Granular Cell Ameloblastoma: A Rare Case Report and Review of Literature

Abstract
Ameloblastoma is a benign locally aggressive type of odontogenic tumor derived exclusively from the epithelium. Histologically, ameloblastoma is classified into many variants, of which granular cell ameloblastoma (GCA) is a rare type, characterized by nest of large eosinophilic granular cells. This article describes a case of GCA in a 50-year-old female patient with clinical, radiological, and histological features along with a systematic review of the literature.

Keywords: Ameloblastoma, granular cell ameloblastoma with its differential diagnosis

Introduction
Odontogenic tumors are lesions derived from the epithelial or mesenchymal remnants of the tooth-forming apparatus.[1] The ameloblastoma is a benign epithelial odontogenic tumor which is considered as a locally aggressive lesion. It is located almost exclusively in the jaw and preferentially affects the mandible.[2] Although it is considered as one of the most common odontogenic neoplasms, it accounts for only 1% of all jaw tumors and 11% of all odontogenic tumors in Caucasians. They are slow-growing, locally invasive tumors having a close resemblance to the enamel organ epithelium.[3–5] The current World Health Organization (WHO-2017) classification of odontogenic tumors divides ameloblastoma into four types as follows: ameloblastoma, unicystic type, ameloblastoma extraosseous or peripheral type, and metastasizing malignant.[6] Ameloblastoma most significantly concerns oral pathologists due to its high incidence among all odontogenic tumors and true neoplastic (infiltrative and recurrent) potential combined with its varieties of histopathological patterns.[7] The six main histopathological subtypes (variants) of ameloblastoma are as follows: (a) follicular, (b) plexiform, (c) acanthomatous, (d) granular cells, (e) basal cell, and (f) desmoplastic form.[8]

Granular cell ameloblastoma (GCA) is a rare histopathological entity accounting for 1%–5% of ameloblastomas (~3.5%[9]); granular cell change in the histopathology of ameloblastoma was first observed by Krompecher in 1918[10] and was called as pseudoxanthomatous cells. GCA histopathologically has numerous large eosinophilic granular cells. These granular cells are formed by transformation of lesional epithelial cells. Although originally considered to represent aging or degenerative changes in long-standing lesions, this variant has been seen in young patients and in clinically aggressive tumors. Histopathologically, when granular cell change is extensive in an ameloblastoma, the designation of GCA is appropriate. The granular cells usually form the central mass (stellate reticulum-like cells) of the epithelial tumor islands and cords. The periphery of the islands consists of nongranular tall columnar cells.

In GCA, there is marked transformation of the cytoplasm, usually of stellate reticulum-like cells; hence, it takes a very coarse, granular eosinophilic appearance. Several cases of this type have been reported as metastasizing.[11,12]

In addition, Robinson and Vincent described that the granular cell pattern centrally includes eosinophilic cytoplasmic granules within the follicular epithelial islands, or within the columnar and cuboidal cells of the follicular or plexiform variants in the Armed Forces Institute of Pathology Atlas of Tumor Pathology.[13] The latter type of GCA is not mentioned in the

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WHO classification and includes a peculiar type composed of predominantly anastomosing strand arrangements of eosinophilic granular cells. This rare GCA resembles salivary gland tumors such as oncocytoma.

Malignancy in the ameloblastoma has been divided into two distinct lesions. A malignant (metastasizing) ameloblastoma is diagnosed when a seemingly histologically benign ameloblastoma produces a metastasis resembling the original lesion. Ameloblastic carcinoma is an odontogenic tumor not only having the overall microscopic architectural features of ameloblastoma but also having malignant cytological features such as marked nuclear atypia and numerous mitotic figures. Both the lesions are microscopically well differentiated.

In 1965, Tsukada et al. reported a case of GCA with metastasis to the lungs. Two years later, a case of GCA with metastasis to cervical vertebrae was reported.

The purpose of this paper is to present an unusual case of GCA and to review the pertinent literature highlighting its unique microscopic features that allow its distinction from other jaw tumors with a granular cell constituency and discuss the molecular aspects of its pathogenesis.

Case Report

A 50-year-old female patient reported to the outpatient department with a history of pain and swelling in the lower left back region of jaw for the past 2 years. History revealed that she underwent an operative procedure in the same region 5 years back. A swelling appeared insidiously in the lower left back tooth region 2 years back about the size of a peanut, and thereafter gradually, it has increased to the present size approximately 7 cm × 5 cm. Extraorally, the presence of facial asymmetry was noted, with swelling extending anteroposteriorly from the midline of jaw to angle of the mandible and superoinferiorly from lower canthus of the eye to inferior border of mandible. The swelling had a smooth surface and the color of the skin over the swelling was normal. Palpatory finding revealed firm consistency and tenderness with absence of buccal cortical plate. Intraoral examination revealed missing 34, 35, 36, 37, and 38. The swelling extended from distal of left canine to retromolar pad. Obliteration of buccal vestibule was noted. Routine biochemical tests were within normal limits. Panoramic view revealed multilocular radiolucency extending from the left side of the ramus of the mandible to distal surface of canine. Clinical and radiological differential diagnoses were odontogenic keratocyst and ameloblastoma. An excisional biopsy was performed with adequate margins and sent for pathology department for confirmation.

Pathology report

Microscopic description

Incisional biopsy was taken from the lesional area for confirmatory diagnosis and sent to the Department of Oral Pathology for histopathological diagnosis. Hematoxylin and eosin stained and studied section revealed the tumor to be composed of islands, nests and cords of epithelial cells interspersed between loose connective tissue stroma. Each island consisted of peripherally placed tall columnar cells with reverse polarized and palisading nucleus resembling ameloblasts and some islands consisting of centrally placed star shaped cells resembling stellate reticulum like cells and few islands that showed marked transformation of stellate reticulum like cells into eosinophil granular cells. The stroma was fibrous and showed moderate mononuclear inflammatory infiltrate. On the basis of the above findings, a diagnosis of GCA was made and the patient was planned for surgery under general anesthesia. The patient was secured with naso-endotracheal tube, and an aseptic protocol was followed. Left composite hemimandibulectomy and reconstructive surgery were performed. Postoperatively, the healing was uneventful and no recurrence was reported up to 6 months of followup period.

Discussion

Ameloblastoma is defined as true neoplasm of enamel organ type which does not undergo differentiation to the point of enamel formation. It is the second-most common odontogenic tumor, arising from rests of the dental lamina or from a developing enamel organ or from the epithelial lining of an odontogenic cyst, or from the basal cells of the oral mucosa.

GCA is one of the rare histopathological variants of ameloblastoma (1.5%–3.5%), first identified by Krompecher in 1918 by the presence of characteristic granular cells. Granularity is due to the marked transformation of the cytoplasm of the stellate reticulum cells into granular eosinophilic appearance. GCA is known to be an aggressive histologic variant of ameloblastoma. Although it is one of the variants of ameloblastoma, it is considered as a separate
entity due to its higher incidence of recurrence, malignancy, and metastasis.[18,19,20]

Generally there are no distinguishing clinical and radiological findings reported when compared from GCA and other histopathological variants of ameloblastoma.[9] Histopathologically, GCA is characterized by the presence of eosinophilic granular cells, measuring approximately about 1 µm in size. These granular cells are seen usually in central area with marked transformation of stellate reticulum cells into granular eosinophilic cells, surrounded by tall columnar cells. Sometimes, they extend to include tall columnar and cuboidal cells as well.[18,21,22] Other than GCA, plexiform ameloblastoma seldom presents granular cell changes and these granular cells may be round, cuboidal, or columnar, with the cytoplasm being filled with acidophilic granules; ultrastructurally, they are considered as lysosomal aggregates.[23] The nuclei of granular cells are pyknotic, hyperchromatic, and palisaded, showing reverse polarization.[24]

Large eosinophilic granular cells present in normal and neoplastic human tissues [Table 1]. These include oxyphilis (parathyroid cells), oncocyes (salivary gland), Hürthle or Askanazy cells (thyroid) and GCA, granular cell ameloblastic fibroma (GCAF), granular cell myoblastoma (GCM), and congenital epulis.[23] Histologically, eosinophilic granular cells can appear in many conditions, of which, GCA, GCAF, GCM, and congenital epulis of newborn show striking resemblance in the presence of granular cells. The main histogenetic difference is that the granular cells of GCA are of epithelial tissue origin, while the GCAF, GCM, and congenital epulis all are derived from mesenchyme.[25] Differential diagnosis and histo-pathological features of GCA [Flow Chart 1].

**Reason for granularity in granular cell ameloblastoma**

There are numerous theories proposed on the origin and nature of granular cells in ameloblastomas. These granular cells are epithelial in origin, and several ultrastructural and histochemical studies have described them and stated that granular cells of ameloblastoma are due to lysosomal overload, metabolic change in response to aging, degenerative mechanism, or an indicator of a more aggressive course, of which the most accepted concepts are aging phenomenon and degenerative changes.[26]

**Electron microscopy of granular cells**

When observed under electron microscope, the granules were pleomorphic osmiophilic. Most of these granules were partly or completely limited by single membrane and are approximately 0.4–1.4 µ in diameter. Their osmiophilia as well as their morphology varied. Variety of patterns are observed electron microscopically, as follows:

- The granules of GCA when observed electron microscopically were of ovoid or round, composed of homogeneous amorphous osmiophilic material of different density
- Some contained concentrically laminated membranes (“myelin figures”)
- Bundles of fine parallel membranes that ran in different directions showing different patterns resembling “fingerprint pattern”
- Presence of coarse granules observed in hematoxylin and eosin stain, which were formed by fusion of several smaller granules.

Presence of eosinophilic inclusion-like structures was noted on hematoxylin and eosin stain, which were large, round degenerative cytoplasmic masses.

Aside from these granules, the cytoplasm contained round or oval mitochondria, well-developed Golgi complexes, scant rough-surfaced endoplasmic reticulum, and pleomorphic vacuoles limited by a single membrane. Some vacuoles appeared almost empty, whereas others contained amorphous osmiophilic material of different density [Flow Chart 2].[23,27-30]
Histochemistry (special stains) and immunohistochemistry in granular cell ameloblastoma

All granular cells including the peripheral lining cells in GCA show periodic acid-Schiff (PAS)-positive and PAS with diastase-positive cytoplasmic granules. Different staining activity of the granular cells and expression of immunohistochemical markers on granularity GCA enlisted in Table 2.

Conclusion

GCA is a rare variant of ameloblastoma with unique histologic features. Granules in GCA ameloblastomas are due to marked transformation of stellate reticulum cells into granular cells, which are considered as lysosomal aggregates due to dysfunction of lysosomal enzymes or other related proteins. GCA should be differentiated from the other variants of ameloblastomas and also from other granular cell lesions.

**Table 1: Electron microscopic appearance of normal and neoplastic granular cells in different conditions**

| 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) |
| Oncocytes (salivary gland) | | Granular cell myoblastoma | |
| Hurthle cells or Askanszy cells | | Granular cell odontogenic fibroma/granular cell odontogenic tumor | |
| Ameloblasts during amelogenesis | Lysosomes (PAS positive; PTAH negative) | Congenital epulis of newborn, congenital epulis | |
| Enamel organ of developing teeth | | Neumann’s tumor | |
| Odontogenic epithelium | | Granular cells leiomyoma | |

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

**Table 2: Histochemistry (special stains) and immunohistochemical (expression) positivity in granular cell ameloblastoma**

| 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[^1] |
| 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[^2] |
| Oil red O (lipid) - + | Notch1, 2 and 3, dental and Jagged 1 are identified in all ameloblastomas including GCA, but not in granular cells[^3] |
| 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
due to its high recurrence rate. Patients should be kept under periodic observation due to their high recurrence rate even up to 8 years after initial treatment. An immunohistochemistry finding helps to identify the molecular pathogenesis behind the granular cell formation in GCA.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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