ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 04 | April - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

GRANULAR CELL AMELOBLASTOMA OF MANDIBLE: REVIEW OF A RARE VARIANT OF AMELOBLASTOMA WITH PRESENTATION OF 3 INTERESTING CASES OF THE SAME.

Dental Science

Dr. Debasmita Mitra Ghosh Assistant Professor, Department of Oral & Maxillofacial Pathology, Burdwan Dental College & Hospital

Dr. Sayani Dutta Assistant Professor, Department of Oral & Maxillofacial Pathology, Burdwan Dental College & Hospital.

ABSTRACT

Ameloblastoma is a benign odontogenic neoplasm derived from odontogenic epithelium with mature fibrous stroma without ectomesenchyme. Based on its clinical,radiographic and histological features,it has been mainly classified under four different types-solid/multicystic,unicystic,peripheral and desmoplastic ameloblastoma. The granular cell ameloblasatoma,a rare histological variant mainly seen in association with plexiform or follicular ameloblastoma of the solid/multicystic type, has been reported in 5% of the cases. The aim of this paper is to present a series of 3 interesting cases of granular cell ameloblastoma with a detailed review on clinical and histopathological features of the same.

KEYWORDS

odontogenic neoplasm, ameloblastoma, granular cell ameloblastoma.

INTRODUCTION

Ameloblastoma was defined by Robinson as an unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent neoplasm. It is a locally invasive benign neoplasm with high rate of recurrence. It is located exclusively in the jaws preferably in the mandible. Various clinical and radiological and histological subtypes like follicular, plexiform, acanthomatous, basaloid, granular cell type and desmoplastic ameloblastoma have been reported. 2022 WHO classification of Odontogenic tumors and cysts of the jaws divides Ameloblastoma under Benign epithelial odontogenic tumours into ameloblastoma, unicystic type, ameloblastomaExtraosseous or peripheral type, adenoid ameloblastoma and metastasizing ameloblastoma.[1]Reichart et al reported follicular ameloblastoma in 32.5% and plexiform ameloblastoma in 28.2% followed by acanthomatous type in 12.1% and desmoplastic variety in only 4-13% of 397 case reports. The rare two vatieties of ameloblastoma are basal cell ameloblastoma and granular cell ameloblastoma[2] The granular cell ameloblastoma was first described by Krompecher in 1918. Although the treatment and prognosis of this rare variety of ameloblastoma is same as that of any other ameloblastoma except the more aggressive desmoplstic one, a thorough knowledge of the histological features will be helpful in arriving at a more accurate diagnosis and management[3].

CASE REPORT

Case 1

A 57 years old female patient referred to the Dept of Oral Pathology with swelling in the lower third of face since last 5-6 months. The patient had no other relevant medical and dental history, family history and no deleterious oral habits. There was no history of trauma, extra-oral sinus or pus discharge.

Extra-oral examination revealed facial asymmetry in the left side of anterior mandible which was bony hard on palpation Fig-1.No associated regional lymphadenopathy was noted.

Intraoral examination revealed obliteration of the mucobuccal fold in relation to 32 to 36 with expansion of buccal cortical plates.Multiple missing teeth were noted. On palpation the swelling was bony hard in consistency with some fluctuant areas.Fig-2.

On radiological examination, O.P.G revealed an ill-defined multilocular radiolucency giving a soap bubble appearance with irregular margins extending from 32 to 36 region.Fig-3

A provisional diagnosis of Ameloblastoma and odontogenic keratocyst was given and an incisional biopsy was done under local anaesthesia with due consent from the patient.

The cut sections stained with H & E revealed the presence of areas of follicles with outer layer of palisading cuboidal or columnar cells resembling preameloblasts and extensive granular transformation of the central stellate reticulum like cells. The connective tissue stroma is loose fibrous. [Fig-4 &5]. Hence, the diagnosis of granular cell ameloblastoma was established and the patient was sent for further treatment .

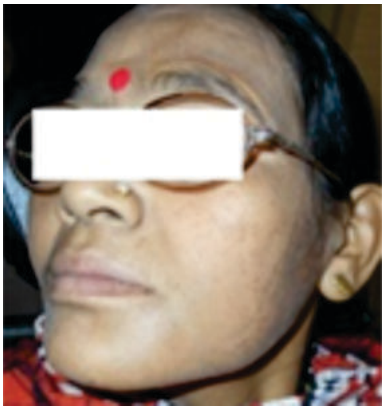


Fig 1- Extra Oral View

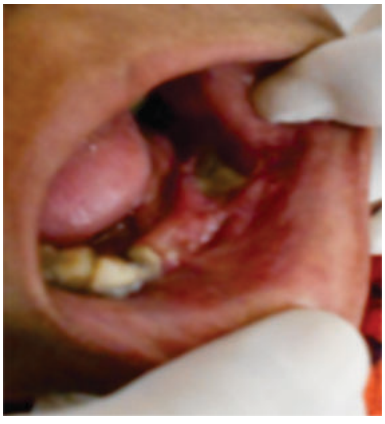


Fig2- Intra Oral View

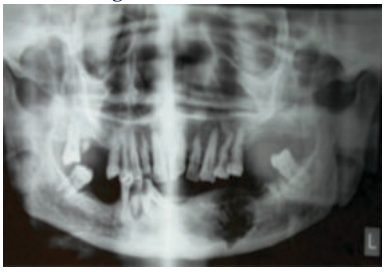


Fig 3- OPG

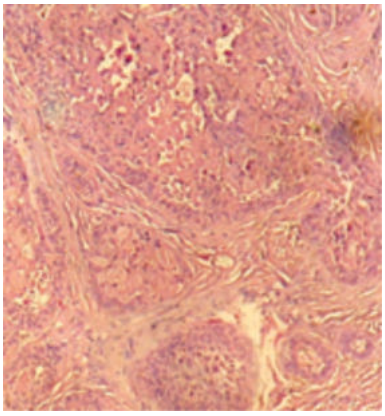


Fig 4- 10x View

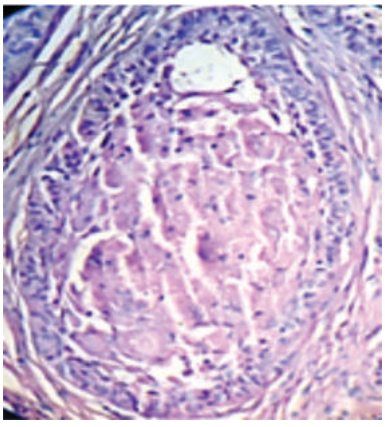


Fig 5- 40x View

Case 2

A 45 years old man reported to the Dept of Oral Pathology with a fast growing swelling in the posterior left tooth region and no other relevant medical and dental history, family history and deleterious oral habits. There was no history of trauma, extra-oral sinus or pus discharge.

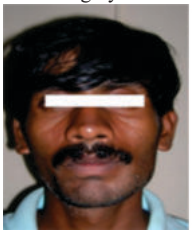
Extra oral examination revealed swelling in the lower third of face. The swelling is bony hard with no regional lymphadenopathy and pus discharge. Fig-6

Intra oral examination revealed a bony hard swelling in the left side of mandible in relation to 34-37 region with expansion of both cortical plates and regional teeth mobility.Fig 7

On radiological examination, O.P.G revealed a multilocular radiolucency involving the peri-apex of 34-38 teeth with root resorption of 35 and 36 with displacement of regional teeth. Fig 8.

A provisional diagnosis of Ameloblastoma and odontogenic myxoma was given and an incisional biopsy was done under local anaesthesia with due consent from the patient.

The cut sections stained with H & E revealed the presence of areas of follicles with outer layer of palisading cuboidal or columnar cells resembling preameloblasts and centrally granular cells with abundant cytoplasm and eosinophilic granules. The connective tissue stroma is loose fibrous. [Fig-9&10]. Hence, the diagnosis of granular cell ameloblastoma was established and the patient was sent to the department of oral surgery for further treatment.



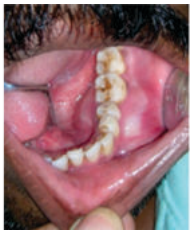


Fig 6- Extra Oral View Fig 7 – Intra Oral View

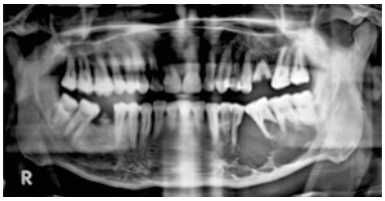


Fig 8- Opg

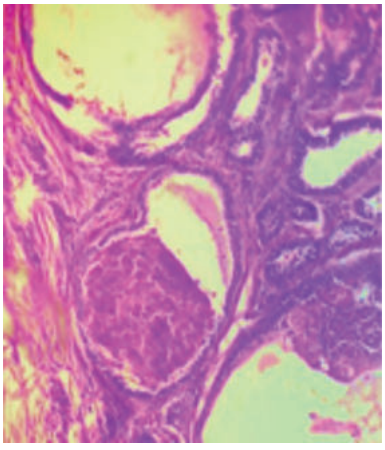


Fig 9 – 10x View

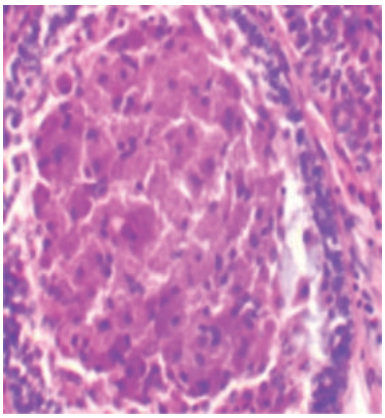


Fig 10- 40x View

Case 3

A 20 years old female patient reported to our Dept of Oral Pathology with the complain of ulceration and swelling in the right side of the face. She had no other relevant dental or medical history and no deleterious habit patients.

Extra oral examination revealed no gross facial asymmetry of the patient. The swelling was firm with no regional lymphadenopathy.Fig 11.

Intra oral examination revealed a selling in the rit side of mandible distal to 36. There was indentation from maxillary posterior teeth. 37 was missing. The swelling was firm in consistency. Fig-12.

On radiological examination,O.P.G revealed a large multilocular radiolucency extending distal to 46 almost upto the ramus of mandible with expansion of the lower border of mandible and involving the ramus.37 is missing. Root resorption of 46 noted.Fig 13

A provisional diagnosis of Ameloblastoma and odontogenic keratocyst was given and an incisional biopsy was done under local anaesthesia with due consent from the patient.

The cut sections stained with H & E revealed the presence of areas of follicles with centrally stellate reticulum like cells with abundant cytoplasm and eosinophilic granules bounded by palisading cuboidal or columnar cells resembling preameloblasts. The connective tissue stroma is loose fibrous. [Fig15&16]. Hence, the diagnosis of granular cell ameloblastoma was established and the patient was sent to the department of oral surgery for further treatment.

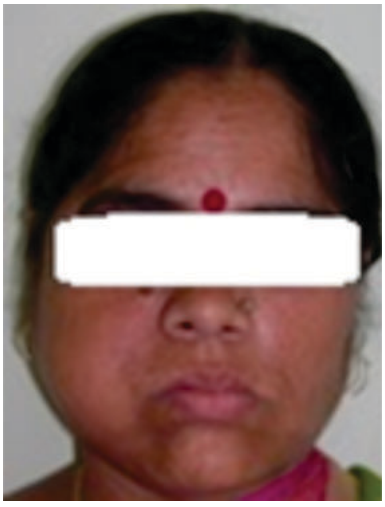


Fig 11- Extraoral View

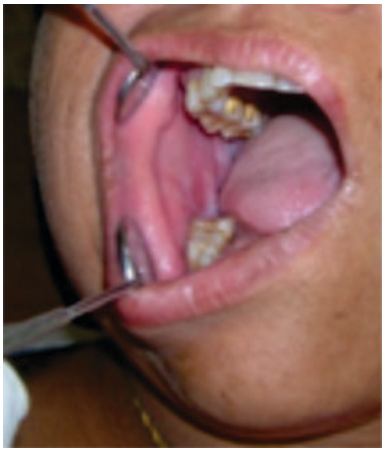


Fig 12- Intra Oral View

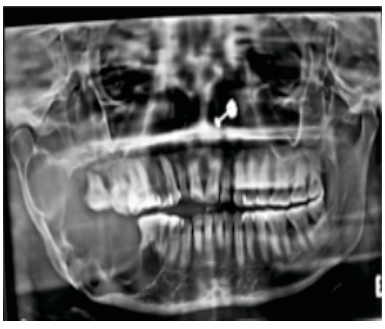


Fig 13- OPG

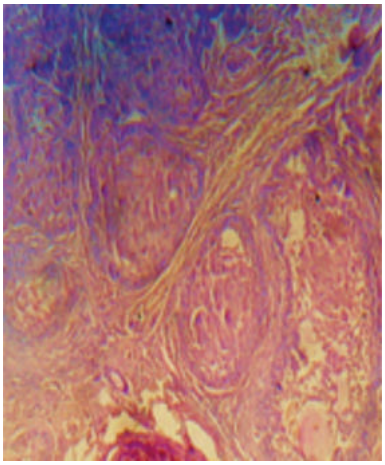


Fig- 14- 10x View

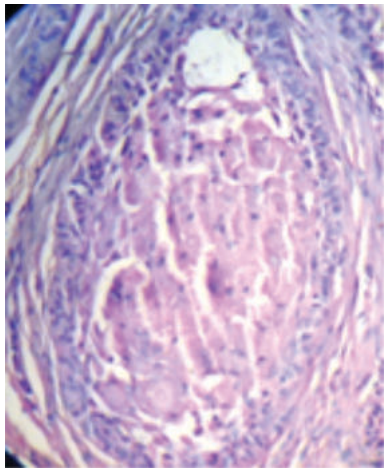


Fig 15- 40x View

Discussion With Review Of Literature:-

AMELOBLASTOMA are tumors ofodontogenic epithelial origin arising from either rests of dental lamina or a developingenamel organ or the epithelial lining of an odontogeniccyst or from the basal cells of the oral mucosa.Ameloblastoma is a slow growing locally invasive benign tumor of odontogenic origin, chiefly reported in wide age range with slight male predilection. Wilis classified Ameloblastoma as malignant[4] though metastasis to regional or distant lymph nodes are rare. Out of 33 cases reported to be malignant by Small and Waldron in 1955, only 3 cases were found to be truly malignant with distant metastasis.[5]

The mean age of occurrence is 39 years for solid/ multicystic ameloblastoma, 22 years for unicystic and 51 years for peripheral variety. (Reichart et al). In our study, we have documented 3 cases; with a mean age of occurrence is 40.67 yrs.

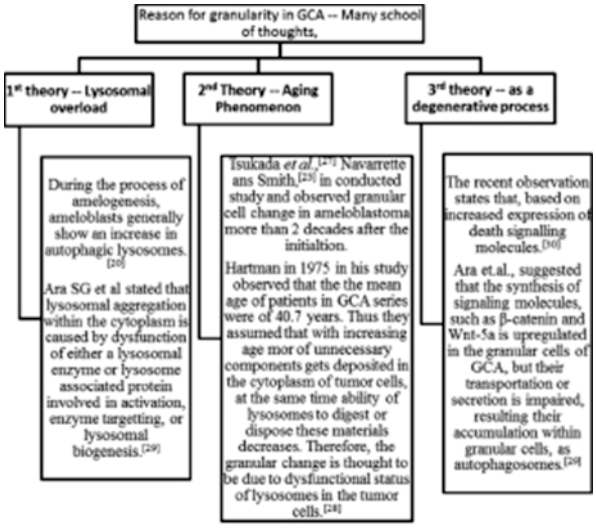
Though Hartman in 1974, found that 8 out of the 20 case of granular cell Ameloblastoma occurred in Non- Caucasian, not much racial predilection noted in the distribution of this rare variant of Ameloblastoma.[6]

From the available histo-pathological data of 1593 ameloblastoma cases, Reichartetal[2] reported only 56 cases (3.5%) of granular cell variety. In a survey of 20 cases of granular cell ameloblastoma, Hartman stated that they account for only 5% of all ameloblastomas[6]. According to Hartman, the mean age range of occurrence is 40.7 years and there was a slight male predilection. Most of the cases were reported in the posterior mandible[4]. The chief presentation was swelling in the jaws and pain. The radiological features resemble that of any ameloblastoma. All the 3 cases documented here are located in the posterior mandible with chief presentation of pain and swelling for past few months. The radiolological and clinical features are also in accordance with that of ameloblastoma. The third case which we have presented here exhibited the feature of aggressive tumor as from the OPG it is found to be extending upto the ramus of mandible with expansion of the inferior border of mandible.

Krompecher in 1918, when first described the presence of granular cells in Ameloblastoma, referred to these peculiar cells as psuedoxanthomatouscells[7]. Smith was of the view that these granules could of ectodermal or mesenchymal origin.[8] The granules in granular Cell Ameloblastic Fibroma was thought to be of mesodermal origin by Waldron et al [9] and also Couch et al [10]. The granular cells of the Granular cell Ameloblastoma then thought to be of ectodermal origin and the transition from stellate reticulum to granular cells is a distinct histological finding.

Malik et al, Tsukada et al, Mori M and Waldron et al were all of the view that these granular cells developed due to degenerative changes in the odontogenic epithelial cells[9,11,12,13]. Tsukada et al were of the view that these granular cells might be the result of aging process as they might be noted in long standing cases and recurrent cases.[11] However these finding of Tsukada et al couldnot be justified in lesions of short duration and also in non recurrent cases. Hoke andHarrelson[14]were of the view that these granular changes in the cytoplasm ofthe neoplastic

ameloblastswas an attempt to form an enamel matrix precursor that was not possible in the unfavorable environment. Gold and Christ, suggested that the granular cells were developing at the basal cell level and the process was that of a metabolic phenomenon ratherthan a degenerative process.[15] The reason for granularity is explained in the Flowchart 1.[16]



Flowchart 1- Different Theories Of Granularity

The most documented histopathological feature was that of a follicular ameloblastoma with large masses of granular cells within the follicles. Granular cells replaced all or part of the stellate reticulum and frequently the peripheral preameloblast like cells. They were large round or polyhedral in shape with densely packed eosinophilic granules when viewed in H&E stained sections. These cells often have distinct cell borders but in some cases they form synctium with pyknoticand eccentrically placednuclei randomly found in the granules. Areas of transition from cells resembling preameloblasts to granular cells often represent an early stage in the development of more typical granular cell ameloblastoma. Originally the granular appearance was considered to be aging or degenerative proccess[1] while recent imunohistochemical studies revealed that granularity might be due to increased apoptotic cell death and phagocytosis by neighbouring neoplastic cells[16]. Hamperl concluded that these granules in cytoplasm were mitochondria[17],while Roth et al stated that these granules were not mitochondria.[18] Navarrete &Smith stated that ultrastructurally these granules consisted of pleomorphic, osmiophilic, lysosome-like granules[19]. Based on histochemical and electron microscopic findings these granular appearances are concluded to be numerous lysosomes. Ultra structurally these granules approach 1 μ meter in size, giant granules of 30πmeter are rarely seen. The granules present various finger-print like membranous structures, myelin figures, small particles, granules, vesicles, lattice and crystalloids. They represent increased cellular action of tumor cells to digest unwanted products.[20]. The different normal cell types and their neoplastic counterpart with different special stains are illustrated in the Table 1 and 2.[16]

Table1- Reason For Granularity.

Normal cells	Reason for granularity and special stains	Neoplastic cells	Reason for granularity and special stains
Oxyphils (parathyroid)	Mitochondria (PAS negative; PTAH positive)	GCA	Lysosomes (PAS positive; PTAH negative)
		Granular cell myoblastoma	
Oucocytes (salivary gland)		Granular cell odontogenic fibroma/granular cell odontogenic tumor	
		Congenital epulis of newborn, congenital epulis	
Hurthle cells or Askanszy cells		Neumann's tumor	
		Granular cells leiomyoma	
Ameloblasts during amelogenesis	Lysosomes (PAS positive; PTAH negative)	Granular cell basal cell carcinoma	
Enamel organ of developing teeth		Calcifying epithelial odontogenic tumor	Polyribosomes PAS negative (few are PAS positive, but disappears on diastase action)
Odontogenic epithelium			

PAS=Periodic acid-Schiff. PTAH=Phosphotungstic acid hemotoxylin. GCA=Granular cell ameloblastoma

Histochemical characterization of cellular differentiation showed that Granular cells show positivity for cytokeratin, CD68, lysozyme and alpha1-antichymotripsin and negative for vimentin, desmin, S-100, neuron specific endolase and CD15,indicating epithelial origin and lysosomal aggregation[13,21]. Dina et al showed granular cells exhibit membranous positivity for cytokeratin and cytoplasmic positivity for CD68.[22]

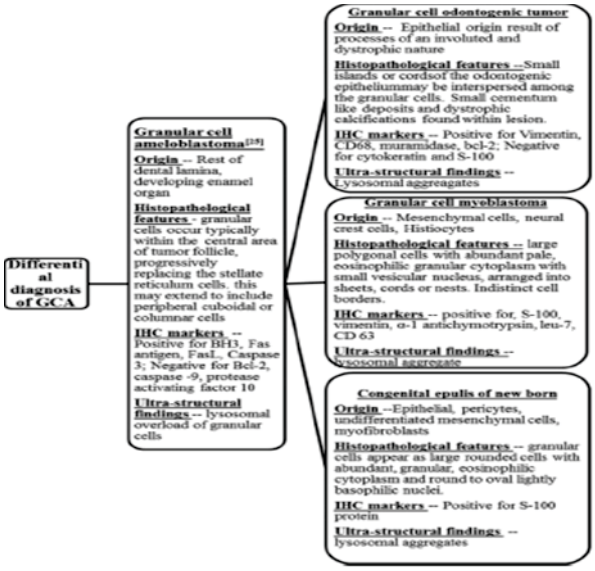
Table 2- Granules and IHC

Histochemistry (special stains)	Immunohistochemistry
PAS (glycogen) - ++	Positive for apoptotic markers, strong positivity for Fas antigen. Weakly positive for FasL, caspase-3, and no expression of Bcl-2 noted[31]
PAS with diastase (no glycogen) - ++	Angiogenic factors in GCA - positive for endothelial cell growth factor / thymidine phosphorylase reactivity in granular neoplastic cells as well as in stromal cells[32]
Oil red O (lipid) - +	Notch1, 2 and 3, dental and Jagged 1 are identified in all ameloblastomas including GCA, but not in granular cells[33]
Duray's technique (lysosomal acid phosphatase) - +++	
r-naphthyl acetate (substrate of ester hydrolases of carboxylic acids) - +	
P-glucuronidase (hydrolysis of glycosyl compounds) - +	

GCA=Granular cell ameloblastoma. PAS=Periodic acid-Schiff. +++: Indicates strong positive

The granular cell ameloblastoma is a locally aggressive tumor with high recurrence rate if not appropriately surgically treated.[23]Reichart et al reported a 33.3% recurrence rate, which was higher as compared to other common variants.[2]. In Hartman's study,11 out of 15 patients (73% cases) developed recurrent lesions. The prognosis is more dependent on the type of surgical treatment and those treated by enucleation or curettage in the initial phase exhibit higher recurrence rate. Hence radical surgical methods recommended.[24]The GCA has a higher malignancy rate and metastasis.[24,25]. Tsukada et al were of the view that malignant transformation with metastasis occurred in patients with long standing history ,extensive local spread and undergone previous surgeries or irradiation.[11]

The differential diagnosis of granular cell ameloblastoma is all other oral lesions with similar granular cell accumulation like granular cell odontogenic tumor, granular cell tumor and congenital epulis. However all these lesions present different biological behaviour and should be differentiated from granular cell ameloblastoma shown in flowchart 2.[26]



Flowchart-2 D/D of GCA

CONCLUSION

Here we have presented a series of 3 rare and unusual variant of ameloblastoma - the Granular Cell Ameloblastoma.

Few cases of metastasis have been previously reported in the literature of Granular cell Ameloblastoma. All those cases were recurrent and aggressive and presented long duration from 18 to 45 years[8,9,10,11] except the latest case report of only two years progression[12]. Thetriggeringmechanism of metastasis is stillunknownin GCA. There are also various benign and malignant tumors which provide the granular cell features. Therefore, knowledge of GCA will help in accurate diagnosis and prevent recurrences and malignant transformation.

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