Granular cell Ameloblastoma of the mandible – A rare case report with brief review of literature

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Abstract:
Ameloblastoma is a locally invasive neoplasm derived from odontogenic epithelium. The tumor is made up of proliferating odontogenic epithelium especially of enamel organ-type tissue that has not undergone differentiation to the point of hard tissue formation. Granular cell ameloblastoma (GSMA), a variant of ameloblastoma, has been known to be a more aggressive form of ameloblastomas, with a higher incidence of metastasis than other forms. The present case is a GSMA of the mandible in a 32-year-old North Indian male, along with the characteristic clinical, radiographic, histopathological features which was managed by segmental mandibular resection followed by immediate soft tissue reconstruction using nasolabial flap and delayed hard tissue reconstruction using iliac crest graft due to the involvement of hard and soft tissue.

Keywords: Ameloblastoma; odontogenic tumors; autograft; reconstructive surgical procedures; mandibular reconstruction; reconstructive surgery, mandible

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Introduction:
Odontogenic tumours and tumour-like lesions constitute a group of heterogeneous diseases that range from hamartomatous or non-neoplastic tissue proliferations to benign neoplasm to malignant tumours with metastatic potential. They are derived from epithelial, ectomesenchymal and/or mesenchymal elements of the tooth-forming apparatus.[¹] Based on clinicopathologic criteria, ameloblastomas are divided into three fairly distinct types: solid or multicystic (SMA), unicystic and peripheral. SMA is a polymorphic neoplasm consisting of proliferating odontogenic epithelium usually occurring in two main patterns; follicular and plexiform. Apart from these common patterns, few variants of SMA have also been documented which include, acanthomatous SMA, Granular cell SMA (GSMA), desmoplastic SMA, basal cell SMA, clear cell SMA, keratoameloblastoma, hemangiomatous ameloblastoma, mucous cell differentiation in SMA and extragnathic adamantinoma.[²] Knowledge of various histopathological subtypes is a prerequisite for accurate diagnosis and management. Hence, here, we report a case of large SMA involving the mandible histologically exhibiting granular cell pattern treated by segmental mandibular resection followed by reconstruction of the defect with iliac crest graft along with review of literature on clinical, histological, theories for occurrence of granularity and treatment.

Case report:
A 32-year-old man reported to our institute with a swelling in the left mandibular region. History revealed that the swelling was initially small in size and grew over time to attain the present size. The swelling was associated with continuous dull pain. No signs of parasthesia and anaesthesia. Extraoral examination revealed a firm to hard swelling causing facial asymmetry due to the large, diffuse swelling extending from right corner of the mouth crossing midline to the left angle region. Skin over the swelling was normal. (Figure 1)

On intraoral examination, the swelling extended from the 38 to 45 region, involving the left buccal vestibule, labial vestibule and floor of the mouth.
Mucosal ulceration in region 35 & 36 was evident. Swelling was firm to palpate & mobility was present from 36 to 45. (Figure 2)

Radiographically, the orthopantomograph showed a radiolucent multilocular lesion extending from 38 to 47 region involving the lower border of the mandible in the left posterior region giving a soap bubble appearance. Associated angular root resorption was evident in all the involved teeth. (Figure 3)

Cone Beam Computed Tomography revealed an intraosseous multiloculated cystic-solid lesion showing bucco-lingual expansion without any definite soft tissue involvement. (Figure 4)

Based on the clinical and radiographic features, a provisional diagnosis of ameloblastoma was given. The differential diagnoses included central giant cell granuloma, odontogenic myxoma, and ameloblastic carcinoma.

An incisional biopsy was done in the left premolar region and sections from the specimen revealed ameloblastomatous odontogenic epithelium arranged in follicles, cords and strands. (Figure 5)

Transformation of the central stellate reticulum-like cells into large polyhedral cells with coarse granular eosinophilic cytoplasm, having an eccentric nucleus and poorly demarcated cell membranes was evident in a majority of ameloblastomatous follicles. In addition, focal areas showing extensive squamous metaplasia, and keratin formation were evident within the islands of tumor cells. Based on these features, a diagnosis of Granular cell ameloblastoma was made. (Figure 5)

The tumor was managed by segmental resection from left body to left angle of mandible with 1 cm margins under general anesthesia via apron incision. Involved ulcerated mucosa was also excised along with bony resection and immediate soft tissue reconstruction was done with right side nasolabial flap. (Figure 6)
Although, mandibular reconstruction using iliac crest graft was intended taking the extent of the defect into consideration, due to the compromised nature of the soft tissue overlying the defect, immediate hard tissue reconstruction could not be performed. The proximal and distal segments were stabilized with locking titanium reconstruction plates and screws. (Figure 7)

Post operative healing was uneventful. The patient was advised for hard tissue reconstruction after 6 months, but he did not turn up for treatment. 18 months later, the patient reported with reconstruction plate fracture (Figure 8) which was removed and mandibular reconstruction was performed using an iliac crest graft.

Histopathological examination of the soft tissue harvested during reconstruction from the resection site was negative for recurrence of the tumour.

Review of literature and Discussion:

Ameloblastoma is a locally invasive neoplasm derived from odontogenic epithelium. The tumor is made up of proliferating odontogenic epithelium especially of enamel organ-type tissue that has not undergone differentiation to the point of hard tissue formation. Characteristically, the tumor lacks enamel and dentin. It has been postulated that the epithelium of origin is derived from one of the following sources: (a) epithelial lining of odontogenic cysts, (b) dental lamina or enamel organ, (c) disturbances of developing enamel organ, (d) basal cells of surface epithelium, or (e) heterotopic epithelium of other parts of the body. [3, 4, 5]

Granular cell ameloblastoma (GSMA), a variant of ameloblastoma, has been demonstrated in one series to be a more aggressive form of ameloblastomas, with a higher incidence of metastasis than other forms. It has been compared to the granular cell basal cell carcinoma. [6, 7, 8] It was first observed by Krompecher in 1918 and was called pseudoxanthomatous cells. [9]

Hartman in the largest reported series, found it to represent 5% of all ameloblastomas. [6] In the clinicopathologic study of Kameyama et al, only 1 out of 77 ameloblastoma cases was classified as the granular cell subtype. [10] Reichart at al reviewed all available literature on ameloblastoma of the jaws from 1960 to 1993 and reported that out of a total of 1593 cases with available data on histologic subtypes, there were only 56 (3.5%) cases of the granular cell variant. [11]

Hartman studied 20 cases of GSMA from the files of Armed Forces Institute of pathology and suggested that the granular-cell ameloblastoma occurs predominantly at the posterior regions of the mandible, with no gender predilection and demonstrates a marked propensity to recur (73%) following conservative therapy. The average age of the patients in this series was 40.7 years (age range 21-65 years). Its age distribution is considered to be quite similar for which an average median age of 35 years old, ranging from 4 to 92 years, is reported. Subsequent reviews confirmed the strong propensity for involvement of the mandible. [6] The present case was reported in a 32 year old male patient in the left mandible.

In keeping with the morphological picture we were able to demonstrate the expression of cytokeratin in...
the granular cell ameloblastoma. Slootweg et al and DeWilde et al obtained identical results in their studies. \[12, 13\]

Granular cells are associated with granular cell tumor, solid/multicystic ameloblastomas, ameloblastic fibroma, odontogenic fibroma, odontogenic cysts, and congenital epulis of the newborn.\[14\]

Numerous theories have been proposed on the origin and nature of these granular cells in ameloblastomas. These granular cells are epithelial in origin and several ultrastructural and histochemical studies have described them as lysosomes. Lysosomal aggregation within the cytoplasm is caused by dysfunction of either a lysosomal enzyme or lysosome-associated protein involved in enzyme activation, enzyme targeting or lysosomal biogenesis.\[15\]

It is evident from the literature, there exist two main lines of interpretation in that some consider it as a metabolic, whilst others of the view that it represent a degenerative process. More recent observations support the later view to be more tenable based on the increased expression of death signaling molecules.\[16\]

Nasu et al speculate that with age, the unnecessary/aged components progressively increase in the cytoplasm of some of the tumor cells, but the ability of lysosomes to dispose of these materials decrease, hence their cytoplasm becomes packed with lysosomal granules.\[17\] Tandler and Rossi in 1977 proposed that these lysosomes might have been a result of some genetic alteration in the granular cell.\[18\] An ultrastructural study by Kumamoto et al suggests that the cytoplasmic granularity might be attributed to the increased apoptotic cell death of the neoplastic granular cells and their subsequent phagocytosis by the adjacent granular cells.\[19\]

Ara et al suggested that the synthesis of signaling molecules, such as b-catenin and Wnt-5a is upregulated in the granular cells of GSMA, transportation or secretion is impaired, resulting their accumulation with granular cells, as autophagosomes.\[20\]

Reichart et al reported a 33% recurrence rate for granular cell ameloblastoma, which was higher, compared to the more common follicular, plexiform and acanthomatous subtypes.\[21\] In Hartman’s study, 73% of the patients developed recurrent lesions. \[6\] However, similar to the other types of SMA, the prognosis is more dependent on the method of surgical treatment i.e. GSMA treated by enucleation or curettage exhibit a high recurrence rate due to the fact that the border of the tumor within cancellous bone lies beyond the apparent macroscopic surface and the radiographic boundaries of the lesion. \[20\]

The aggressiveness of this has been correlated with an enhanced DNA synthesis and can also be attributed to the similarity of behavioural features between ameloblastoma and the dental lamina; complete surgical excision is the treatment of choice. Ameloblastoma is a tumor that frequently recurs after conservative treatment. The rate of recurrence ranges from 45% for enbloc resection to 54.1% for conservative therapy. \[20\]

Considering the behavior of the GSMA, in order to minimize the risk of recurrence, in the present case, segmental resection along with excision of the involved mucosa was performed which resulted in a large soft tissue and mandibular defect. The functional and aesthetic outcomes after segmental mandibular resection are closely related to the technique used during mandibular reconstruction with bone graft. In patients with large soft tissue and mandibular defect, free fibula mucocutaneous flap is the method of choice for reconstruction. Surgical skills and the availability of facilities are the limitations for such reconstructive procedures. At first, soft tissue reconstruction was carried out using nasolabial flap to facilitate a successful delayed reconstruction and to avoid graft exposure and resorption. Patient is under follow-up till date and shows no signs of recurrence. In order to improve the functional ability, prosthetic rehabilitation with implants is intended in future.

**Conclusion:**

The granular cell ameloblastoma is a rare condition with unique histopathologic and immunohistochemical findings; its treatment and prognosis do not significantly differ from those of other subtypes of the solid/ multicystic ameloblastoma. However, it should be differentiated from the other granular cell lesions primarily because of its higher recurrence rate. A better understanding of the molecular pathogenesis of ameloblastoma and its subtypes is under way and may provide diagnostic and therapeutic benefits.

**References:**


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