multiple OOC

A 30-year-old female reported with a complaint of swelling in her left lower and right upper side of face for 1 year. Her medical and personal history were non commendable. She gave history of intermittent, low intensity pain associated. On examination gross facial asymmetry with no surface skin changes was noted. Intra oral examination revealed bicortical expansion from upper right second premolar to third molar and the lower left molars. The Orthopantamogram showed well-defined radiolucent lesions with sclerotic margins associated with unerupted tooth in right upper (18) and left lower jaw (38) measuring approx. 3x2.5cm and 6.5x4cm respectively (Figure 1 a). Differential diagnosis of multiple Odontogenic Keratocysts and multiple dentigerous cysts was given due to the association of the cysts with unerupted teeth and aggressiveness of the lesions. On surgical excision large tissue sample, associated teeth with attached lining and lot of thin friable material were obtained (Figure 1 b and 1c). On histopathological examination the hematoxylin and eosin-stained section of both upper and lower lesions revealed orthokeratinized stratified squamous epithelium having a flat epithelium and connective tissue interface (Figure 2 a). At areas the epithelium was detached from the underlying tissue and is of varied thickness due to the underlying inflammation (Figure 2 b). Flat to cuboidal cells are noted in the basal layer along with prominent granular cell layer. The cystic lumen is filled with lamellated keratin flakes giving an onion peel appearance (Figure 2 c). Hence, a final diagnosis of Sporadic Orthokeratinized odontogenic cyst was made after clinically ruling out Nevoid Basal Cell carcinoma Syndrome obliviating the need for aggressive treatment.

2.2. Case 2

A 29-year-old male complained of pain in his lower front tooth region for 20 days. His medical and personal history were non commendable. No changes noted on extra oral examination. Well defined intra oral swelling was noted with respect to the lower canines, non-tender and bony hard in consistency. The Orthopantomogram showed large lytic

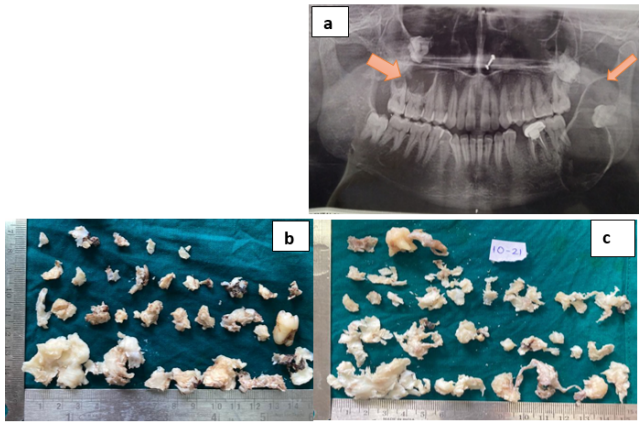

Fig. 1: **a**: Unilocular radiolucency involving 18 and 38; **b**: Excisional biopsy specimen of lower lesion; **c**: Excisional biopsy specimen of upper lesion

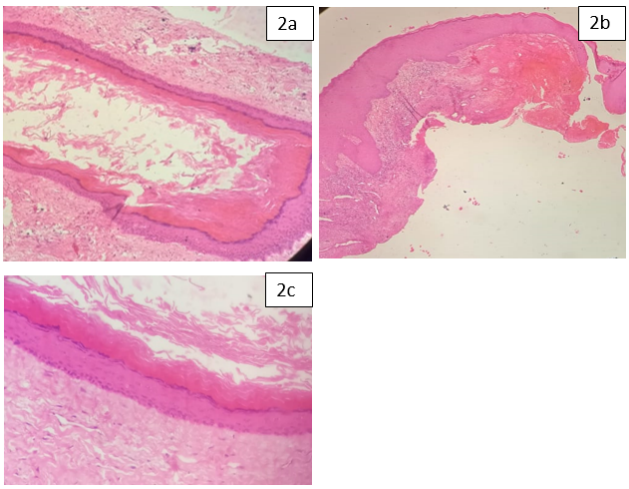

Fig. 2: Hematoxylin and eosin-stained section, 40x magnification, basal layer showing flat to cuboidal cells with prominent granular cell layer and onion peel appearance of keratin

lesion surrounding the impacted lower canine, displacing and resorbing the adjacent teeth (Figure 3 a). On aspiration 2.5 ml blood-tinged thick fluid (Figure 3 b) was obtained which revealed numerous cholesterol crystals, red blood cells (RBCs) and few inflammatory cells like lymphocytes. A provisional diagnosis of dentigerous cyst was given following which an incisional biopsy was performed to rule out Unicystic Ameloblastoma or other aggressive lesions so that appropriate treatment can be devised.

2.3. Case 3

A 30-year-old male was referred to us after incision and drainage of a large extra oral abscess (Figure 4 a) which had developed over a period of two weeks. Swelling and pain had subsided for the patient, after which a radiograph

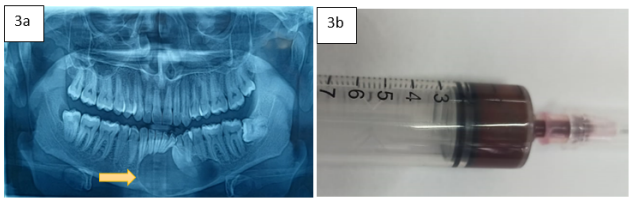

Fig. 3: a: Unilocular radiolucency surrounding left lower canine; **b:** 2.5ml blood-tinged thick fluid

was recorded that showed well-defined radiolucent lesions in relation to periapical and distal aspect of the third molar (Figure 4 b). Excisional biopsy was done and a provisional diagnosis of OKC was made. Cystic capsule and tooth with attached lining were obtained along with few thin friable bits (Figure 4 c).

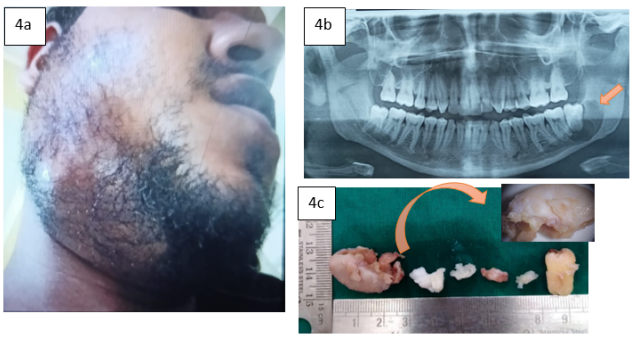

Fig. 4: a: Extra oral abscess; **b:** Multilocular radiolucency surrounding 38; **c:** Cystic capsule sent for histopathology

2.4. *Case 4*

A young adult male complained of pain and swelling in lower right back tooth region for one week. On extra oral examination a diffuse swelling of size 1.5x3cm was noted over the body of mandible. Radiographically a well corticated radiolucent lesion was seen extending from 44 to 48, displacing their roots (Figure 5). A provisional diagnosis of Ameloblastoma was given. Incisional biopsy specimen was sent for histopathological confirmation to proceed with further treatment.

2.5. *Case 5*

A 54-year male reported with a complaint of pain in lower right back tooth region for 1 month. Medical and personal history of the patient were satisfactory. Radiographically there was an ill-defined radiolucent lesion growing in an antero-posterior direction from partially impacted third molar till the premolars on the same side (Figure 6). A provisional diagnosis of OKC was given and excisional biopsy sample sent for histopathological examination.

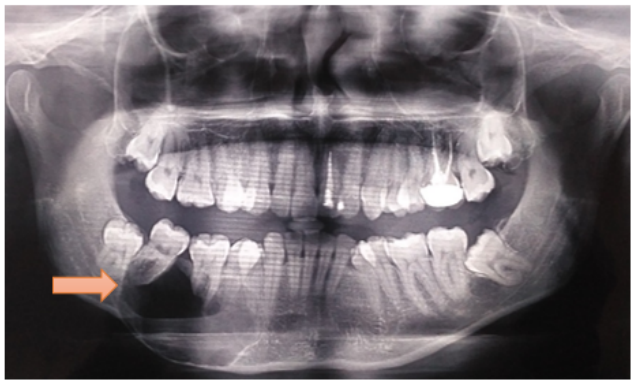

Fig. 5: Multilocular radiolucency displacing the adjacent roots

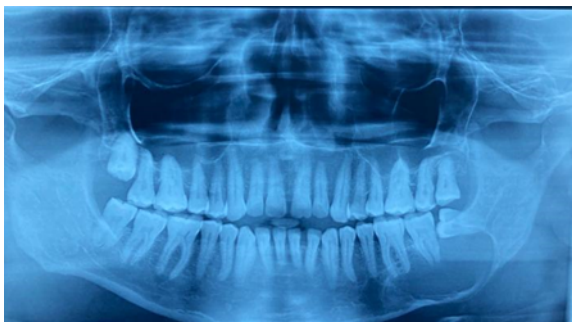

Fig. 6: Well-defined unilocular radiolucency displacing the adjacent roots

2.6. *Case 6*

A 48-year-old female gave a history of pain and swelling over lower third of face since a month. She had history of betel quid chewing for 10 years daily. On intraoral examination erythematous change of the mucosa was seen with no obvious bony expansion (Figure 7). The swelling was tender and bony hard in consistency. Her submandibular lymph node was palpable, mobile, non-tender and soft in consistency. We were unable to procure her radiograph for the purpose of this article. The provisional diagnosis of Odontogenic Keratocyst cyst was made as there was no cortical expansion. Excisional biopsy was sent to us consisting of a large cystic capsule.

2.7. *Histopathological description of all cases*

Histology of all the lesions revealed the same microscopic features. The hematoxylin and eosin-stained section showed cystic capsule lined by orthokeratinized stratified squamous epithelium and sub epithelial connective tissue (Figures 8 and 9). Most part of the epithelium was thin and regular having a flat interface with the underlying connective tissue, at areas the epithelium was detached from the connective tissue (Figure 10). No evidence of basal cell palisading or reversal of nuclear polarity was evident.

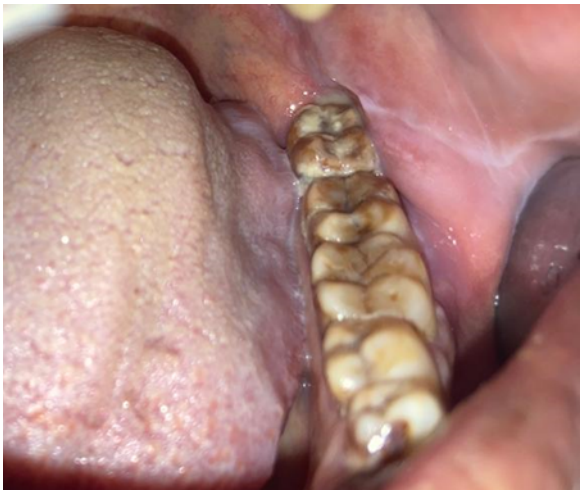

Fig. 7: Hematoxylin and eosin stained section, 10x magnification, uniform orthokeratinized stratified squamous epithelium lining the cystic capsule, lumen filled with orthokeratin

It is made up of flat to cuboidal basal cells, prominent granular cell layer, lamellated keratin flakes filing the lumen, with few areas showing thickening of epithelium (Figure 11). Surface corrugation was absent in most of the cases. Rete ridge formation was noted in certain areas along with spongiosis and acanthosis of superficial layers owing to the underlying inflammation. In case number three the cystic epithelium closely resembled dentigerous cyst in few sections (Figure 12). The cystic wall was made of mature fibrous connective tissue, containing numerous blood vessels, few inflammatory cells and plump fibroblasts.

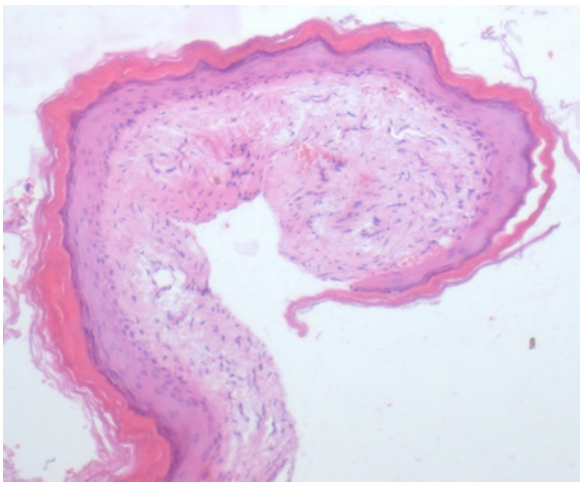

Fig. 8: Hematoxylin and eosin stained section, 10x magnification, orthokeratinized stratified squamous epithelium showing surface corrugations

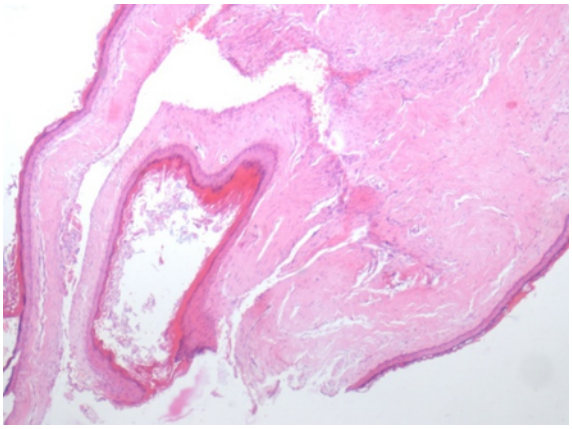

Fig. 9: Hematoxylin and eosin stained section, 10x magnification, uniform orthokeratinized stratified squamous epithelium lining the cystic capsule, lumen filled with orthokeratin

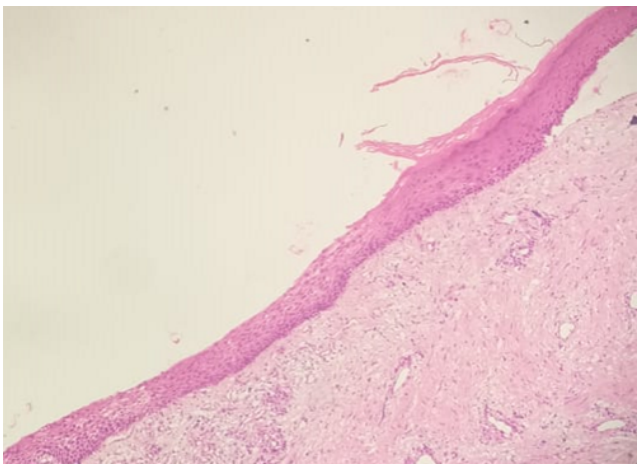

Fig. 10: Hematoxylin and eosin stained section, 20x magnification, separation of epithelium from underlying connective tissue

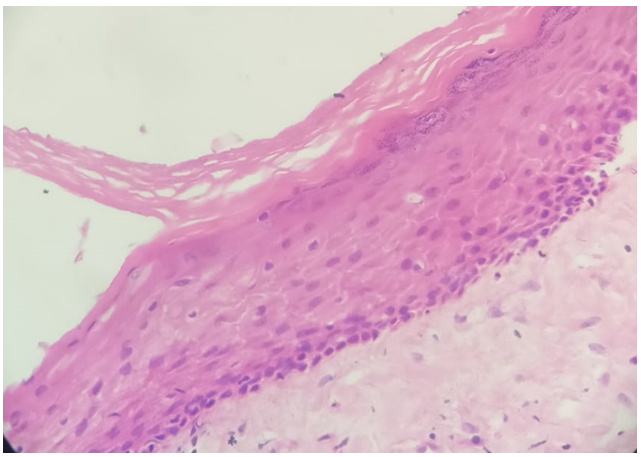

Fig. 11: Hematoxylin and eosin-stained section, 40x magnification, flat to cuboidal basal cells with prominent granular cell layer

Table 1: Data on demographic, radiographic data and recurrence of patients

S No.	Age (in years)	Gender	Location & impacted tooth involved	No. of cysts	Root resorption of adjacent teeth	Radiographic size of the lesion	Locularity	Recurrence
1.	33	Female	Posterior maxilla wrt 18 Posterior mandible wrt 38	2	Not present	3x2.5cm 6.5x4cm	Unilocular Unilocular	Under treatment
2.	29	Male	Anterior mandible wrt 33	1	Present	6x2.5cm	Unilocular	Under treatment
3.	30	Male	Posterior mandible wrt 38	1	Present	4x2cm	Multilocular	Under treatment
4.	27	Male	Posterior mandible wrt 48	1	Present	5.5x4cm	Unilocular	No (34months)
5.	54	Male	Posterior mandible wrt 38	1	Not present	4x2.5cm	Unilocular	Under treatment
6.	48	Female	Posterior mandible wrt 38	1	Present	-	-	No (24months)

Abbreviations: wrt- with respect to

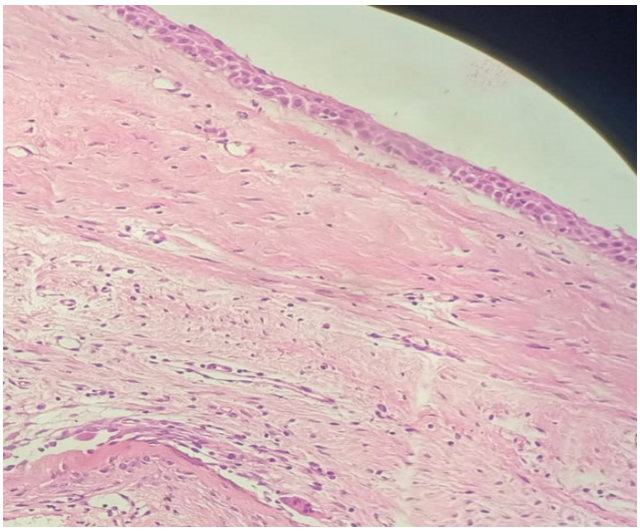

Fig. 12: Hematoxylin and eosin-stained section, 20x magnification, 2 to 4 cell thickness of flat to cuboidal cells mimicking dentigerous cyst

3. Discussion

Orthokeratinized odontogenic cyst is a rare odontogenic cyst occurring in the jaw bones.[6] Various theories for pathogenesis of OOC have been proposed, few say it is actually a Dentigerous cyst with orthokeratinization or it represents a central dermoid cyst.[7] Another view is that it develops from the oral epithelium under the influence of dental papilla or from cell rests.[8] The mean age of occurrence noted here is 36±11.3 years, which is in agreement with a systematic review stating that lesions initially presented around third decade of life with an age range of 10 to 75 years.[9] In our study too there is a male predominance noted similar to a systematic review that found male-to-female ratio to be 2.6:1.[10] The ratio of OOC seen in mandible to maxilla is 2.5:1according to a study[9] and in this case seriestoo there is a high predilection in the mandibular posterior region. Pain and swelling were the initial complaint in all of the cases discussed which is in contrast to the studies so far which reported OOCs as incidental findings.[2] In the six cases that we have reported here, all showed a clinically aggressive behavior which is in contrast to the reported literature. All but one lesion has got a unilocular appearance which is in accordance with a review of OOCs showing 93% of cases to be unilocular.[9] Root resorption is an uncommon finding in OOC in the cases published so far,[11] but in four of our lesions root resorption and displacement has been noted. Of the seven lesions recorded here six are associated with third molars and only one is associated with the canine mimicking Dentigerous cyst, backing up the literature.[12] Data about the size of the lesion and recurrence is mentioned in Table 1.

These cases reported here highlight the importance of establishing the accurate diagnosis in order to plan appropriate treatment. OOC was never considered in their clinical diagnosis, and their provisional diagnosis was either dentigerous cyst, OKC or Ameloblastoma. Almost all of our cases have shown bicortical expansion of the bone, helping us to distinguish between OKC and OOC.

OOC and OKC were together known as Buttery cyst because of their unusual thick buttery content rather than the common watery serous liquid.[13] The thin friable creamish tissue obtained during biopsy was suggestive of keratin and the same was confirmed histologically. It gives the classic onion peel appearance under the microscope as was noted in all our cases.

Nevoid Basal Cell Carcinoma was ruled out in the female with multiple OOCs due to absence of any clinical signs and symptoms. Hence, it was diagnosed as sporadic OOC. Our diagnosis is in accordance with the WHO 2017 classification criteria for histopathologic analysis:[1] a

thin, regular epithelial lining;[2] an orthokeratinized surface that is not corrugated but lamellated, with a prominent granular cell layer;[3] flat or cuboidal basal cells that do not show palisading; and[4] no or only focal areas of non- or parakeratinization associated with inflammation.[1] Along with the characteristic features of the epithelium, the connective tissue was mature and fibrous in all the reported cases. However, inflammation may obscure these classic features as was noted in case number three. But thorough examination and deeper sections of the tissue will help arrive at the correct diagnosis. Previously it was thought that an OOC is actually a dentigerous cyst with orthokeratinization but recent studies could not establish any such association based on immunohistochemical studies.[12] In case number three the lining epithelium closely resembled dentigerous cyst histologically raising a possibility towards this theory.

Enucleation is the most common treatment option for OOCs in the literature due to its low proliferation index compared to OKC.[5] All our lesions are planned or treated with enucleation after marsupialization owing to the large size of the lesions. Data on follow up and recurrence could not be assessed as marsupialization is still in progress in our cases. Only a few OOC cases have been reported to recur after enucleation and, intriguingly, most of the recurrent cases underwent malignant transformation in the literature reported so far.[10]

4. Conclusion

Odontogenic cysts are encountered routinely in the pathology departments and pose a diagnostic dilemma for the oral pathologists. Having an in-depth knowledge of clinical and radiographic features is utmost important along with histopathologic findings to rule out closely mimicking cysts. Orthokeratinized odontogenic cyst is relatively an uncommon cyst but can be diagnosed easily by closely observing the clinical, radiographic and histopathology features, and most of the time does not require any special stains in its diagnosis.

5. Source of Funding

None.

Conflict of Interest

None.

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