

Gorlin's Cyst – A Pathologist's Enigma: Case Report with Literature Review

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ABSTRACT

Introduction: Gorlin Cyst or Calcifying Odontogenic Cyst (COC) is an uncommon developmental odontogenic cyst lined by ameloblast like basal cells where stellate reticulum like cells overlaid. It is pathognomically characterized by presence of ghost cells and dentinoids. Controversy revolves around its behavior which portrays it as either a cyst or a neoplasm. Numerous identical pathological entities are found in the literature with different nomenclatures.

Case presentation: A 45 year old male patient reported to us with 03 years history of slow-growing, asymptomatic, hard intraosseous swelling of the mandibular body region which was subsequently diagnosed as Gorlin cyst based on clinical, radiological and histopathological features.

Management and prognosis: Conservative surgical enucleation was performed without any signs of recurrence for the next 01 year.

Conclusion: COC is a pathologist's enigma needs critical observation to be differentiated from similar jaw lesions containing ghost cells such as odontome, odontome with other odontogenic neoplasms, dentinogenic ghost cell tumor (DGCT) and ghost cell odontogenic carcinoma. Its locally aggressive behavior deceptively demonstrates the mysterious conjuncture of being a cyst and a neoplasm. Periodic follow up is necessary to rule out recurrence.

Keywords: Gorlin Cyst, Ghost Cell, Dentinogenic Ghost Cell Tumor (DGCT), Abberant keratinization, Wnt-Notch pathway
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INTRODUCTION:

Calcifying Odontogenic Cyst (COC), well known as "Gorlin Cyst" is a rare pathological entity of the jaws developing from odontogenic epithelium possessing an average occurrence rate of 1-2% among all the odontogenic lesions¹. Gorlin et al. in 1962 described COC for the first time as an analogue to cutaneous calcifying epithelioma of Malherbe and enlightened the crucial differences between these two². COC comprises a number of variants, showing features of benign odontogenic neoplasm which was revised by Praetorius et al. (1981) who considered it as a cyst and a neoplasm simultaneously³. Calcifying cystic odontogenic tumor (CCOT), Calcifying ghost cell odontogenic cyst, and Dentinogenic ghost cell tumor (DGCT) are synonymous to this entity⁴. Classically being an intraosseous lesion, it also revealed extraosseous or peripheral counterpart having almost equal sex and site predilection for both maxilla and mandible³. It exhibits a wide age range with a peak incidence at second decade³. Conventional and advanced radiography demonstrate well to ill-defined uni or multilocular radiolucencies often associated with irregular radioopaque flecks suggestive of focal calcifications rendering a wide range of differential diagnosis⁵. Sometimes it may be associated with unerrupted teeth³. The striking histopathology unveils presence of multiple ghost cells and dentinoid substances near the cystic lining which is composed of odontogenic epithelium³. Palisade of cuboidal ameloblast like cells are found in the basal layer where stellate reticulum like cells overlay these in the cystic lining [3]. The opted treatment for COC is conservative surgical enucleation until local recurrences^{1,3}. The present case describes

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systematic diagnosis of COC in mandible in a middle aged male patient with pertinent clinico-pathological attributes.

CASE REPORT:

A 45 years old male patient presented to our departmental OPD with history of slowly expansile hard swelling associated with occasional mild pain over the right lower dento-alveolar region since last 03 years. Extra-oral profile [Fig. 1a and b] revealed ill-defined, non-tender, bony-hard bulged out swelling on right side of body of the mandible. Expansion of the lower border of mandible was also noted on the ipsilateral side without any signs of region-

al lymphadenopathy. Intra-oral [Fig. 2a and b] examination showed obliteration of right lower buccal vestibule along with expansion of lingual cortical plates in relation to 46, 47 and 48. Overlying mucosa was normal. 46 was carious while 47 and 48 were mobile. Regional teeth were vital. The patient was anaemic and heterozygous state of β -thalassemia was diagnosed in early childhood through serum electrophoresis of protein. No other co-morbidity was reported. High Performance Liquid Chromatography (HPLC) of Hemoglobin was also performed in the hematology department where the result was also suggestive of this. Orthopantomogram [Fig. 3a] of the jaws revealed ill-defined mixed features of radio-opacity and radiolucency on the peri-radicular area of 45, 46 and 47. CT-scan [Fig. 3b] of the jaws revealed expansion of both the cortical plates along with perforation of lingual cortical plate. Small flecks of radio-opacities on the right lower dento-alveolar region were also appreciated.

Aspiration was negative. Based on the clinical and radiological findings, provisional diagnosis of benign odontogenic neoplasms was made and Calcifying Cystic Odontogenic Tumor (CCOT), Calcifying Epithelial Odontogenic Tumor, Ameloblastic Fibroma, Ameloblastic Fibro-odontoma etc. were considered. However, differentiation from fibro-osseous lesions was also to be made.

Routine Hematological investigation, Blood Sugar Profile, Liver Function Test and Serology were performed where all the parameters were within normal limits except for the Hb conc. and RBC values. The patient's Hb% was 8.2 gm%. As per the prescription of the consultant hematologist, the patient's Hb was raised to 10.2 gm% after transfusion of 2 unit of PRBC.

Patient was sero-negative for HIV I and II, HBV and HCV. With regain of hemodynamical stability, written consent was obtained from the patient as well as from the hematologist for performing minor surgical procedure. Under hematologist's supervision, incisional biopsy was performed after the patient was haemodynamically stable and the specimen was processed thereafter. Light microscopic evaluation [Fig. 4 and 5] revealed presence of cystic cavity lined by tags of odontogenic epithelium at places chiefly consisting of stellate reticulum like cells being backed by fibrovascular connective tissue stroma in routine hematoxylin and eosin stain. The most striking feature [Fig. 6] is the presence of few clumps of multiple, ellipsoid, ballooned, anucleated cells of aberrant morphology resembling 'ghost cells' within the cystic cavity and near the cystic lining. Van Geison (VG) staining [Fig. 7a and b] revealed yellowish orangophilia of the ghost cells which was characteristic. The overall histopathological features were suggestive of Calcifying Odontogenic Cyst or Gorlin Cyst. Patient was referred to Dept. of Oral and Maxillofacial Surgery for complete surgical enucleation of the cyst and histopathologically reconfirmed as Gorlin cyst. One year follow up showed no signs of recurrence.

Table 1. Classification of Ghost Cell lesions by Praetorius et al. (2006)³:

Group 1	Simple cyst Calcifying Odontogenic Cyst (COC)
Group 2	Cysts associated with odontogenic hamartoma or benign neoplasms: calcifying cystic odontogenic tumor (CCOT)
Group 3	Solid benign odontogenic neoplasms with similar cell morphology to that in the COC with dentinoid formation: Dentinogenic Ghost Cell Tumor
Group 4	Malignant odontogenic neoplasms with features similar to these odontogenic ghost cell tumor Ghost cell odontogenic carcinoma



Fig.1. Photographs showing bulged out appearance of right lower third of face (near the angle of mandible).



Fig.2: Photographs showing a. buccal and b. lingual cortical plate expansion with overlying normal mucosa.

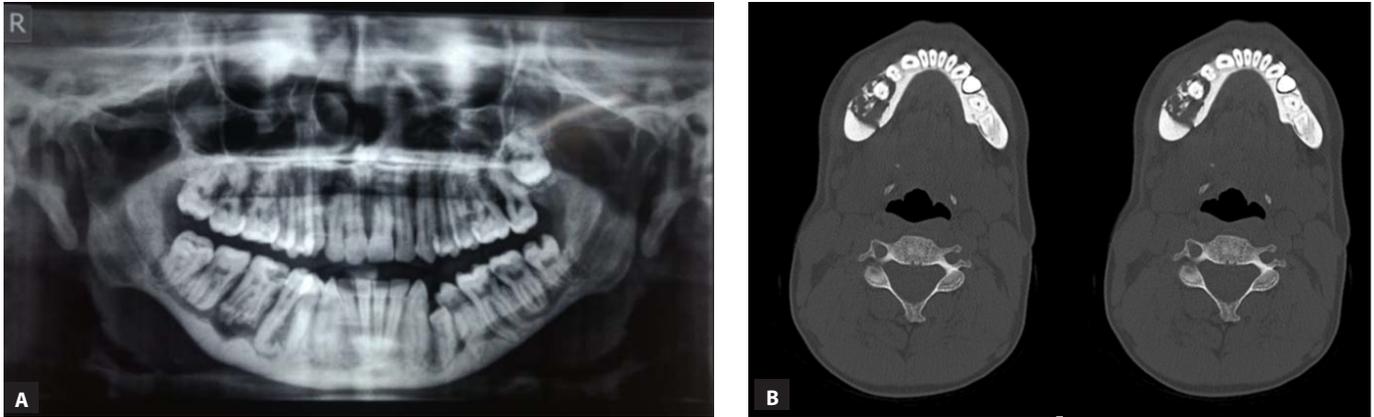


Fig.3. Radiographs showing a. panoramic view of the lesion and b. CT-findings of the lesion where bucco-lingual cortical plate expansion along with perforation of the lingual cortical plate with flecks of calcifications are seen.

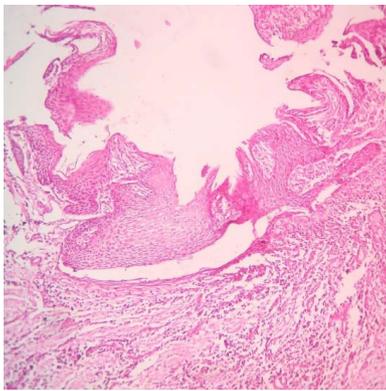


Fig. 4. Photomicrograph (H and E stain, 10x) showing fragmented odontogenic epithelium in the cystic lining.

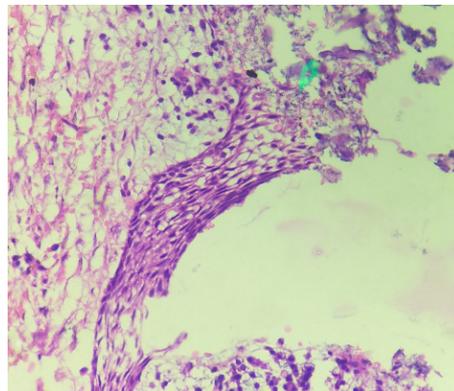


Fig.5. Photomicrograph (H and E stain, 40x) showing stellate-reticulum like cells in the cystic lining backed by myxomatous and fibrovascular stroma.

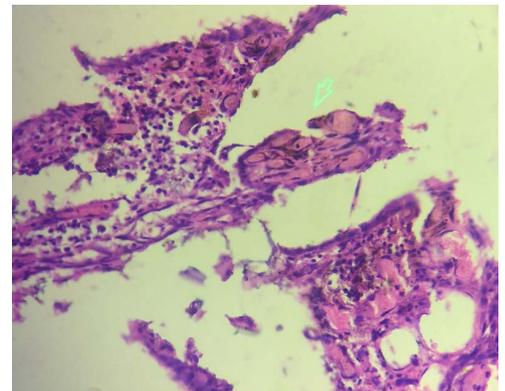


Fig. 6. Photomicrograph (H and E stain, 40 x) showing clumps of eosinophilic, balloon shaped, anucleated ghost cells.

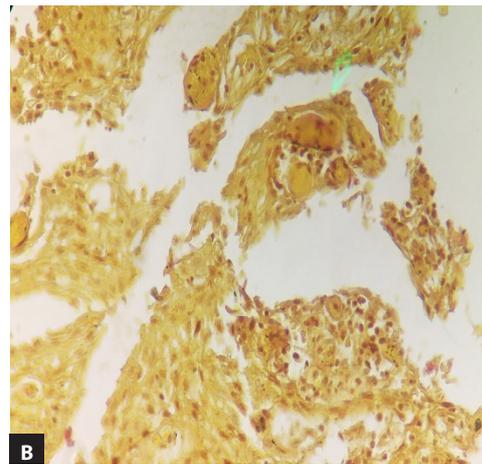
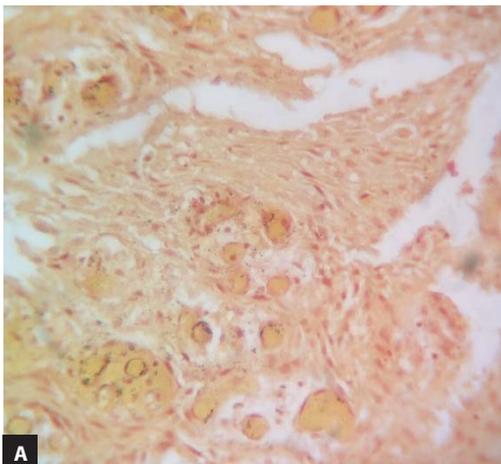


Fig 7a and 7b: Photomicrographs (VG stain, 40x) showing yellowish, round to ovoid, anucleated ghost cells with definite cellular outline.

DISCUSSION:

COC, described as a non-neoplastic lesion in 1971 was re-classified as a tumor in 1992 by World Health Organization (WHO)⁶. In 2005, WHO redefined ghost cell lesions in the publications under the

headings of 'Dentinogenic Ghost Cell Tumor (DGCT)' and 'ghost cell odontogenic carcinoma' where DGCT was mentioned as 'calcifying ghost cell odontogenic tumor', 'odontogenic ghost cell tumor' and 'dentinoameloblastoma' as solid variant of calcifying odontogenic cyst³. Praetorius in 2006, proposed a classification for ghost cell le-

sions [Table. 1] considering cystic, benign and malignant components³. WHO defined COC in 1992 as "a cystic lesion in which the epithelial lining shows a well-defined basal layers of columnar cells, an overlying thick layer of stellate reticulum like cells and masses of 'ghost' epithelial cell that may be in the epithelial lining or in the fibrous capsule. The 'ghost' epithelial cells may become calcified"³. Revised definition of DGCT proposed by WHO in 2005 was, "A locally invasive neoplasm characterized by ameloblastoma-like islands of epithelial cells in a mature connective tissue stroma. Aberrant keratinization may be found in the form of ghost cells in association with varying amounts of dysplastic dentin"⁷.

COC is a rarely encountered central jaw lesion where 88% revealed cystic nature leaving 12% of neoplastic or solid pattern¹. Fejerskov and Krogh in 1972 demystified the behavioural change of COC opining the concept of cystic changes in a pre-existing neoplastic DGCT rather than neoplastic transformation in a pre-existing cyst lining⁸. COC involves both the mandible and maxilla at an almost equal rate showing a mild preponderance for the anterior region¹. Li and Gao had reported maxilla to be a more frequently involved site⁹. It shows almost equal gender predilection without any definite racial involvement³. Though a wide age range has been reported so far, Praetorius et al. had mentioned bimodal age distribution for this lesion under discussion³. The present case referred to a male patient of 5th decade bearing intraosseous lower jaw lesion which was diagnosed as Gorlin Cyst or COC where demographic data was in accordance with the previous literatures.

Similar to other intraosseous jaw lesions, it clinically manifests as asymptomatic, expansile, bony hard swelling with variable extent of buccal and lingual cortical plate involvement and its perforation with displacement of regional teeth^{3,6}. A very rare peripheral or extraosseous variant may present as sessile or pedunculated, soft to firm, non-tender, smooth-surfaced, pink mass on the gingiva radiologically producing saucerizing erosion of the superficial bone^{3,10}. Panoramic radiograph reveals well-defined or ill-defined unilocular/multilocular radiolucency admixed with small, often tooth-like bits of radio-opacities in one-third to half of the cases¹¹. Root resorption along with displacement of teeth and cortical bone perforation can occasionally be seen precluding its considerable growth potential³. CT findings corroborates to all these imaging characteristics with much finer details¹². The current case here ratified all these clinico-radiological parameters relating to previous authors. Clinical and radiological features gave us the clue to provisionally diagnose this as a benign odontogenic neoplasm with broad spectrum of differential diagnosis previously mentioned.

Being a cyst, it exhibits a cystic cavity lined by basal ameloblast like cells having reverse nuclear polarity with superficial layer of stellate reticulum like cells approximated to ghost cells and dentinoid material¹³. Ghost cells are inexplicable pathological features of uncertain histogenesis though multiple developmental hypothesis encircle its origin. From its earliest description by Highman and Ogden in 1936 in pilomatricoma to Gorlin's report of its evidence in COC later in 1962, the most accepted theory till date is the abnormal or aberrant keratinization¹³ which is supported by Abrams & Howell¹⁴ and Shear et al.³. These elliptoid, oval, eosinophilic cells are bounded by definite cellular outline while they are devoid of nuclei. Often it shows nuclear remnants depicting stages of degeneration³. Gold et al. drew a conjecture of origin of ghost cells from any of the epithelial cell layers¹⁵. Kusama et al. (2005) and Fragnani et al. (2003) demonstrated presence of hard α -keratin and AE1/AE3 cytokeratin markers in the ghost cells³. Hong et al. had speculated

the theory of coagulative necrosis behind formation of the ghost cells¹⁵. Levy et al. had suggested squamous metaplasia followed by dystrophic calcification due to local tissue hypoxia¹⁶. Landmark study regarding enormous role of Wnt (Wingless gene of vertebrate homologue integrated 1) pathway together with Notch signaling pathway conveyed mechanism of organogenesis of epithelial origin where odontogenesis covers an important chapter. They are functionally synergistic and aberrant operation of these pathways are believed to be responsible for ghost cell formation in this modern era of molecular pathology¹³. Dentinoid or dysplastic dentin is sometimes found in relation to the cystic lining demonstrating the propensity of calcification of these cells [3]. Sapp and Gardner (1977) indicated presence of dystrophic calcification juxtaposed to mass of ghost cells appearing as fine powdery elements or coarse basophilic granules under light microscope. Fluorescent dye like rhodamine B and other stain like Van Geison (VG) stain can fairly distinguish ghost cells from surrounding dentinoid structures exhibiting yellow fluorescence and yellow appearance of the ghost cells respectively³. In the present case, histopathological features were consistent with the cystic characteristics of COC described in the previous literatures though ameloblast like basal cells and dentinoid material were inconspicuous. Prominent clumps of eosinophilic ghost cells were evident in routine H and E stains which shows positivity in VG stain as well.

Clinical and radiological differential diagnosis include CEOT, ameloblastic fibroma, ameloblastic fibro-odontoma, odontoma etc.⁶ Histopathology dictates a broad spectrum of differential diagnosis including ameloblastic fibroma, ameloblastic fibro-odontoma, complex and compound odontoma or ghost cell odontogenic carcinoma⁶. Extent of ghost cells and associated dentinoid material vary in the benign lesions whereas malignant characteristics prevail in carcinoma³.

The most accepted treatment option for Gorlin cyst is complete surgical enucleation until recurrence is observed¹³. Radical excision of the lesion is preferred in case of neoplastic component of COC better known as Calcifying Cystic Odontogenic Tumor or Dentinogenic Ghost Cell Tumor¹. Recurrences are very rare with few reported cases¹⁷. Present case of COC was enucleated and periodically followed up for 01 year without any sign of recurrence.

CONCLUSION:

Overlapping neoplastic and cystic characters offer diagnostic dilemma which requires utmost knowledge of cells with diverse histomorphology. A definitive diagnosis is amenable owing to amalgamation of proper clinical, radiological and histopathological features. Periodic follow up remains a part of the management since there is a little chance of recurrence.

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