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RESEARCH ARTICLE
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CALCIFYING ODONTOGENIC CYST WITH AMELOBLASTOMATOUS PROLIFERATION: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract
The calcifying odontogenic cyst (COC), also known as a Gorlin cyst, is an uncommon odontogenic lesion, accounting for only 1-2% of all jaw cysts. Initially described by Gorlin in 1962 [3], it exhibits a diverse range of clinical and histopathological characteristics. The coexistence of ameloblastomatous proliferation within a COC is exceptionally rare, with fewer than 25 reported cases globally, posing significant diagnostic and management challenges. [6,7,10] This rare finding not only highlights the uniqueness of the case but also emphasizes the critical need for meticulous histopathological examination to ensure accurate diagnosis and appropriate management, thereby improving patient outcomes.

INTRODUCTION

Calcifying odontogenic cysts (COCs) are rare developmental odontogenic lesions characterized by the presence of ghost cells, which can undergo calcification. The Calcifying Odontogenic Cyst (COC), also known as the calcifying cystic odontogenic tumor, was initially introduced by Gorlin et al. in 1962. [3] This rare odontogenic lesion accounts for approximately 2% of all odontogenic lesions and typically manifests as a cyst, though a small percentage (less than 5%) can present as a solid tumor-like mass. Within cystic COCs, three distinct histological subtypes are recognized. The most common is the Simple Unicystic type, comprising about 65% of cases, featuring squamous or stellate reticulum-like epithelium, with or without basal cell palisading, large eosinophilic ghost cells (often calcified), and sometimes dentinoid material and melanin deposits. The Odontoma-associated type, making up roughly 22% of cases, displays the microscopic characteristics of the simple cystic type but with an accompanying odontoma. Lastly, the Ameloblastomatous type is identified by stellate reticulum-like areas, palisaded basal cells, reverse nuclear polarization, and the presence of ameloblastoma proliferations within the cyst wall.

CASE REPORT

A 65-year-old male presented with a chief complaint of pain and swelling in the lower right ridge region for one week, with a prior history of progressive swelling in the same area for six months. The patient's dental history revealed extraction of the lower anterior teeth around one year back. He reported chronic bidi smoking and tobacco chewing for 35 years. Extraoral examination showed no gross facial deformity, sinus, fistula, or pus discharge. Intraorally, there was a single, well-defined swelling, measuring approximately 2 × 2 cm, located in the cuspid–bicuspid region anterior to tooth 45. On palpation, it was found to be soft, tender, nonreducible, and noncompressible.

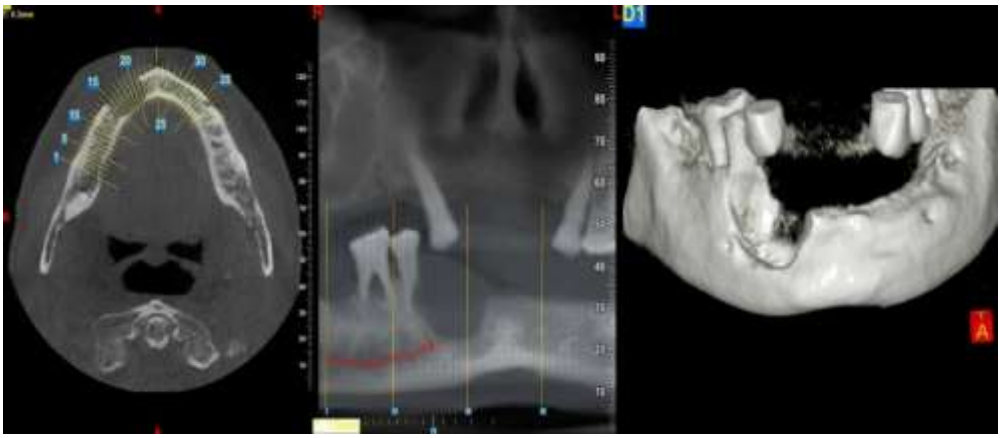


Figure 1: CBCT coronal, axial view and 3D construction view showing unilocular radiolucency involving medial aspect of mandibular right second premolar

Patient was subjected to CBCT. Radiographic evaluation revealed a well-defined, unilocular radiolucency in the affected region, accompanied by buccal bone perforation and root resorption associated with tooth 45.

A provisional diagnosis of residual cyst was made, with a differential diagnosis including odontogenic keratocyst and unicystic ameloblastoma. The patient underwent complete cystic enucleation, and the tissue sample was sent for histopathological examination to the Department of Oral Pathology. Multiple soft tissue specimens along with extracted mandibular right second premolar tooth. Creamish brown in colour with the size of specimen- ranging from 0.6 x 0.4 x 0.2cm^3 to 1.7 x 1.4 x 0.6cm^3 having soft to firm consistency.

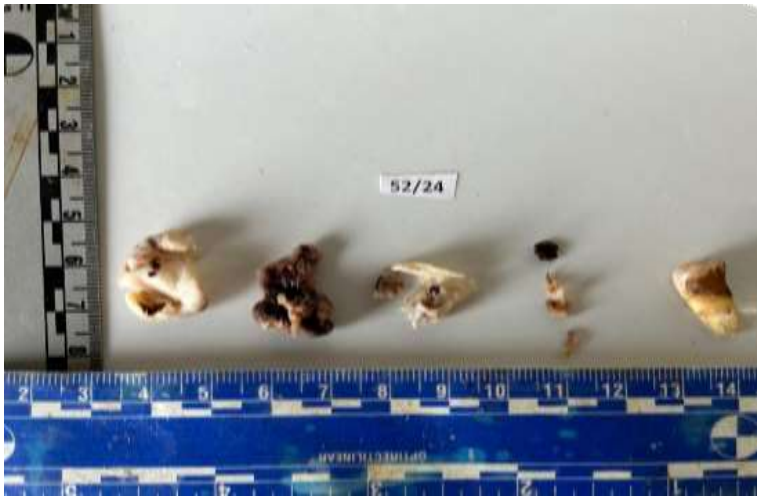


Figure 2: Gross specimen received showing multiple soft tissue specimens along with mandibular right second premolar.

Microscopic examination showed cystic cavity lined by odontogenic epithelium, with the presence of ghost cells and areas of calcification characteristic of a calcifying odontogenic cyst. Notably, anastomosing cords of odontogenic epithelium resembling pre-ameloblast-like tall columnar cells, with central regions composed of loosely arranged, stellate reticulum-like cells, were seen. Multiple ghost cells were also found within the connective tissue stroma, consistent with ameloblastomatous proliferation.

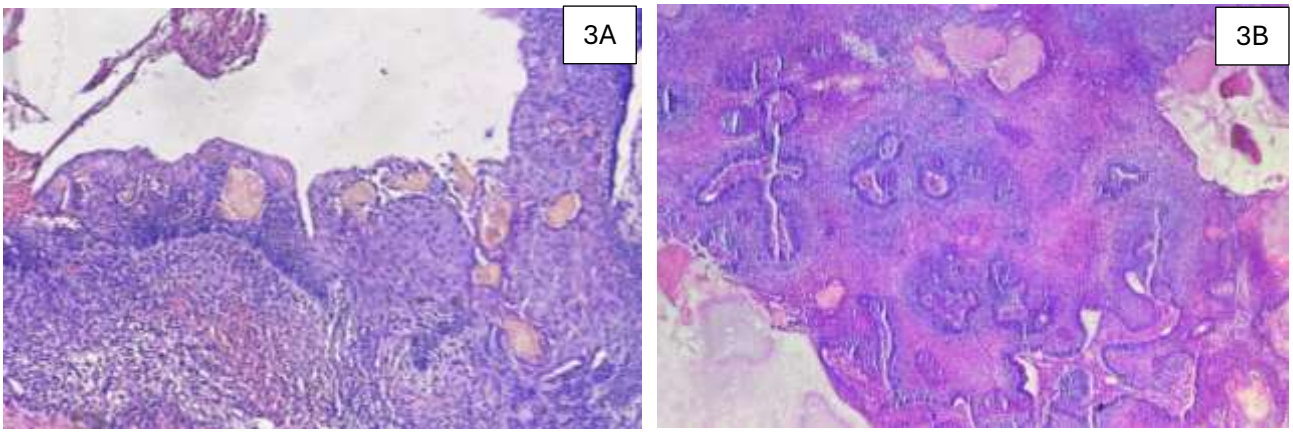


Figure 3 (A): H&E stain tissue section showing cystic cavity lined by odontogenic epithelium having pre ameloblast like columnar basal cells, loosely arranged parabasal cells resembling stellate reticulum and groups of ghost cells(40x) and (B) showing ameloblastic follicles in the connective tissue stroma (10x)

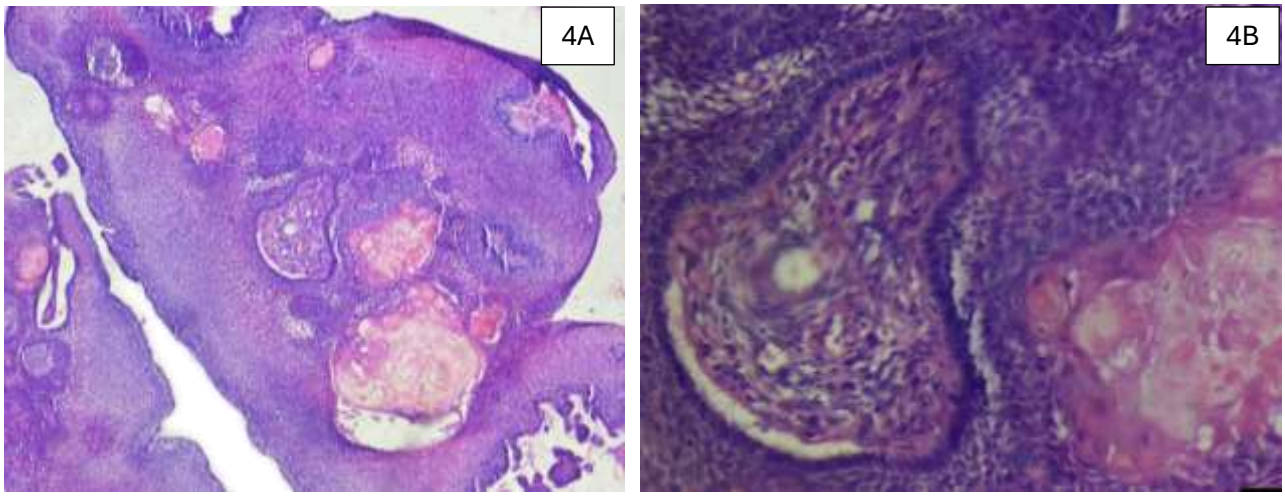
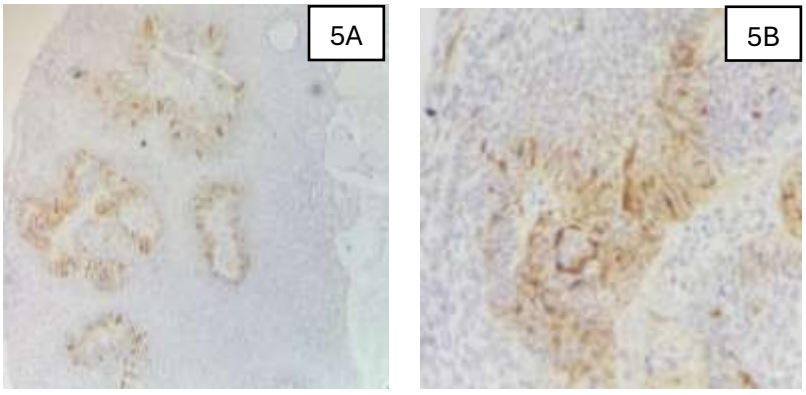


Figure 4 A: H&E-stained section showing follicles of odontogenic epithelium having pre-ameloblast like tall columnar cells with centrally located loosely arranged polygonal cells resembling stellate reticulum cells with some groups of ghost cells are seen in the connective tissue stroma (10x) and (B) (40 x)

Immunohistochemistry was performed for confirmation of ameloblastomatous proliferation in connective and demonstrated positivity for Calretinin in tall columnar ameloblast-like cells, supporting the diagnosis of a calcifying odontogenic cyst with ameloblastomatous proliferation.



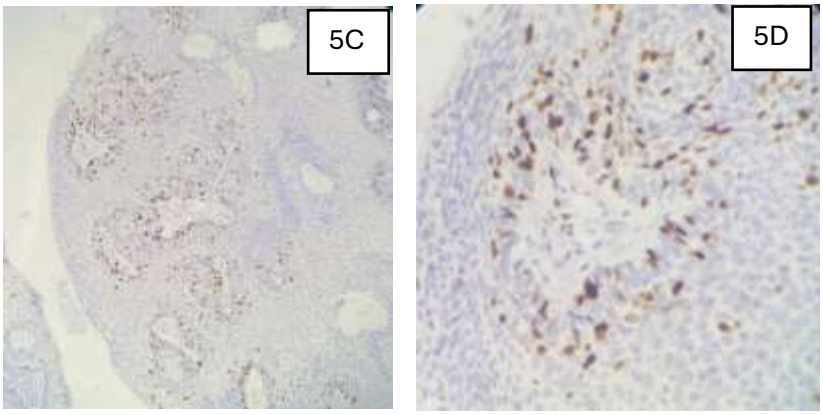


Figure 5 A & B: IHC Calretinin tall columnar ameloblast like cell shows positivity for Calretinin in low and high-power view. 5C & 5D IHC images of Ki 67.

Based on Histological features and IHC findings, a definite diagnosis of calcifying odontogenic cyst with ameloblastomatous proliferation was given.

DISCUSSION

Calcifying odontogenic cysts exhibit considerable histologic diversity and variable clinical behavior. The World Health Organization (WHO) has reclassified COCs several times, reflecting their complex nature, and currently categorizes them as odontogenic tumors due to their neoplastic potential (Gorlin et al., 1962; WHO, 2005) (Table 1). However, in 2017 WHO classification, it was reclassified in the group of odontogenic cysts and is still continued as odontogenic cyst in WHO 2022 classification.

Name of researcher	**Year**	**Name given for COC**
Gorlin et al.	1962	COC
Gorlin et al.	1962	COC
Gold	1963	Keratinizing COC
Bhaskar	1965	Keratinizing ameloblastoma
Fejerskov and Krogh	1972	Calcifying ghost cell odontogenic tumor
Freedman et al.	1975	Cystic calcifying odontogenic tumor
Praetorius et al.	1981	Dentinogenic ghost cell tumor
Ellis and Shmookler	1986	Epithelial odontogenic ghost cell tumor
Colmenero et al.	1990	Odontogenic ghost cell tumor
Shear	1994	Odontogenic ghost cell ameloblastoma
Wirshberg et al.	1994	Odontocalcifying odontogenic tumor
Toida et al.	1998	Calcifying ghost cell odontogenic cyst
WHO	2005	Calcifying cystic odontogenic tumor
COC- calcifying odontogenic cyst, WHO – world health organisation		

Table 1: Various names for calcifying odontogenic cyst

COCs are relatively rare, making up about 1-2% of all odontogenic cysts (Gorlin et al., 1962). The subtype with ameloblastomatous proliferation is even rare. According to a **study by Hong et al. (2007),** which reviewed 92 cases of COCs, only 11 (approximately 12%) were of the ameloblastomatous type. This subtype's prevalence is thus estimated to be significantly lower than that of typical COCs. The literature review by **Praetorius et al. (1981**) and other studies indicates that these cases are sporadically reported, with fewer than 25 cases documented worldwide, including only a few from India. It has been accepted that there are two variants of COC: cystic and neoplastic. Due to this, dualistic nature various classifications have been proposed by different clinicians (Table 2, table 3).

Type 1	Type 2
Cystic type	**Neoplastic type**
1. Simple unicystic type 1. Odontoma producing type 2. Ameloblastomatous proliferating type	3. DGCT Slightly modified from Praetoriu S et al., 1981

Table 2: Classification of calcifying odontogenic cyst proposed by Praetorius et al. [4]

Calcifying cystic odontogenic tumor (CCOT) includes peripheral and central cases	
CCOT type 1	Simple cystic CCOT. Includes pigmented and clear cell variants
CCOT type 2	Odontoma-associated CCOT
CCOT type 3	Ameloblastomatous proliferating CCOT
CCOT type 4	CCOT associated with benign odontogenic tumours other than odontoma
Dentinogenic ghost cell tumour (DGCT)	
DGCT type 1	Central, solid, aggressive variant
DGCT type 2	Peripheral, less aggressive variant
Ghost cell odontogenic carcinoma (GCOC)	
GCOC arising 'de novo'	Not associated with a previous DGCT or CCOT, but with areas suggesting DGCT
GCOC ex-CCOT	GCOC arising from a previous CCOT
GCOC ex-DGCT	GCOC arising from a previous DGCT

Table 3: Classification of calcifying odontogenic cyst proposed by Ledesma-Montes et al. [4]

A 2008 international study of 122 cases found that nearly 90% were benign cystic lesions with low recurrence, leading to the current recommendation to reclassify CCOT. COCs are relatively rare, making up about 1-2% of all odontogenic cysts **(Gorlin et al., 1962**). The subtype with ameloblastomatous proliferation is even rarer. Table 4 shows comparison of demographics and clinical, histologic and radiographic appearances of previous cases of ameloblastomatous calcifying odontogenic cyst.

According to **Hong et al (1991). and Ledesma-Montes et al (2008),** on microscopic examination, ameloblastomatous COC resembles unicystic ameloblastoma except for the ghost cells and calcifications within the proliferative epithelium. Despite the diversity in clinical presentation, there are several histopathological features that are consistently observed across the cases:

1. Ghost Cells: These are altered epithelial cells characterized by their lack of nuclei and eosinophilic cytoplasm, often observed in association with calcifications.

2. Ameloblastic Proliferations: Many cases exhibit areas of ameloblastic differentiation, which are similar to those seen in ameloblastomas.

3. Cystic Structures: The presence of cystic structures lined by odontogenic epithelium is a hallmark of these lesions. 4. Calcifications: Variable amounts of calcified material are present within the cystic and ameloblastic components.

4.**Calcifications:** Variable amounts of calcified material are present within the cystic and ameloblastic components.

In cases with ameloblastomatous proliferation, the epithelial component not only shows increased layering and hyperplasia but also resembles the architecture of an ameloblastoma. This includes the presence of palisaded columnar cells with polarized nuclei that are typical of ameloblasts. The overlying stellate reticulum-like area can appear more extensive compared to typical COCs. Immunohistochemical analysis often reveals a high Ki-67 labelling index, indicating a significant proliferative activity within these regions **(Kumamoto et al., 2005; Suzuki et al., 2005).**

In ameloblastomatous COCs, the interaction between ghost cells and surrounding epithelial cells might contribute to the aggressive nature of the cyst by inducing local inflammation and possibly aiding in the invasive potential of the epithelium **(Suzuki et al., 2005)**

Reference	Age & Sex	Presentation	Bone Involved	Size of Lesion	Root Resorption	Cortical Plate	Radiology	Recurrence	Histologic Diagnosis	Impacted Teeth
Aithal et al. [6]	28 years, female	Tender swelling in lower left posterior region	Mandibular left posterior region	2.5 cm × 2 cm	Absent	Buccal plate expanded	Multilocular radiolucency from 33 to 37 region	Absent	Ameloblastomatous COC	Absent
Iida et al. [7]	17 years, male	Tender right facial swelling	Mandibular right posterior region	DNF	Absent	Buccolingual expansion	Multilocular radiolucency from 47 to right ramus	Absent	Ameloblastomatous COC	Present
Kamboj and Juneja [8]	58 years, female	Tender right facial swelling	Mandibular left posterior	DNF	Absent	Buccolingual expansion	Multilocular radiolucency 43 to condyle-coronoid region	DNF	Ameloblastomatous COC	Absent
Ledesma-Montes et al. [9]	22 years, male	Nontender swelling-right facial region	Mandibular right posterior region	DNF	Present in mandibular right first and second molar	Buccolingual expansion	Unilocular radiolucency from 46 to 48 region	Absent	Ameloblastomatous COC	Present
Nosrati and Seyedmajidi [10]	22 years, male	Nontender swelling - right facial region	Mandibular right posterior region	DNF	Present in mandibular right first and second molar	Buccolingual expansion	Unilocular radiolucency from 46 to 48 region	Absent	Ameloblastomatous COC	Present
Gupta and Gupta [11]	65 years, male	Tender swelling in lower left jaw	Mandibular left posterior	4 cm × 5 cm	Absent	Buccal bone perforated	Bilocular radiolucency 37 to 38 region	Absent	Multicystic ameloblastomatous	Absent
Singh et al. [12]	24 years, female	Left facial swelling	Mandibular left anterior region	5 cm × 3 cm	Absent	Buccolingual expansion	Unilocular radiolucency from 35 to 48 region	Absent	Ameloblastomatous calcifying ghost cell odontogenic cyst	Absent
Tamanna et al. [13]	21 years, male	Tender swelling on lower left jaw	Mandibular left second molar region	DNF	Present	Buccolingual expansion	Unilocular radiolucency in left ramus	Present	Ameloblastomatous COC	Present
Shah U et al. [11]	20 years, female	Asymptomatic	Mandibular right posterior region	8 cm × 8 cm	Present in mandibular right second molar region	Buccolingual expansion	Unilocular radiolucency from 37 to condyle-coronoid region	Absent	Ameloblastomatous COC	Present
Present case	65 years, male	Swelling	Mandibular right second premolar	2 cm × 2 cm	Mandibular right second premolar	Buccolingual expansion and perforation	Unilocular radiolucency irt 45 region	Absent	Ameloblastomatous calcifying ghost cell odontogenic cyst	Absent

Table 4: Comparison of previous cases of ameloblastomatous calcifying odontogenic cyst. [11]

Calretinin, a 29 kDa calcium-binding protein, primarily expressed in certain subtypes of neurons, has been shown to be positive in the odontogenic epithelium during different stages of odontogenesis. In the enamel organ of developing tooth, calretinin expression in the stellate reticulum-like cells is reported to be moderate-to-intense and nonuniform during the early and late bell stages of tooth development which is similar to that observed in the stellate reticulum-like cells in ameloblastomas. The lack of uniformity in staining intensity could be due to variable expression of calretinin, which is governed by the metabolic activity of the cells. [13]

The present study shows calretinin positivity in peripheral ameloblast like cells which is in accordance with the results of **D'Silva et al.** that reported the positivity in peripheral ameloblast-like cells in all their cases. In the study by **Amrutha Rudraraju et al** immunopositivity was confined to the stellate reticulum-like cells in unicystic ameloblastomas. No staining of the basal ameloblast-like cells was observed, also no calretinin expression was observed in the other odontogenic tumors.

Expression of calretinin in peripheral ameloblast-like cells was different from that during normal odontogenesis. The inner enamel epithelial cells do not attain functional maturation as secretory ameloblasts in ameloblastoma, which has been attributed to the mutation of ameloblastin. [13]

Ki-67 is a protein associated with cell proliferation, and its expression is often examined in ameloblastomas, particularly in relation to calcifying odontogenic cysts (COCs) and their potential impact on tumor behavior. The presence of a COC within or adjacent to an ameloblastoma may

influence Ki-67 expression and potentially affect the tumor's proliferative capacity. [15][16][17] Table 5 shows differential diagnosis, key features and possible IHC markers for different odontogenic lesions.

Differential diagnosis	**Key histopathological features**	**Positive IHC markers**
Calcifying odontogenic cyst	Presence of ghost cells and calcifications but without aggressive ameloblastomatous proliferation	CK19, Amelogenin, Ki 67 (Variable)
Unicystic ameloblastoma	Cystic structure with ameloblast like epithelial cells, lacks ghost cells and calcifications.	CK19, Amelogenin, Calretinin, Ki 67 (High proliferation index)
Dentigerous cyst	Unilocular radiolucency associated with impacted tooth; thin epithelial lining; lack ghost cells	CK19, Amelogenin Bcl-2 (variable)
Odontogenic keratocyst (OKC)	Parakeratinized epithelial lining; absence of ghost cells and calcifications; high recurrence rate.	CK19, Amelogenin Bcl-2 (high expression)
Ameloblastic fibroma	Odontogenic epithelial components in fibrous stroma; lacks ghost cells and extensive calcifications.	CK19, Vimentin, Amelogenin, Calretinin (Negative)

Table 5: showing differential diagnosis, key features and possible IHC markers for different odontogenic lesions.

SURGICAL MANAGEMENT:

Enucleation: It involves the complete removal of the cystic lesion, which helps in reducing the recurrence risk. This method is frequently recommended as the primary treatment for COCs with ameloblastomatous proliferation. For instance, cases have reported no recurrence when thorough enucleation was performed, as highlighted by **Nosrati and Seyedmajidi et. al (2009),** who successfully treated a 22-year-old male patient with surgical enucleation and observed no recurrence in follow-up periods.

Marsupialization: In instances where the cyst is large or in a critical anatomical location, marsupialization can be employed. This method reduces the cyst's size, making subsequent definitive surgical procedures less invasive. **Tamanna et al. (2013)** documented a case where initial marsupialization was followed by recurrence, requiring subsequent surgical removal, which then prevented further recurrence.

Wide Surgical Excision: For recurrent or particularly aggressive lesions, wide surgical excision with clear margins is often necessary. This approach ensures complete removal of the proliferative tissue, thereby minimizing the chance of recurrence. Studies such as those by **Singh et al. (2012**) support this approach, documenting successful outcomes without recurrence following wide excision.

FOLLOW-UP AND RECURRENCE MANAGEMENT:

Monitoring and Long-Term Follow-Up: Taylor et al. (2009) stress the importance of long-term follow-up, noting that regular monitoring can detect recurrences early, which is crucial for managing these potentially aggressive cysts. The frequency of follow-up recommended varies, but the consensus points towards more frequent evaluations in the first few years' post-treatment.

CONCLUSION

COC with Ameloblastomas proliferation is a rare histologic variant. There are very few cases reported with this variety of COC in the literature. Several authors have suggested that if COC is associated with an ameloblastoma, its behavior and prognosis will be that of an ameloblastoma, not of COC. Careful postoperative observations are necessary for COCs which are associated with ameloblastoma.

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