

Massive granular cell ameloblastoma with dural extension and atypical morphology

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Abstract

Ameloblastomas are rare histologically benign, locally aggressive tumors arising from the oral ectoderm that occasionally reach a gigantic size. Giant ameloblastomas are a rarity these days with the advent of panoramic radiography in routine dental practice. Furthermore, the granular cell variant is an uncommon histological subtype of ameloblastoma where the central stellate reticulum like cells in tumor follicles is replaced by granular cells. Although granular cell ameloblastoma (GCA) is considered to be a destructive tumor with a high recurrence rate, the significance of granular cells in predicting its biologic behavior is debatable. However, we present a rare case of giant GCA of remarkable histomorphology showing extensive craniofacial involvement and dural extension that rendered a good prognosis following treatment.

Keywords: Dural extension, giant ameloblastoma, granular cell ameloblastoma, granular cells

Introduction

Ameloblastoma, a benign epithelial odontogenic tumor of the jaws accounting for 1% of all oral tumors and 9–11% of odontogenic tumors with an incidence of 3/10 million.^[1] The hallmark of this tumor is its locally aggressive behavior owing to its alarming growth rate which may sometimes reach enormous proportions. Modern day radiography techniques however overcome this problem and facilitate early diagnosis. In fact, a Medline – PubMed search for giant ameloblastomas revealed about 31 reported cases, most of which were either of the follicular, plexiform or combined follicular and plexiform variants and only belonged to the granular cell type.^[2] Granular cell ameloblastoma (GCA) is an unusual variant accounting for 3.5% of all ameloblastomas where granular changes generally occur in the central portion of

the tumor follicles. It is a highly aggressive tumor considered to be associated with a high recurrence rate.^[3] However, we report a case of giant GCA that showed extensive involvement of mandible, maxilla, temporal bone and dura, but bore a good prognosis. The demographics of this pathology, *raison d'être* behind occurrence of granular cells and the differential diagnosis of common oral granular cell lesions is discussed.

Case Report

A 60-year-old Indian male relative of a patient visiting the dental outpatient department was noticed with a massive swelling on the right side of his face. Verbal consent was obtained from him for examination. History revealed a slowly growing painless swelling of the right mandible of 30 years duration that gradually extended to involve the upper jaw, right side of face and temporal region. The swelling was well-circumscribed, roughly ovoid, lobulated, nontender and firm and measured 18 cm × 12 cm × 11 cm, extending 3 cm above supraorbital margin superiorly and behind pinna of the ear laterally on the right side. Intra oral examination revealed a huge nontender fleshy mass of the right mandible of differing consistency displacing the tongue, obliterating buccal sulci and extending from lower right canine to retromolar area. There was partial and spontaneous loss of dentition. Posterior-anterior view of the skull revealed a huge soft tissue mass shadow on the right side of face involving posterior part of the maxilla and with mandibular destruction [Figure 1]. Coronal section of computed tomography (CT) showed lesion extended from temporo-parietal region till the hyoid bone with displacement of greater wing of sphenoid, temporal bone and maxillary antrum. Axial section of CT scan at a higher level showed erosion of the temporal bone with dural extension. Three-dimensional reconstructed views showed the entire tumor extent that had resorbed the mandible, zygoma and temporal bone on the right side [Figure 2].

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| Quick Response Code: | Website: www.contemplindent.org |
|  | DOI: 10.4103/0976-237X.142827 |

Baseline laboratory investigations revealed low hematocrit, raised platelet count and erythrocyte sedimentation rate, but normal protein levels. The patient was provisionally diagnosed with multicystic ameloblastoma. Fine-needle aspiration cytology from the swelling yielded a hemorrhagic, cystic fluid consisting of inflammatory cells in a fibrinous background. Histopathological examination of the tissue specimen obtained by incisional biopsy from the swelling revealed typical ameloblastomatous follicles with varying amounts of granular cell changes, cystic degeneration, and squamous metaplasia in the follicles [Figure 3]. It was thus diagnosed as a GCA. After improving patient's hematocrit, hemimandibulectomy with disarticulation was performed. The tumor mass was resected along with the parotid gland, facial nerve, zygoma and zygomatic arch of the ipsilateral side. Intra operatively, a 2 cm squamous part of the temporal bone was resorbed with a dural tear, but there was no cerebrospinal fluid leakage. Reconstruction was done with pectoralis major myocutaneous flap. The excised specimen measured

17 cm × 11 cm × 9 cm and weighed 500 g. The interior showed multiple locules, few with whitish nodular projections. Histopathological findings from the specimen samples were in agreement with the initial diagnosis. However, our attention was drawn to the unique epithelial changes seen in this case. There were bland looking epithelial cells with flattened epithelium and whorling resembling squamous odontogenic tumor and conventional ameloblastomatous islands budding from the oral epithelium with focal to extensive proliferations of GCA islands form oral epithelium. Granular cell changes were noted extending right across the entire oral epithelium, from the basal and spinous layers up to the superficial layers [Figure 4]. To ascertain the nature of granular cells, immunohistochemistry was performed with CD68, bcl-2, and

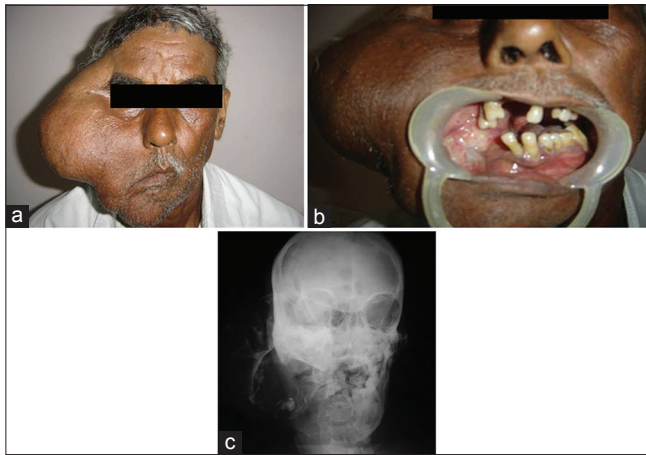


Figure 1: (a and b) Extra- and intra-oral involvement of tumor mass; (c) posterior-anterior view skull showing destruction of posterior part of maxilla and right mandible

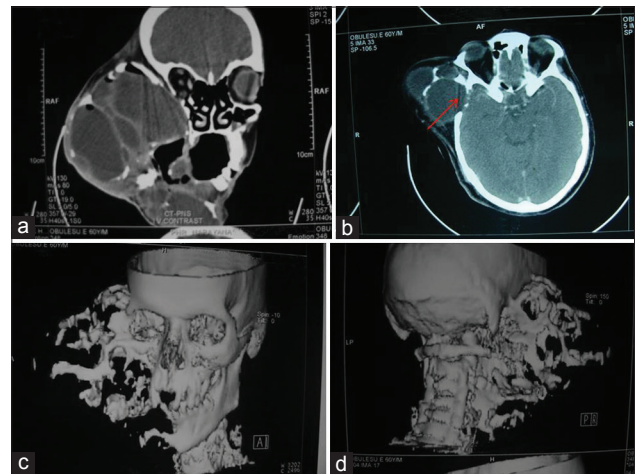


Figure 2: (a) Coronal computed tomography (CT) scan with contrast showing tumor infiltration into maxilla and temporal region; (b) axial CT scan showing dural extension of tumor (arrow), (c and d) three-dimensional reconstructed frontal and occipital views showing entire tumor extent with destruction of right side mandible

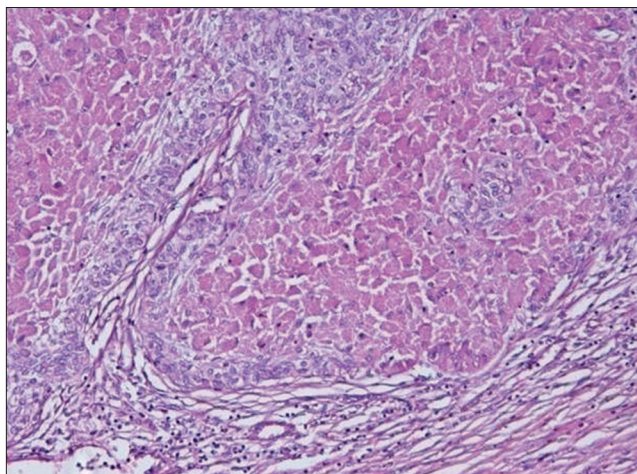


Figure 3: Follicles of granular cell ameloblastoma in the connective tissue stroma (H and E stain, ×10)

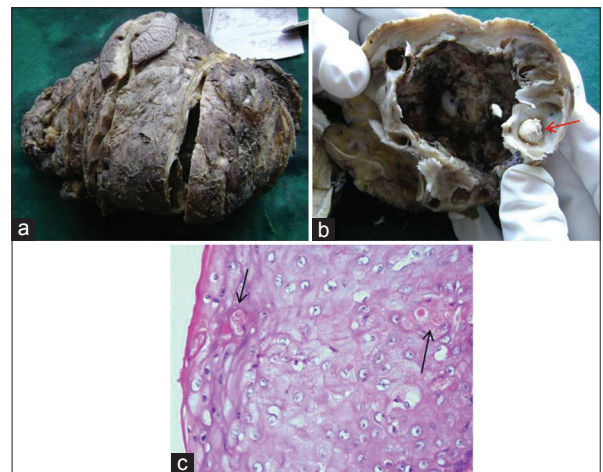


Figure 4: (a) Postsurgical excised specimen; (b) grossly cut tumor showing whitish nodular projection (arrow) within cystic locule, (c) granular cells (arrow) in overlying oral epithelium (H and E stain, ×10)

Ki-67. Intense positivity for CD68 was shown by granular cells in the follicles, but not by the peripheral ameloblastic cells. The latter however showed moderate staining to bcl-2 and weak staining to Ki-67. The granular cells showed occasional faint to no reactivity toward Ki-67 [Figure 5]. The patient was disease free in a 4-year follow-up.

Discussion

Hughes *et al.* proposed that the term giant ameloblastoma be reserved for lesions that are truly large, cause gross asymmetry, and regional dysfunction.^[4] Neglected ameloblastomas that become enormous are rare in developed societies, but can occur in patients who delay treatment due to lack of oral dysfunction or fear of surgery, to which the present case conforms.^[5] Ameloblastomas are broadly classified into multicystic, unicystic, desmoplastic and peripheral types and histologically, the multicystic type is further divided into follicular, plexiform, acanthomatous, basal cell and granular cell variants. GCA is a rare subtype of ameloblastoma that shows granular transformation of its cytoplasm and is considered to be a more aggressive variant that occurs at a later age.^[3] Of the 30 reported cases of giant ameloblastomas, only one GCA is recognized, showing its rarity.^[2] Present case may be the largest reported GCA, to the best of our knowledge. In a series of 20 cases of GCA, the average age was found to be 40.7 years with no gender predilection and they occurred in the posterior mandible.^[6] Our case occurred at a much later age, which may have contributed to a particularly large size. GCA is also associated with an increased recurrence rate of 33.3% and higher incidence of malignancy and metastasis.^[6] However, the present case was unique in that it showed neither recurrence nor metastasis.

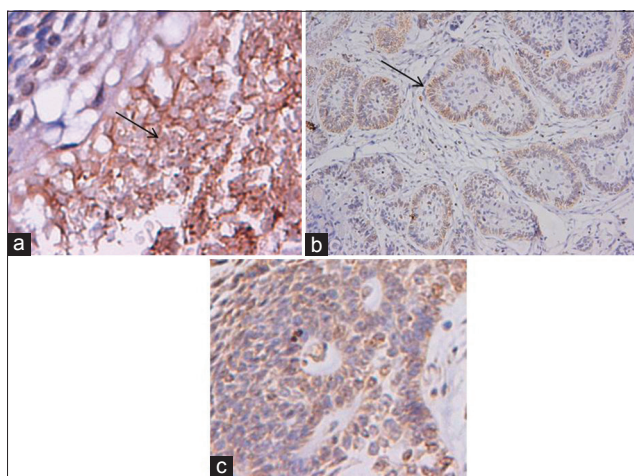


Figure 5: (a) Intense cytoplasmic positivity to CD68 shown by granular cells (arrow) ($\times 10$); (b) moderate reactivity to bcl-2 shown by peripheral ameloblastic cells (arrow) in follicles, but absent in central cells ($\times 4$); (c) weak reactivity to Ki-67 by ameloblastic cells and occasional granular cells within the follicles ($\times 4$)

Granular cells are characteristically encountered in other oral tumors also such as granular cell tumor, congenital epulides, granular cell ameloblastic fibroma, central granular cell odontogenic tumor, granular cell variant of odontogenic fibroma, in some mesenchymal tumors, neural tumors, salivary gland tumors, histiocytic tumors, metastatic tumors, and in melanoma.^[7,8] However, the characteristic ameloblastomatous epithelium in GCA helps in ruling out other granular cell lesions. In GCA, the granular cells that replace the stellate reticulum like cells in the center of the ameloblastomatous follicles are large oval to polyhedral cells with small pyknotic nuclei, bulky cytoplasm with coarse eosinophilic granules.^[1] However, the multifocal continuity of GCA islands with oral epithelium and granular changes in oral epithelium observed in the present case was unexpected and may have been as a result of simple fusion between the tumor and epithelium as ameloblastomatous cells have a propensity to fuse with mucosal epithelial cells, mimicking the eruption process. This nature of occurrence has not been described before, and its impact on the biologic behavior of GCA is unknown.

Granularity in a normal tissue is an innocuous change and may be encountered even during normal amelogenesis. Ultrastructural, histochemical, and immunohistochemical studies on the nature of granules in GCA show that they are lysosomes, but their pathological significance is debatable.^[9-11] Gold and Christ hypothesized that granular cells represent a metabolic process.^[12] It has also been proposed that granular changes in ameloblastoma represent a dysfunctional status of neoplastic cells, which may be part of an aging process or degenerative process in long-standing lesions.^[10,13] Few authors have stated that the average age of onset of GCA is 8 years older than that for conventional ameloblastoma and the tumors have a long duration of symptoms of about 15.3 years compared to 2.3–5.8 years in the latter.^[1,14] Strong positivity of granular cells to basement membrane proteins like laminin-1, 5 and fibronectin also suggest an age related transformation.^[15] However, the presence of granular cells in recurrent tumors similar to original tumors and unchanged number of granular cells in follow-up cases negate this hypothesis.^[6,16] Immunohistochemically, granular cells in GCA are positive for CD68, lysozyme and $\alpha 1$ antichymotrypsin, but negative for vimentin, desmin, S-100, neuron specific enolase and CD15. Recent immunohistochemical and ultrastructural study by Kumamoto and Ooya suggested that cytoplasmic granularity in GCA is due to apoptotic cell death in neoplastic cells and its following phagocytosis by neighboring neoplastic cells.^[17] In our case, strong CD68 positivity in granular cells proves their lysosomal nature and absence of anti-apoptotic marker bcl-2 staining in them is indicative of an underlying apoptotic phenomenon. Furthermore, weak to no staining by Ki-67 marks a low proliferative index of the granular cells.

The appropriate treatment for GCA is marginal resection with 1 cm extension past the radiographic margins or

in case of very large tumors, partial jaw resection.^[1,2] When considering treatment of such extreme lesions, we have to address questions pertaining to its dimensions, weight, involvement of maxilla or mandible, extension to vital structures and the extent of compromise in oral functions. In this case, although tumor size was immense and involved multiple bones including cranium it caused least morbidity and no compromise in oral functions. It is hypothesized that protein leakage occurs in large cystic ameloblastomas, thus causing secondary hypoproteinemia, but this finding was lacking in the present case.^[5] Prognosis of GCA is favorable if appropriate treatment is instituted. Those lesions showing recurrence and/or metastasis have been associated with long duration of tumor or inadequate treatment at the beginning.

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How to cite this article: Raghunath V, Rath R, Kamal F, Misra SR. Massive granular cell ameloblastoma with dural extension and atypical morphology. *Contemp Clin Dent* 2014;5:535-8.

Source of Support: Nil. **Conflict of Interest:** None declared.