

'Hybrid' desmoplastic ameloblastoma: an unusual case report with immunohistochemical investigation for TGF- β and review of literature

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Abstract. Ameloblastoma, a relatively common epithelial odontogenic tumor includes several histopathologic subtypes like follicular, plexiform, acanthomatous and desmoplastic variants. Hybrid desmoplastic ameloblastoma (DA) composed of typical desmoplastic ameloblastoma along with areas of follicular/plexiform ameloblastoma is an extremely rare variant of ameloblastoma and to date only 16 cases have been documented. We report a new case of hybrid DA which additionally showed remarkable histologic findings of extensive bone formation and presence of mucous cells. It occurred in a 64 year old female patient involving the left maxilla from lateral incisor to distal to first molar. A comprehensive review of hybrid DA and the unusual findings aimed to offer an insight into the pathogenesis of these heterogeneities in odontogenic epithelium and clinical implications was also undertaken. Hybrid DA showed characteristic clinicopathologic features of a desmoplastic ameloblastoma with the exception of predominant mandibular occurrence. A likelihood of areas of solid multicystic ameloblastoma being a part of histopathologic spectrum of DA questioning the need for use of term "hybrid" was observed. Regarding the osteoplasia, most cases occurred in Asians and in anterior maxilla. The prominent TGF- β expression seen in our case adds emphasis to its role in desmoplasia and osteoplasia. Furthermore, we identified an interesting association of desmoplasia with incidence of mucous cell metaplasia in ameloblastoma.

Key words: Ameloblastoma; hybrid desmoplastic ameloblastoma, osteoplasia, mucous cells, TGF- β

1. Introduction

Ameloblastoma is a relatively rare benign epithelial odontogenic tumor characterized by a local invasiveness and high frequency of recurrence. It includes several clinico-radiographic and histologic subtypes like follicular, plexiform, acanthomatous, basaloid and granular cell types (1-3). Recently, the histomorphologic spectrum of ameloblastoma has been expanded to include a desmoplastic variant (4,5). Follicular and plexiform are the commonly encountered variants accounting for 32.5% and

28.2% respectively; followed by the acanthomatous subtype with 12.1% while desmoplastic is extremely uncommon with incidence rates ranging from 4-13% in various reports (1).

Desmoplastic ameloblastoma (DA) was first described in detail by Eversole et al in 1984 and is defined as "a variant of ameloblastoma with specific clinical, imaging and histological features" in the recent WHO classification of odontogenic tumors. Thus, it often occurs in the anterior region of jaws, presents with unique radiographic appearance resembling fibrous lesions and show distinct histopathology characterized by extensive stromal collagenisation or desmoplasia surrounding compressed islands of odontogenic epithelium making it a distinct entity (6-10).

A possible transitional form of DA, showing microscopic features of desmoplastic variant together with areas of classical follicular/plexiform ameloblastoma has been described as a "hybrid lesion"(5). It is an extremely unusual

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variant and was first described in detail by Waldron & El-Mofty in 1987(11). A recent review reports a total of 12 cases being of hybrid variant (8). However, a comprehensive review of English language literature revealed four more cases, to which we add an additional case to enhance the knowledge of this interesting tumor.

The other noteworthy finding noticed in the present case was extensive osteoplasia/new bone formation which has been previously reported in only five cases (12-15). Additionally, an extremely rare phenomenon of mucous cell differentiation in several islands was apparent. This has been previously reported in only 7 cases (16).

The present paper reports this unusual case and reviews the pertinent literature to elucidate these remarkable heterogeneities of odontogenic epithelium. Furthermore, we also investigated the expression of TGF- β , a potent extracellular matrix modulator in this subset of ameloblastoma.

2. Case report

A 64 year old female presented with a gradually progressive swelling on the left side of 6 months duration. The patient gave a significant history of having been operated for a similar swelling 20 years back which recurred two years later, for which she was re-operated subsequently. The patient however did not have any histopathology report or details of the surgery for the same.

Extraoral examination revealed a mildly discernible swelling in the left middle third of the face with obliteration of the nasolabial fold. Intraorally, a swelling measuring around 3x2 cms was seen obliterating the buccal vestibule extending from maxillary left lateral incisor distal to the first molar. It was bony hard and slightly tender on palpation. The overlying mucosa was intact but appeared stretched. Mobility and displacement of associated teeth was also observed. (Fig. 1A)

Radiographs (OPG & PNS views) revealed an ill defined radiolucent lesion in the left maxilla with flecks of radio-opacity extending from maxillary left central incisor to first molar with displacement of associated roots (Fig.1B). Computed tomography scans revealed an expansile radiolucent radiopaque lesion measuring around 3x4 cms involving the left maxilla. There was no obvious extension into the maxillary sinus (Fig.1C). A provisional diagnosis of ossifying fibroma was considered and keeping in mind, the history of recurrence; a partial maxillectomy was performed.

Macroscopically, a resected left maxilla which was brownish white in color and extremely hard in consistency was received. The cut section demonstrated a granular, gritty, creamish white solid appearance (Fig.1D). Radiograph of the specimen showed ground glass like appearance with small cyst like radiolucencies. Resorption of roots of associated teeth was observed (Fig.1E)



Fig. 1. A: Intraoral clinical photograph of the tumor in the left maxilla. B, PNS view demonstrating a mixed radiolucent and radiopaque appearance with opacification of the sinus. Computed tomography scan demonstrating a mixed radiolucent –radiopaque lesion (C). Cut surface of the gross specimen demonstrating a solid, granular, creamish white lesion (D). E: Radiograph of the gross specimen depicting a mottled appearance with focal radiolucencies.

Histopathologically, numerous ameloblastic islands dispersed in a densely fibrous and hyalinised stroma exhibiting areas of myxoid degeneration were seen. The islands appeared small and compressed reminiscent of a desmoplastic ameloblastoma (Fig 2A). However, in other areas; well defined ameloblastic follicles exhibiting squamous metaplasia and extensive cystic degeneration were apparent (Fig 2B, 2C, 2D). An interesting finding was presence of numerous areas of new bone rimmed by plump osteoblasts distributed evenly throughout the stroma with ameloblastic islands interspersed within it (Fig. 2B, C, D). Layers of osteocementum were observed in the resorbed root surfaces. A further unusual finding noticed was presence of mucous cells in few of the islands. These mucous cells were seen singly and in clusters and were present in ameloblastic islands exhibiting squamous metaplasia and cystic degeneration. Large and small cysts containing globules and pools of mucin and few duct-like

areas were also observed. These cells were positive for PAS with diastase and mucicarmine stains (Fig 3A, B). Immunohistochemically, the typical DA areas as well as the conventional follicular areas in our hybrid lesion exhibited marked TGF β expression (Fig 4A, B, C, D). The patient has been followed up for one year without any evidence of recurrence. A diagnosis of hybrid desmoplastic ameloblastoma with osteoplasia and exhibiting mucous cells was given.

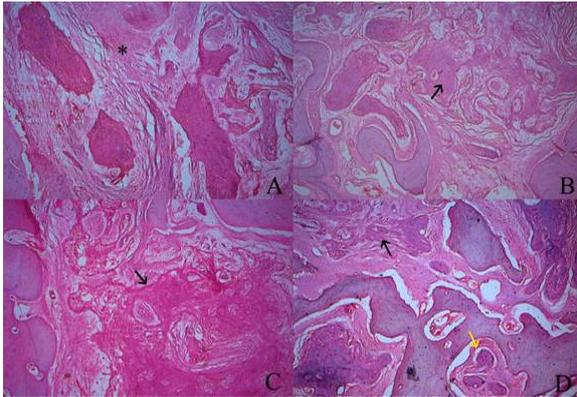


Fig. 2. A: Photomicrograph exhibiting compressed odontogenic epithelial islands in a desmoplastic stroma (*) (H&E, x100). Areas of conventional follicular ameloblastoma (Black Arrow) showing squamous metaplasia and cystic degeneration interspersed between bony trabeculae (B & C) (H&E, x400). D: Areas of desmoplastic ameloblastoma (Yellow Arrow) and conventional ameloblastoma (Black arrow) in a densely fibrous stroma exhibiting extensive osteoplasia (H&E, x100).

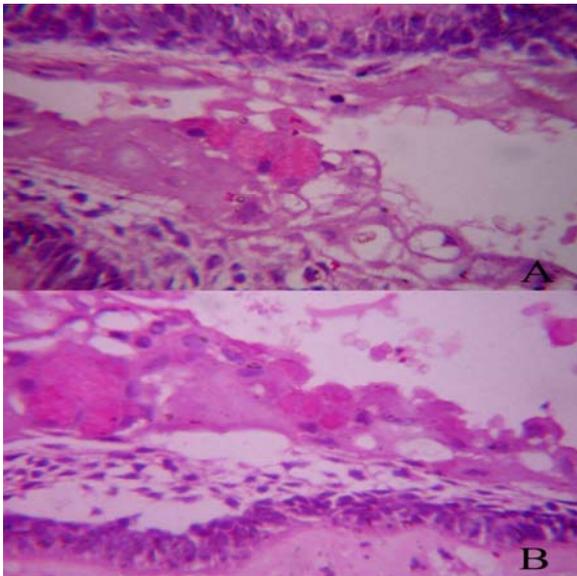


Fig. 3. A: High power view demonstrating presence of mucous cells singly and in clusters. (Mucicarmine stain x400.) B: A cluster of mucous cells with underlying ameloblast like cells exhibiting reversal of polarity is seen. (Mucicarmine stain x400)

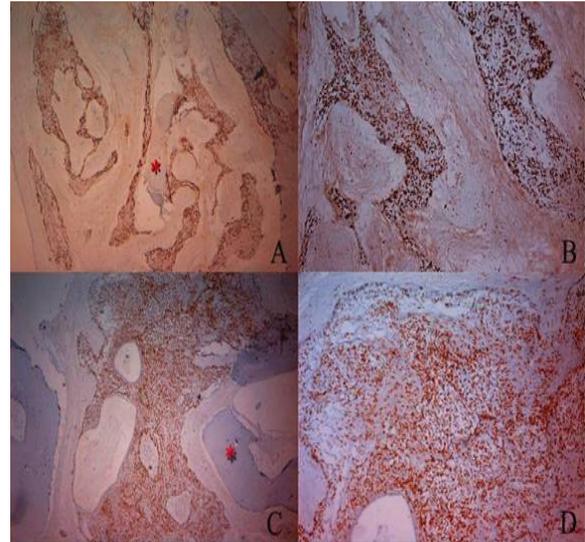


Fig. 4. Intense TGF- β expression noted in desmoplastic ameloblastoma like area (A: x40, B:x100) and in hybrid follicular ameloblastoma (C x40, D x100). Bony trabeculae are seen distributed throughout the tumor (red asterisk)

3. Discussion

Ameloblastoma is a rare odontogenic tumor accounting for around 1% of all the cysts and tumors in the jaws (1). It encompasses several histological variants like follicular, plexiform, basaloid, acanthomatous and desmoplastic variants (10). Since the first description of desmoplastic ameloblastoma by Eversole et al (5), a total 115 cases have been reported (8). It is somewhat new and a rare entity accounting for 4%-13% of all ameloblastomas (4, 8). The striking difference in the anatomic location i.e. occurrence in the anterior-premolar region of maxilla/mandible, unusual radiologic presentation of mixed radiolucency-radiopacities with ill-defined borders and distinctive histopathology of extensive stromal desmoplasia with scattered odontogenic epithelium makes it a distinct clinicopathologic entity. Additional findings reported for DA are almost equal sex predilection and relative higher frequency of occurrence in Asians (17-20).

“Hybrid” lesion of desmoplastic ameloblastoma and conventional ameloblastoma is an unusual variant of ameloblastoma, which was first described by Waldron & El Mofty in 1987 (11). Hybrid lesions show typical microscopic features of desmoplastic ameloblastoma characterized by pronounced stromal desmoplasia together with areas of follicular, plexiform and acanthomatous ameloblastoma (4, 11). The number of published cases of this variant are limited. Table 1 is the summary of the clinicopathological findings of

the reported cases of Hybrid DA including the present case (Total = 17 cases) (11-29).

The hybrid DAs demonstrated an almost equal sex predilection and occurred in a wide age range of 17-82 years. Strikingly, they have been reported predominantly in Asians i.e Japanese, Chinese, Indians, Iranian and one each in a Brazilian and African. The predilection for these races needs corroboration with newer case reports. The cases showed definite mandibular predilection with 13 cases occurring in mandible and 3 cases being reported in maxilla. An interesting finding was that majority of cases occurred predominantly in the anterior region of the jaw either in maxilla or mandible with around 5 cases presenting in the posterior mandible. The duration of the lesions varied from 2 months to 3 yrs and the size was fairly large ranging from 3 to 8 cms (Table 1).

The radiological features were mostly that of a mixed radiolucency with radiopacities and demonstrated ill defined borders. Two cases of Higuchi et al (21), presented primarily as a multilocular radiolucency, while Takata et al's case presented as a multilocular radiolucency in the anterior region and unilocular radiolucency in the molar region (24). Other radiographic findings reported are root resorption and displacement of teeth (Table 1).

Histopathologically, all the cases showed areas of typical DA i.e compressed odontogenic epithelial islands surrounded by dense desmoplasia along with areas of typical follicular/plexiform/acanthomatous ameloblastoma. Ashman et al (23), reported a case of desmoplastic ameloblastoma which demonstrated granular cell transformation in some of the tumor cells along with areas of follicular and plexiform ameloblastoma while Hirota et al (26), reported a case of desmoplastic ameloblastoma depicting associated follicular, plexiform, acanthomatous and basaloid changes. We have included both these cases too as hybrid DA and believe that this term should encompass any histological variant of solid multicystic ameloblastoma (SMA) presenting along with typical desmoplastic ameloblastoma.

Whether, the hybrid lesions represent an alteration in a preexisting desmoplastic tumor or whether the desmoplastic areas represent some form of alteration of stroma and epithelial morphology is a matter of conjecture (1). However, Waldron and El Mofty (11) believe that since most conventional ameloblastoma rarely show areas of desmoplasia, they believe that DA

may itself on occasion undergo at least a partial alteration to the morphology of conventional ameloblastoma. This is supported by our review which demonstrates that the hybrid lesions show characteristic features of a typical desmoplastic ameloblastoma i.e no definite gender preference, site predilection of anterior region of jaws and mixed RL-RO appearance except for the histologic presence of areas of conventional ameloblastoma along with areas of DA and a striking mandibular predilection. This review thus refutes the suggestion that the hybrid lesion should be considered as a collision tumor. (4) Melrose wrote that designation "hybrid tumor" serves no real purpose and if taken, literally, might overstate the significance of finding a DA in combination with islands of solid multicystic ameloblastoma (SMA) (30). We are in harmony with this statement and believe that areas of conventional ameloblastoma may in fact be a part of histopathologic spectrum of DA, however; the prognostic significance of their presence needs corroboration with many more cases than those published now with detailed clinical, radiologic and histopathologic analysis. Santos et al, postulated that extracellular matrix molecules like tenascin demonstrable in the stroma of follicular part of a hybrid lesion and type I collagen and fibronectin seen throughout the lesion, may participate in tumoral modulation of hybrid desmoplastic ameloblastoma (27).

The presence of extensive osteoplasia noticed in our case is exceptional and there are only five cases till date in English Literature that have reported prominent bone formation in DA.(Table 2) (12-15). This review excludes two cases by Raubeinemer et al (31) as no clinical details are available and three cases in Japanese literature referred to by Riechart et al (1,32-34). The cases demonstrating new bone formation showed no specific sex preference and occurred over a wide age range of 21-64 years. But, surprisingly all occurred in the Asians (ie Japanese, Chinese) with our case being the first to be reported in an Indian. A definite predilection to anterior maxilla was noted with the lesions being widespread extending from anterior region to molar region exhibiting an average size of around 3.5cms. Radiologically, all cases presented with mixed RL-RO appearance with ill-defined borders and histologically were cases of desmoplastic ameloblastoma with only our case being a hybrid DA. The metaplastic bony trabeculae varied from woven to mature bone which contained

Table 1. Clinicopathologic features of Cases demonstrating Hybrid Desmoplastic ameloblastoma

Author and Year.	Age/ Sex	Location	Size in cms	Radiologic features	Histopathology	Management	Follow Up
Waldron & El Mofty, 1987 ¹¹	25-82 years 2 Cases-Male 3 cases Female	4 Cases- Posterior Mandible 1 case- NA	NA	NA	DA with Follicular ameloblastoma	NA	NA- 1 case was stated to be recurrent
Higuchi et al, 1991 ²¹	58/M Japanese	Mand Anterior- Posterior	3.2x2.6	Soap Bubble and Multicystic	Hybrid DA	Enucleation, Bone curettage	No Recurrence
Higuchi et al, 1991 ²¹	70/M Japanese	Mand Posterior	3.1x2.8	Multicystic as a whole	Hybrid DA	Sectional Mandibulectomy	No Recurrence
Philipsen et al, 1992 ²²	55/M Chinese	Mandible, Anterior Canine to Molar		Multilocular Radiolucency with focular radiopacities. Root resorption was seen	DA with follicular and plexiform ameloblastoma	Marginal Block Resection with preservation of lower border of mandible	NA
Ashman et al, 1993 ²³	53/M African	Mandibular anterior	8X5	Well circumscribed mixed RL-RO lesion	DA with follicular, plexiform, acanthomatous and granular changes	Marginal Resection	9 months, No Recurrence
Takata et al, 1999 ²⁴	48/M Japanese	Mandible, Lateral Incisor to first molar	6.6X 5.4	Honeycomb appearance in the anterior region and unicystic radiolucency in molar region of mandibular body.	DA with follicular ameloblastoma, squamous metaplasia and cystic degeneration	Enucleation of the lesion and Marsupialisation of cystic cavity	Tumor tissues reappeared at 3,5,7 and 14 months after surgery, the patient has remained disease free for 11 years after vaporization by CO2 laser of recurred tumor
Wakoh et al, 2002 ²⁵	35/F Japanese	Mandibular Canine- PM region	3x4	Mixed RL –RO Lesion with adjacent cystic radiolucent area. Displacement of tooth.	DA with follicular ameloblastoma	Segmental Mandibulectomy	No Recurrence
Hirota et al, 2005 ²⁶	17/F Japanese	Maxilla Canine - PM Region	NA	Mixed RL-RO lesion with well defined borders	DA with follicular, plexiform, acanthomatous and basal cell ameloblastoma features.	Partial Maxillectomy	7 Years follow up No evidence of recurrence
Santos et al, 2008 ²⁷	36/M Brazilian	Mandibular anterior- PM region	NA	Ill defined RL	DA with follicular ameloblastoma, squamous metaplasia and cystic degeneration	Block Resection	NA
Sivapathasundaram et al, 2009 ²⁸	31/F Indian	Mandibular anterior – PM Region Crossing the midline	NA	Mixed RL-RO, Poorly defined borders, Displacement of teeth	DA with follicular ameloblastoma	Resection	NA
Sivapathasundaram et al, 2009 ²⁸	40/M Indian	Maxillary Anterior- Molar	NA	Mixed RL/RO with ill defined borders	DA with follicular ameloblastoma	Resection	NA
Yazdi et al, 2009 ²⁹	48/F Iranian	Mandibular anterior region	0.7x0.5	Mixed RL/RO with ill defined borders	DA with follicular ameloblastoma	Marginal Resection	One year, No Recurrence
Present Case	64/F Indian	Maxilla Anterior- Molar	3x2	Ill defined RL RO lesion. Displacement of teeth and root resorption	DA with follicular ameloblastoma, squamous metaplasia and cystic degeneration	Partial Maxillectomy	1 year, No Recurrence

NA- Not Available M-Male F- Female RL- Radiolucency RO-Radiopacity DA- Desmoplastic ameloblastoma

Table 2. Clinicopathologic Features of DA demonstrating extensive osteoplasia

Author & Year	Age/Sex	Site	Size	Radiographic Presentation	Histopathology	Management	Follow up
Phillipsen et al, 1992 ¹²	21/M Chinese	Maxillary Ant – Molar Region, Crossing the midline	NA, Extensive	Radiolucency with ill defined borders, tooth displacement and root resorption	Desmoplastic ameloblastoma with extensive osteoplasia	Total right and Partial left maxillectomy	NA
Phillipsen et al 1992 ¹²	53/M Chinese	Maxillary Ant - Molar	NA- Extensive	Ill defined Radiolucency with multiple floccular radiopacity Root resorption of 21,22	Desmoplastic ameloblastoma with extensive osteoplasia. Layers of osteocementum seen with resorbed roots.	Maxillectomy	NA
Okada Y et al, 1986 ¹³	31/M Japanese	Mandibular canine premolar region	2x2cm	Radiopaque lesion with divergence of roots	DA with prominent bone formation	Partial resection of mandible	2 years,8 months No Recurrence
Thompson IOC, 1996 ¹⁴	31/F Black	Maxilla Anterior - Molar	NA	Mixed RL –RO lesion with illdefined borders. Divergence of roots	DA with prominent bone formation.	Partial hemi-maxillaectomy	3 years, No Recurrence
Iida et al, 2002 ¹⁵	52/M Japanese	Maxilla Anterior-Premolar	NA	RL- RO Lesion with few cyst like areas and ill defined borders	DA with evidence of new bone formation.	Partial Maxillectomy	No Recurrence
Present Case	64/F Indian	Maxilla Anterior-Molar	3x2cms	Ill defined RL RO lesion.Displacement of teeth and root resorption	Hybrid DA with extensive new bone formation. Layers of osteocementum seen with resorbed roots.	Partial Maxillectomy	1 year, No Recurrence

NA- Not Available M-Male F- Female RL- Radiolucency RO-Radiopacity DA- Desmoplastic ameloblastoma

osteocytes and were lined by plump active osteoblasts. They were randomly scattered throughout the dense collagenous stroma similar to our case (12-15). Layers of osteocementum around resorbed roots seen in this case has been previously reported by Phillipsen et al (12). Consequently, it appears that at least in some DA's in addition to desmoplasia, osteoplastic changes can also occur. Some authors thought that this could explain the mixed radiopaque/radiolucent appearance in DA (13,14). However, most DA cases do not show pronounced osteoplasia within the tumor tissues but still exhibit the characteristic mixed RL –RO appearance (20). Raubenhimer (31) believed that the prominent bone formation appeared to be reactive in nature, probably linked to a process of interstitial connective tissue metaplasia rather than the result of induction, as the bony deposits were generally separated from the neoplastic epithelium by a broad band of inactive connective tissue. However, Phillipsen et al (1) demonstrated intense collagen type VI staining adjacent to tumor islands in DA as compared to SMA and proposed that the finding indicated an active

synthesis of extracellular matrix proteins. Therefore, they proposed that the tumor stroma in DA was not a scar tissue but rather newly produced connective tissue. Thus, if the desmoplasia is caused by tumor cell stimulation of stromal fibroblasts, then it would seem probable that the stimuli could also affect another cell type i.e. osteoblasts for formation of new bone (osteoplasia) (12). Takata et al (35) studied the immunolocalisation of TGF-β which is potent local factor for modulating extracellular matrix formation and reported marked immunoeexpression of TGF-β in 6 out of 7 DA cases in contrast to SMA suggesting that TGF-β produced by DA tumor cells plays a part in desmoplastic matrix formation. In a hybrid lesion studied by them, TGF-β was intensely expressed in areas of DA and not in areas of follicular ameloblastoma. However, contrastingly in our case; intense immunoeexpression was noted in both areas of DA as well as in conventional follicular areas. It was predominantly noted in the nuclei of the odontogenic epithelial cells as previously reported (35). In vivo studies have shown that

Table 3. Desmoplastic ameloblastoma exhibiting mucus metaplasia

Author and Year	Age/ Sex	Location	Size in cms	Radiologic Features	Histopathology	Management	Follow up
Takata T, 1999 ²⁰	51yrs/M	Anterior Maxilla Canine to premolar	2.5X3 cms	Unilocular RL	Desmoplastic ameloblastoma containing mucous cells in form of acini/glands.	Resection.	No recurrence
Wilson ,2001 ⁴²	31yrs/M	Anterior mandible-canine to second molar	NA	Multilocular RL, crossing midline	Desmoplastic ameloblastoma with squamous metaplasia. Foci of mucous cells lining the epithelium of cystic cavities, within epithelial islands in the form of clumps or linear arrays. Few acini and duct like structures	En Bloc Resection	NA
Angadi,2008 ¹⁶	32yrs/M	Anterior Maxilla, Incisor to premolar	3x2.5 cms	Ill defined RL, specks of RO, associated with impacted canine.	Desmoplastic ameloblastoma with extensive squamous metaplasia and densely hyalinised stroma. Mucus cells in the form of glands/acini, singly and solid clumps in the islands.	Curretage	No recurrence after 1.5 yrs
Present Case	64/F	Anterior Maxilla Incisor to Molar	3x4 cms	Ill defined RL -RO lesion..Displacement of teeth and root resorption	Hybrid DA with prominent desmoplasia and osteoplasia. Mucus cells in the form of clumps, singly in the islands exhibiting squamous metaplasia and cystic degeneration	Partial Maxillectomy	No Recurrence after 1year

NA- Not Available M-Male F- Female RL- Radiolucency RO-Radiopacity DA- Desmoplastic ameloblastoma

TGFβ enhances bone formation and has diverse effects on osteoblast proliferation and differentiation (36-38). The osteo-inductive properties of TGF-β has also been demonstrated in nasal polyps where it has been attributed for osseous metaplasia (39). Accordingly, it may also contribute to the prominent osteoplasia noted in our case. This may be in response to the bone resorption caused by the infiltrating DA as several reports have suggested that TGF-β is released during bone degradation and stimulates bone formation (40). However, the lack of this type of bone formation in most ameloblastoma is surprising and points to an intricate epithelial mesenchymal interaction leading to diverse cellular differentiation in individual tumors (41). This needs further clarification by studying TGF-β in ameloblastoma without bone formation. Another striking finding observed in our case was presence of mucous cells which have been rarely documented in ameloblastoma. A recent review sums a total of 7 cases till date to which we add another case (16). Surprisingly, 4 cases including ours were of desmoplastic ameloblastoma (Table 3) (16,20,42) with majority involving the anterior maxilla. The mucous cells in the present case were arranged singly and in

groups and were present in ameloblastic islands demonstrating extensive cystic degeneration and squamous metaplasia as previously observed. This further supports the implication of close relationship between squamous epithelium and mucous cells as postulated by Hudson (43). A similar association has been reported in squamous epithelium of odontogenic cysts undergoing mucus metaplasia and concurrent occurrence of squamous and mucus metaplasia in Warthin's tumor (41, 44-46). These findings were usually associated with areas of inflammation and necrosis. Necrosis is extremely rare in odontogenic lesions while inflammation has been known to produce metaplasia in odontogenic cysts; however its role in ameloblastoma remains uncertain as most cases of ameloblastoma did not show inflammation in stroma. An association with cystic degeneration further adds an avenue of cyst contents providing the stimuli for mucous metaplasia (16,44,45). Taxy et al, have reported incidence of squamous and mucinous metaplasia in some salivary gland tumors with stroma showing extensive fibrosis but without evidence of necrosis (47). This could be attributed to ischemia and tissue anoxia secondary to fibrosis (41). Similarly, the association of mucous cell

metaplasia with desmoplasia in ameloblastoma is noteworthy and the possibility of the desmoplastic stroma in some way inducing the mucous metaplasia in the odontogenic epithelium needs more elucidation. The scarcity of cases and the inadequate understanding of the biologic behavior and prognosis of desmoplastic ameloblastoma, its treatment thereof is not appropriately defined so far. The radiological and histological findings of poor encapsulation and ill defined borders here first of all warrants a long term follow up and secondly, the findings till date likely indicate that; they have a potential for recurrence (15.9%) similar to other intraosseous ameloblastoma variants. Thus, complete surgical resection of tumor appears to be curative for this entity (1,4,8,11,18). In our review, it was noticed that most cases of hybrid DA were treated radically with resection and no recurrence has been documented in these cases (11,21-29).

Only two cases (11,24) of hybrid DA have been reported to have recurred, one of which was treated by enucleation (24) while there is no documentation regarding the management in the other case (11). Our case had a history of recurrence twice before the patient approached us; however the previous surgical details and histopathologic reports were unavailable. This makes it difficult to determine whether the lesion was a conventional ameloblastoma that recurred as a hybrid lesion or it was a true hybrid lesion de novo and recurred twice. As said before, many more cases of hybrid DA are required to clarify the true biologic behavior of this variant. Until such time, the recommended treatment is similar to other infiltrative ameloblastoma (4,7,48).

The present paper reports an unusual case of hybrid DA depicting extensive osteoplasia and presence of mucous cells with review of pertinent literature. The prominent TGF- β expression observed in our case adds emphasis to its role in desmoplasia and osteoplasia. It highlights the need for added investigation of the DA tumoral stroma to clarify the nature of this outstanding stroma growth and its relation to the epithelial component. Additionally, it emphasizes the differentiation potential of neoplastic odontogenic epithelium to determine the prognostic significance if any of these rarities.

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