

Desmoplastic Ameloblastoma: A case report with a brief review

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ABSTRACT

Desmoplastic ameloblastoma (DA) is relatively rare histologic variant of solid multicystic ameloblastoma (SMA) which is characterized by its peculiar histomorphology, that is stromal collagenization which has led to the term 'ameloblastoma with pronounced desmoplasia'. Radiographically it presents

as a mixed radio-lucent, radio-opaque lesion that mimics a fibro-osseous lesion. We hereby present a case of desmoplastic ameloblastoma in a 22 year female and have made an attempt to discuss the various molecular and genetic markers of ameloblastoma that could affect the treatment plan and aid for the better prognosis.

Key Words: Desmoplasia; Stromal changes; Immunohistochemical markers

INTRODUCTION

Ameloblastoma is the second most common odontogenic tumor of epithelial origin (1). It is a slow growing tumor and has a locally invasive behavior with high recurrence rate (2). Ameloblastoma has three clinical variants namely solid or multicystic, unicystic and extraosseous. Histologically the tumor occurs in different patterns namely follicular, plexiform, basal, granular and acanthomatous (1). Basal cell, clear cell, keratoameloblastoma, papilliferous and desmoplastic are the other rare histological variants (2).

Desmoplastic ameloblastoma (DA), a rare histologic variant of solid multicystic ameloblastoma (SMA) was first reported in 1981 (3). A detailed report was given in 1984 by Eversole and his coworkers on this variant of ameloblastoma. They called this variant as 'ameloblastoma with pronounced desmoplasia' (4). The information regarding the clinical, radiological presentation and pathology of DAs has led World Health Organization to include this variant in 'histopathological Typing of odontogenic Tumors' in the year 2005 (5). The origin of the tumor is either from the epithelial rests of malassez in the periodontal membrane or from the oxytalan fibres of the periodontal membrane (2).

DA may be defined as 'a benign but locally infiltrative variant of solid/multicystic ameloblastoma comprising of proliferating, irregular, bizarre shaped islands and cords of odontogenic epithelium which is often "compressed" and supported by collagenized stroma' (6). It differs from SMA in the clinical, radiological, and histological features and thus should be considered as a separate entity (1). The incidence of DA varies from 0.9% to 12.1% of all ameloblastomas (7). This paper highlights the typical histopathological features of DA and also the various molecular markers expressed in Ameloblastoma, DA & Adenomatoid Odontogenic Tumor (AOT). This gives an overview of genes that should be targeted by drugs thereby modifying the therapeutic approach which aids in better prognosis.

CASE REPORT

A 22 year old female patient has reported to the dental OPD complaining of pain and swelling in the maxillary anterior region. The duration of the swelling was one month. Extra oral examination did not reveal any asymmetry and the findings were non-contributory. Intra oral examination revealed swelling in the maxillary anterior region. The swelling present on the anterior alveolar gingiva was hard and non-tender on palpation with obliteration of nasolabial fold (Figure 1).

Cervical lymph nodes were not palpable. The patient had no habit history. Orthopantomogram (OPG) showed well defined unilocular radiolucency, extending from the region of 14 to 21. Displacement of the roots of 12 and 13 was also found (Figure 2).



Figure 1) Clinical picture showing swelling in the right maxillary anterior region



Figure 2) Orthopantomograph showing well defined radiolucency in the maxillary anterior region extending from 14 to 21

Cone Beam Computed Tomography (CBCT) revealed the expansion and destruction of buccal cortical bone with thinning of the lingual cortical bone (Figure 3).

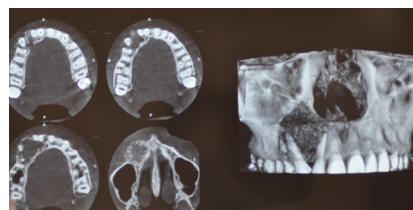


Figure 3) Cone beam computed tomography (CBCT) showing expansion and destruction of buccal and lingual cortical plates

A provisional diagnosis of Ameloblastoma/ Adenomatoid Odontogenic tumor was given based on clinical and radiographic findings.

Hemi-maxillectomy was done and the specimen was submitted to the Department of Oral and Maxillofacial Pathology for the histopathological examination.

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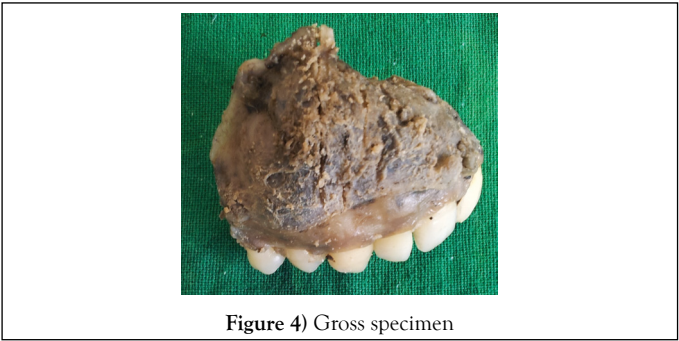
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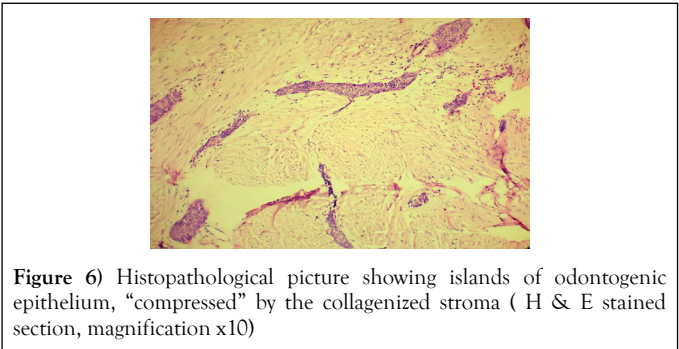


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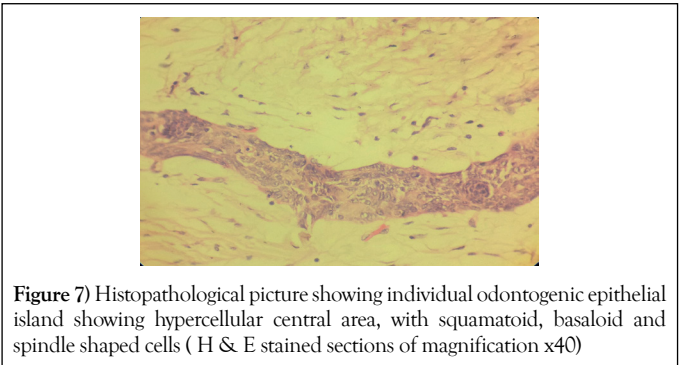
Gross examination revealed that the specimen mass was solid, greyish black in color, measuring approximately 4 x 3cm in size. The cut surface of the specimen has gritty consistency (Figure 4, 5).



Histological examination of the slides stained with Haematoxylin & Eosin showed numerous islands of odontogenic epithelium in a dense collagenous connective tissue stroma (Figure 6).

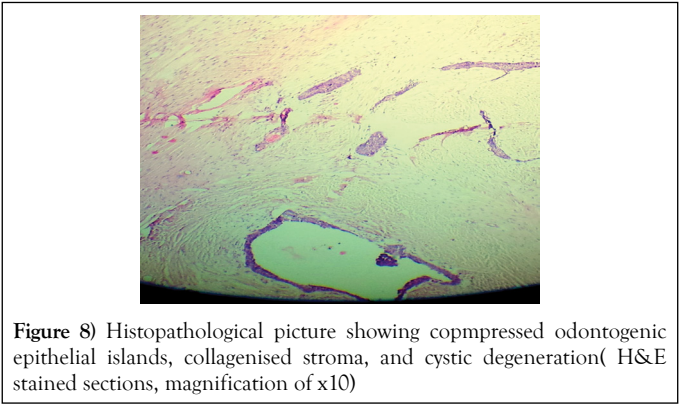


Some odontogenic islands were compressed by the densely collagenous connective tissue stroma and few islands resembled open follicles (Figure 7).



The follicles were occasionally lined by peripheral cuboidal cells and showed hypercellular central area, with squamatoïd, basaloid and spindle shaped cells. Some islands exhibited cystic degeneration (Figure 8).

The lesion also showed few blood vessels lined by endothelial cells, with extravasated red blood corpuscles (RBC) and bony spicules in the connective tissue. The diagnosis of Desmoplastic ameloblastoma was made based on the clinical, radiological and histological features.



DISCUSSION

DA is a locally infiltrative neoplasm marked by stromal desmoplasia. Clinically it is seen more commonly in the 4th and 5th decades of life, with mean age being 42.8 years. Frequency of DA is more in females and the maxillary anterior region is the common site of occurrence. The thin cortical bone of the maxilla favors dissemination of the tumor and also the juxtaposition of the maxillary lesions to the vital structures and the sinus makes the tumor more insidious (8).

Radiographically there are 3 types of DA (Table 1) (9). In the present case, DA was seen as a mixed radiolucent-opaque lesion which falls under type I (osteofibrosis), which is the most common type thus mimicking a fibro-osseous lesion on radiographic diagnosis. The osseous metaplasia within the dense fibrous septa gives characteristic mixed radiographic appearance to the lesion (10). The study conducted by Takata et al., states that the peculiar radiographic picture expresses its infiltrative nature (11).

Table 1
Radiographic types of DA

Type 1:Osteofibrosis	Has radiolucent as well as radiopaque appearance
Type 2:Radiolucent type	Completely radiolucent
Type 3:Compound type	Radiolucent as well as radiopaque appearance combined with a large radiolucent change

The histological features of DA includes:

- (1) Stromal desmoplasia with abundant collagen in the form of moderately cellular and fibrous connective tissue,
- (2) Islands of different shapes (kite-like, animal-like, bizarre) in the epithelial component,
- (3) Peripheral layer of cuboidal cells,
- (4) Hypercellular central area composed of spindle-shaped or squamous cells,
- (5) Osseous metaplasia
- (6) Myxoid changes of the juxtaepithelial stroma,
- (7) Absence of fibrous capsule corresponding to the radiographically poorly defined tumor margin [12].

The histological findings in our case are in accordance with other case reports of DA. The pressure exerted by the collagenous stroma elicits the changes in the epithelial islands [13]. The more aggressiveness of the DA when compared to other ameloblastomas is due to:

- (1) Potential to grow to a larger size,
- (2) Maxillary location (common) favouring early invasion of adjacent structures,
- (3) Inconspicuous radiographic margins, and
- (4) Bony invasion [14].

Immunohistochemical (IHC) studies conducted by Molina et al., showed positive expression of cytokeratin (CK) in the basal & suprabasal cells (Table 2).

TABLE 2

Time of day of NHSIII PEWS scores that would trigger a response

Lesion	Marker	Molecular markers overexpressed and are suggestive of
SMA	MMP-2,MMP-9, syndecan1,17, perlecan,α-dystroglycan, integrin β1,18 CD10, osteopontin	Local invasiveness, aggressiveness, recurrence
	RANKL and MMP-9	Induce osteoclastogenesis, subsequently causing rapid destruction of the bone marrow.
	IL-1α,T IL-6 TNF, RANKL	caused bone resorption & related to the tumor size
	Ki67, CD10	Recurrence
	p53 and murine double minute 2 (MDM2)	Oncogenesis & pathogenesis of SMA
	TGF-Beta	Aggressive biological behavior
	WNT proteins	Tumor differentiation & invasion.
	Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)	neoplastic transformation of odontogenic epithelium
	FAS (CD95), FAS ligand, caspase-3	Responsible for intrinsic regulation of neoplastic cell proliferation and death, thus elucidating their slow growth and inability to metastasize
	Podoplanin	Cell migration
AOT	p21,p27	Cell proliferation
	Hepatocyte growth factor (HGF) and c-met	Effect on squamous differentiation of the odontogenic epithelium of AOT
	Amelogenin, Ameloblastin, and Amelotin, TGF-β are more intensely expressed in AOTs	less aggressive behavior, cytodifferentiation and apoptosis than ameloblastomas.
Desmoplastic ameloblastoma	TGF-beta, Type VI collagen, desmin, S-100	Suggest extracellular matrix.

MMP: Matrix metalloproteinase, RANKL: Receptor activator of nuclear factor κB ligand, TNF: Tumor necrosis factor, WNT: Wingless type 1 glycoprotein, IL: Interleukin,

CK14 was positive in the central cells, CD138 also showed positivity for the epithelial cells. They also found low proliferative index of Ki67 and P53 (15). These results are in accordance with the study of Lee et al., where they found low index of Proliferating Cell Nuclear Antigen (PCNA) and ki67, which thereby elucidates benign biological behavior of DA (16). The over-expression

of MMP-9 in SMA correlates with its invasive & aggressive behavior, which may also be responsible for its recurrence (17).

Higher expression of syndecan 1 in DA suggests better cell to cell adhesion and explains its lesser amount of invasiveness. The positive expression of laminin V & IV suggests an inductive effect of the epithelium over the fibrous stroma, which may result in a duplicated basal lamina. These findings were supported by the study of Lam et al., in which inductive effects were expressed in the form of deposits of an acellular eosinophilic matrix associated to epithelial islands (17).

Molecular studies done by Ng and Siar., found the expression of desmin & S-100 protein and also a strong positive reaction to collagen VI (ruling out scar tissue), which gave the impression of extracellular matrix (18).

TGF-β has an important role in epithelial-mesenchymal transition induction and extracellular matrix formation enhancement by stimulating fibroblasts. DA shows higher expression of TGF-β which results in induction of desmoplastic stroma. Vimentin, a type of intermediate filament, is found in mesenchymal cells. DA has high vimentin expression indicating collagen formation (19).

DA shows variable expression of S-100 and desmin, marked immunoreexpression of TGF-α, higher expression of p63, caspase-3 and Fas, decreased expression of CK19. The desmoplastic stroma shows a strong positive reaction for collagen type VI (20). Other molecular markers expressed in ameloblastoma, DA and AOT have been listed in the Tables 2 & 3. These markers help to modify therapeutic approach by targeting a particular gene and thereby help to improve the treatment with better prognosis.

The histopathological differential diagnosis for DA includes ameloblastic fibroma (AF), odontogenic fibroma (OF), and squamous odontogenic tumor (SOT) (Table 3).

Table 3

Molecular markers downregulat

Lesion	Markers	Suggestive of
Ameloblastoma	Syndecan 1, 32,33 WNT-related bone-forming genes of WDR5 and runt-related transcription factor 2 (RUNX2)	More invasiveness Impedes bone formation
DA	PCNA, Ki67	Low proliferative index of the tumor.
AOT	p53 and MDM2	Less aggressive behavior than SMA

AF shows interlacing scattered thin island of odontogenic epithelium with peripheral columnar cells and central stellate cells. These islands are scattered in primitive mesenchyme. OF is a non-infiltrating lesion composed of mature collagen fiber interspersed with plump fibroblasts and small nests or island of inactive odontogenic epithelium. SOT is composed of the round or broad based island of mature squamous epithelium with peripheral flat or cuboidal cells. The fibrous stroma consists of mature collagen fiber bundles without inductive effect. But DA shows dense collagen stroma that appears hyalinized and hypocellular compressing odontogenic epithelium into bizarre, irregular shaped islands (12-14).

SMA and DA have high recurrence rate therefore the management is controversial (18). Conservative surgical treatment such as enucleation and curettage resulted in recurrence (21). Thus, SMA requires radical surgical intervention. Recurrence is seen even after 5-10 years of surgery. Therefore thorough examination of surgical sites is needed for at least 10 years.

The reason for recurrence of DA may be:

- (1) Inconspicuous margin making the demarcation between lesion and normal bone difficult.
- (2) The more frequent occurrence in the maxilla which results in an early encroachment of the nearby structures.

DA lacks capsule, resulting in the infiltration of tumor cells into trabeculae of the cancellous bone. This results in the inconspicuous radiographic margins and leading to recurrence. Therefore, the recommended technique includes resection with safety margin of 1 cm of bone beyond the radiographic margin (12).

In the present case the mode of treatment done was hemi-maxillectomy (Figure 9). There was no recurrence and the patient is under regular follow up.

CONCLUSION

Desmoplastic ameloblastoma is a rare histological variant of ameloblastoma. It is known for its different biological behavior and histological architecture. Radiographic picture suggests its infiltrative nature especially in the anterior maxilla. The previous studies give an conflicting results regarding the recurrence following surgical intervention. The definitive diagnosis should be based on histopathological examination and a proper post-surgical follow up is mandatory.

DETAILS OF CONTRIBUTORS

All authors contributed to the conception of the work; EDE and AO to the acquisition of data, BWM to the analysis of data, CVEP to the interpretation of data for the work.

BWM and EDE drafted the manuscript; CVEP and AO revised it critically for important intellectual content. All authors approved the final version of the manuscript submitted for publication.

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ETHICAL APPROVAL

Ethical approval for the original data collection was granted by the South East Wales Local Research Ethics Committee

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