Ameloblastoma with Multiple Histologic Variants: A Case Report with Review of Literature
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Abstract
Ameloblastoma is the second most common true neoplasm of odontogenic epithelial origin. Its incidence, approximately 1% of all oral tumour and 18% of all odontogenic tumour, combined with its clinical behavior, makes ameloblastoma the most significant odontogenic neoplasm. The ameloblastoma histopathologically presents with variable features. Hybrid lesion in ameloblastoma is comparatively a newer histopathologic variant and the occurrence of the lesion is not frequently seen. The present case is characterized by stromal desmoplasia and osteoplasia with classical follicular islands, granular and acanthomatous differentiation in the collision with luminal and intraluminal unicystic ameloblastoma with features of Calcifying Odontogenic Cyst ex ameloblastoma in a tumor arising in a 50-year-old male patient.

Key words: Acanthomatous; Ameloblastoma; Desmoplasia; Follicular; Hybrid; Odontogenic Tumor.


Introduction
Tumors and tumor-like growths arising from odontogenic tissues constitute a heterogenous group of particularly interesting lesions as they display the various inductive interactions that normally occur among the embryological components of the developing tooth germ. Ameloblastomas constitute almost half (48.9%) of the odontogenic tumors with female: male and maxilla: mandible ratios of 1:1.7 and 1:8 respectively. It was described by Robinson in 1937 as a benign tumor that is “usually unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent”. The World Health Organization (1991) defined ameloblastoma as a benign but locally aggressive tumor with a high tendency to recur, consisting of proliferating odontogenic epithelium lying in a fibrous stroma.

It’s a neoplasm with variable clinical expression and accounts for 1% of all cysts/tumors of jaws and 18% of all odontogenic neoplasms. It is a true neoplasm of enamel organ type tissue which does not undergo differentiation to the point of enamel formation. Its histological appearance is similar to that of the early cap-stage ameloblastic elements of development without complete differentiation to a stage of enamel formation. It generally occurs in bone, and it has been postulated that the epithelium of origin is derived from one of the following sources: (1) Cell rests of the enamel organ, (2) Epithelium of odontogenic cysts, (3) disturbances of the developing enamel organ, (4) basal cells of the surface epithelium or (5) heterotrophic epithelium in other parts of the body.

Numerous cases presented have thrown light on the variety of histological variants and patterns seen in ameloblastoma. Follicular and plexiform are the main histological variants. Cytomorphogenic subtypes of the above two main patterns are basaloïd, acanthomatous, granular cell, unicystic and more recently, clear cell, papilliferous, kerato-variant and desmoplastic ameloblastoma (DA). Hybrid Ameloblastoma (HA) is a rare type of ameloblastoma that is presently receiving attention in some quarters. Till the date reported, HAs have shown the most common histologic feature of combination of desmoplasia with follicular variant among the cases reported. The present report is a case of ameloblastoma with an unusual clinical behavioral pattern of the tumor but showing considerably unusual histological picture with predominant acanthomatous differentiation along with follicular, desmoplastic, granular cell type showing osteoplasia along with luminal, intraluminal, intramural with features of Calcifying odontogenic cyst (COC) lining.

Case Report
A 50 years-old male patient presented with the chief complaint of swelling on the left side of the face since four years. Patient was apparently normal four years back, when he...
developed pain in lower left back tooth region of the jaw which was sudden in onset, dull, intermittent aggravated while eating food and relieved by taking rest. He visited a local practitioner and underwent extraction of tooth. After one month of extraction swelling started on the left side of the face, which was small in size and gradually increased to the large size, was non-tender and not associated with pain. There was gradual decrease in mouth opening since four years.

Extra-oral examination revealed facial asymmetry due to a solitary well circumscribed swelling present on left middle & lower 1/3rd of the face, measuring approximately about 6×7 cm in diameter, extending anteriorly from left corner of the mouth to posteriorly up to the tragus of the ear and superiorly just beneath the ala-tragus line and inferiorly 1 cm beyond the lower border of the mandible (Figure 1a). The swelling was non tender on palpation, hard in consistency, skin over the swelling was normal, and swelling was fixed to the underlying bony structures. On intraoral examination a diffuse swelling was present in the lower left posterior jaw region measuring 3×2 cm in size approximately, extending anteriorly from buccal sulcus of 36, posteriorly up to retromolar area and ascending ramus region causing the obliteration of the buccal and lingual vestibule. Swelling was non-tender on palpation and bony hard in consistency in relation to 37 & 38 tooth region.

Figure 1: The extraoral photograph showing prominent facial asymmetry on left middle & lower 1/3rd of the face (a). The orthopantomogram shows multilocular radiolucency extending from 36 involving the entire ramus by sparing condyle, inferiorly extending beyond the inferior border of the mandible with resorption of the distal root of 36 (b). The 3D CBCT in the front (c) and lateral view (d) shows a multilocular radiolucency involving the entire ramus, causing bucco-lingual plate expansion, extending inferiorly beyond the inferior border of the mandible and superiorly involving coronoid process. The gross appearance (e) of the resected posterior part of the mandible was brownish black in color, firm in consistency and measuring about 10×7 cm in dimension.

Orthopantomogram revealed multilocular radiolucency extending from 36 involving the entire ramus by sparing condyle, inferiorly extending beyond the inferior border of the mandible. Root resorption of the distal root of 36 was observed (Figure 1b). Front (Figure 1c) and lateral view (Figure 1d) 3D Cone Beam Computed Tomography (CBCT)
showed a multilocular radiolucency involving the entire ramus by sparing condyle, inferiorly extending beyond the inferior border of the mandible and causing the areas of bone resorption. Inferiorly thinning of the cortical border at the angle of the mandible was also observed. Concurrent with clinical, radiographic findings and incisional biopsy, diagnosis of Ameloblastoma was given. Surgical excision of the lesion was planned. The excised specimen was received and numerous sections from different site were prepared (Figure 1e).

Figure 2: The Photomicrograph of H & E stained section shows (A) follicular type of islands (B) squamous metaplasia suggestive of acanthomatous transformation (C) compressed ameloblastic follicle due to desmoplasia. (D) Large ameloblastic follicle with granular cells showing eosinophilic cytoplasmic granules (E) Luminal unicystic lining (F) osteoid area. (G) Intraluminal proliferation of the cystic lining (H) intraluminal unicystic lining (I) mural proliferation of the unicystic lining. (J) Lining showing ghost cells typical of COC.

Numerous Hematoxylin & Eosin stained sections showed small and large ameloblastic odontogenic epithelial islands. Most of the follicular types of ameloblastic
islands were lined by cuboidal ameloblast like cells and central granular cells with acidophilic granular cytoplasm. Few areas of central stellate reticulum like cells showed squamous metaplasia indicating acanthomatous differentiation. The luminal, intraluminal and intramural proliferation of the follicles were observed. There was presence of peripheral cystic lining showing large number of ghost cells simulating COC. Stroma showed desmoplasia along with marked osteoblastic activity. Few stromal areas showed large amount of blood vessels and numerous giant cells in vicinity. Multiple occurrence of the histologic features suggested Hybrid ameloblastoma ex COC (Figure 2).

Discussion
In the World Health Organization histological typing of odontogenic tumours, ameloblastoma was classified as belonging to the group of lesions in which there is odontogenic epithelium without morphologically identifiable odontogenic ectomesenchyme. A recently published biological profile based on 3,677 ameloblastoma cases, has clearly demonstrated that it is no longer appropriate in any scientific study to use the diagnosis of ameloblastoma without specifying the type. Hence, based on clinical and radiographic characteristics, histopathology, and behavioral and prognostic features, subtypes or variants of ameloblastoma can be presently distinguished as follows. 1. The classic solid / multicystic ameloblastoma (SMA) 2. The unicystic ameloblastoma (UA) 3. The peripheral ameloblastoma (PA) 4. The desmoplastic ameloblastoma (DA), including the so-called hybrid Lesions.

In 1827, Cusak published a report describing what obviously an ameloblastoma was. Ameloblastomas are said to comprise between 10% and 50% of all odontogenic tumors. The age group predilection peaks in the 20 and 30 years, with the average age being between 30 and 40 years. The majority of cases occur between the 30 to 60 years age group. Nagata, et al. presented a case of ameloblastoma in the mandible of an 82-year-oldman. They account for about 1-3% of tumors and cysts of the jaws and about 1% of mandibular and maxillary tumors and cysts with predilection in mandible than maxilla. The described case report of a 50-year-old male patient with a classical presentation of the lesion in the left posterior region of the mandible to be of ameloblastoma.

Radiographically, in most cases, ameloblastoma presents characteristic but not diagnostic features. A unilocular or multilocular radiolucency with a honeycomb or soap bubble appearance is the most striking feature. Ameloblastoma is an osteolytic lesion and does not produce mineralized components except in rare cases. The present case showed multilocular radiolucency in 3D CT scan imaging, with considerable bone resorption involving entire of the ramus extending to the coronoid process. Panoramic view also showed resorption of the root in 36 which is not an uncommon finding regarding ameloblastomatous lesion.

Vickers and Gorlin in 1970 defined the histopathological features of ameloblastoma. Most of them present variable range of patterns. These patterns may include follicular, plexiform, granular cell, desmoplastic, acanthomatous, basal cell type, and unicystic types. In a large case study, it was suggested that individually these pattern comprises 28.2%, 32.5%, 4.28%, 4-13%, 12.1%, 2.02%, and 6% of cases included respectively. The present case showed histological picture with more than one type of histologic variant. Granular cell variant was predominant along with areas of follicular subtypes, acanthomatous differentiation, luminal intraluminal and intramural unicystic types with the areas showing desmoplasia and osteoplasia. Some areas resemble typical lining resembling Calcifying odontogenic cyst (COC) with the presence of ghost cells which gave the lesion direction of being ameloblastoma ex COC. It was added to the cases earlier reported with more than one histologic pattern. In the study conducted by Fulco GM et al, 75.5% of the solid lesions included were made up by more than one histological pattern. Similarly, in the study carried out by Adeline et al., 68.6% of the solid ameloblastomas revealed more than one histological pattern. Nonetheless, only 16.1% and 19.7% of the solid lesions evaluated by Reichart, et al. and Kim and Jang, respectively, showed more than one histological type. According to Adebiyi et al., and Waldron and El-Mofy, ameloblastomas, especially the large ones, are made up of numerous histological patterns.
Waldron and El-Mofty first described the HA as an individual histologic variant showing follicular or plexiform pattern co-existing with areas of characteristic DA. It was speculated that the desmoplastic changes occur secondarily in the stroma of preexisting SMA. It has been suggested that the hybrid tumor should be considered a collision tumor. As rare incident Siar CH, et al., presented a case which is an example of radicular cysts and ameloblastoma occurring as a collision phenomenon.

Balve RM, et al. reported an interesting case of hybrid lesion which histologically showed areas of desmoplasia with typical areas of follicular and plexiform patterns along with osteoplastic activity. They proposed three possible variants of desmoplastic ameloblastoma among which hybrid lesion was the third variant. They suggested that the osteoplastic activity in the stroma may be induced by tumor cells resulting in bone formation in a pattern very similar to the formation of desmoplasia. In the present case large amount of osteoplastic activity was noticed. It is suggested that the stimuli which cause stromal fibroblast to cause desmoplasia may also lead to differentiation of stromal mesenchymal cells to form osteoblast causing osteoplasia.

Kumamoto and Ooya suggested that granularity of the cytoplasm of the granular cells might be the result of increased apoptotic cell death and associated phagocytosis by neighboring neoplastic cells. The present case depicted large amount of granular cells activity within the follicles. Mahades, et al. reported a case of HA with luminal, intraluminal and mural proliferation of unicystic type of lining. Toida proposed three groups of calcifying odontogenic cyst in which third category is COC associated with odontomas, ameloblastomas and other odontogenic lesions. Intraluminal cystic lining was seen in the present case with ghost cells, though the absence of dentinoid appearance should be visualized in the direction of lesion that might have developed from pre-existing COC. Hong et al. reported 92 cases of COC out of which 14% were ameloblastomatous COC. But as the present case is a frank HA the lesion can said to be Hybrid ameloblastoma ex COC.

Altogether, less than 30 cases of the HA have been reported in the scientific literature, thus calling for the need to report more cases in order to add to the body of knowledge on this lesion. Reports from the scientific literature show that most cases of HA present as mixed radiolucent and radiopaque lesions with irregular borders similar to the common radiological pattern observed in DA (with osteoplasia) or fibro osseous lesions although a few cases of HA have been observed to present radiographically as multicystic radiolucency similar to the common radiographic pattern of conventional ameloblastoma. The literature till the date reveals HA (Table 1) with the most common histologic feature of a combination of desmoplaisia with follicular variant among the cases reported.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Case</th>
<th>Radiographic Features</th>
<th>Histopathological Features</th>
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<td>Waldron et al., 1987</td>
<td>5</td>
<td>INA*</td>
<td>Coexistence of desmoplastic and follicular ameloblastoma</td>
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<td>Higuchi et al., 1991</td>
<td>2</td>
<td>1st case: soap bubble and multicystic</td>
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<td>Philipsen et al., 1992</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Takata et al, 1999</td>
<td>1</td>
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<td>Wakoh et al, 2002</td>
<td>1</td>
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<td>Follicular-type ameloblastoma with desmoplasia</td>
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<td>Hirota et al, 2005</td>
<td>1</td>
<td>Well defined radiolucent lesion</td>
<td>Follicular, plexiform, acanthomatous, and basal cell patterns of ameloblastoma with desmoplasia</td>
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<td>Pathology</td>
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<td>dos Santos et al., 2006</td>
<td>Ill-defined radiolucency</td>
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<td>Desai et al., 2006</td>
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<td>Sivapathasundaram et al., 2009</td>
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<td>Yazdi et al., 2009</td>
<td>Mixed radiolucent and radiopaque lesion with ill-defined borders</td>
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<td>Gade et al., 2010</td>
<td>Radiolucency with radiopaque specks</td>
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<td>Gupta et al., 2011</td>
<td>Ill-defined hazy, radiolucent lesion with flecks of radiopacity</td>
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<td>Mahadesh et al., 2011</td>
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<td>Bavle et al., 2013</td>
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<td>Effiom et al., 2013</td>
<td>Mixed radiolucent and radiopaque</td>
<td>Keratinizing follicular ameloblastoma and desmoplastic ameloblastoma with osteoplasia</td>
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<td>Rastogi et al., 2013</td>
<td>Mixed radiolucent and radiopaque</td>
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<tr>
<td>Raj Rai et al., 2014</td>
<td>Mixed radiolucent and radiopaque</td>
<td>Desmoplastic and plexiform ameloblastoma</td>
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<tr>
<td>Present case 2015</td>
<td>Well defined multilocular radiolucent lesion</td>
<td>Granular cell variant was predominant with areas of follicular, acanthomatous, luminal intraluminal and mural unicystic types with desmoplasia and osteoplasia. Some areas resemble typical lining of Calcifying odontogenic cyst.</td>
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**Table 1: Cases reported in literature**

A suggestion that ‘hybrid tumour’ is considered a “collision tumour” was therefore proposed. Collision tumours are considered to be two or more tumors that arise from independent topographic sites. It is possible that the conventional and DA variants of the HA develop simultaneously thereby favoring the collision concept. It is not worthless to add a note that the present case is a HA or a collision tumor with unusual combination of follicular, acanthomatous and granular cell pattern in desmoplastic ameloblastoma with osteoplasia, luminal, intraluminal, mural type reported. Presence of cystic lining resembling COC with ghost cells is also a unique feature with the hybrid ameloblastoma.

**Conclusion**

Hybrid lesion in ameloblastoma is proven histopathological variant. Usually such lesion is histologically present with desmoplasia with follicular, acanthomatous and basaloid
patterns. Additionally, the present case showed granular cell type pattern, osteoplasia and unicystic lining with luminal, intraluminal and mural proliferation which is not common. There is requirement of examination and inclusion of new cases of such hybrid lesions of ameloblastoma with their detailed data of clinical and radiographic presentations with corresponding histopathological variations to understand the behavior and further clinical implication.

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