Hybrid Lesion of Ameloblastoma: A Perplexing Pathological Entity

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Abstract

Ameloblastoma is a benign epithelial odontogenic tumor. "Hybrid" lesion of ameloblastoma is a tumor variant in which histologically, areas of follicular or plexiform ameloblastoma coexist with characteristic areas of ameloblastoma exhibiting pronounced stromal desmoplasia. The purpose of this article is to present a case of "hybrid" lesion of desmoplastic ameloblastoma and conventional plexiform ameloblastoma, and to throw a light on various mysterious, controversial and perplexing aspects associated with this debatable lesion.

Key Words: Ameloblastoma, Desmoplastic, Hybrid lesion, Odontogenic tumors, Plexiform

Introduction

Ameloblastoma is a slowly growing, locally invasive, epithelial odontogenic tumor of the jaws with a high rate of recurrence if not removed adequately, but with virtually no tendency to metastasize. According to World Health Organization, three or four subtypes of ameloblastomas can presently be distinguished: classic Solid/Multicystic Ameloblastoma (SMA), Unicystic Ameloblastoma (UA), Peripheral Ameloblastoma (PA), Desmoplastic Amelobiastoma (DA), including so-called hybrid lesions of ameloblastoma (HLA) [1]. HLA is a tumor variant in which histologically, areas of follicular or plexiform ameloblastoma coexist with characteristic areas of ameloblastoma exhibiting pronounced stromal desmoplasia [2]. The biologic profile of this tumor is not fully understood because of its complexity and limited numbers of cases in the literature [3]. The paucity of reported cases is evident from perusal of scientific literature which revealed that less than 30 cases of HLA have been reported (*Table 1*) [4]. The purpose of this article is to present an uncommon case of "hybrid" lesion of DA and conventional plexiform ameloblastoma, to discuss the various controversial and perplexing aspects associated with this lesion, and thus to assist in better understanding of this mysterious lesion.

Case Report

50-year-old female patient presented with a complaint of a painful enlarging swelling, 8 x 7 cm in maximum dimension, of two and a half years duration in the left maxillary region. The swelling extended superoinferiorly from left infraorbital margin to the inferior border of the mandible and anteroposteriorly from left angle of the mouth to the anterior border of the ramus (*Figure 1a*). On palpation, there was significant buccal & lingual cortical expansion.

Orthopantomograph revealed a mixed radiolucent and radiopaque lesion extending from the midline to the region of left maxillary tuberosity; superiorly it extended beyond the left infraorbital margin (*Figure 2*). Intra-oral periapical radiographs revealed mixed radiolucent radiopaque picture in the affected region with resorption of the roots of the involved teeth (*Figure 3*). Paranasal sinus view showed a similar picture with haziness observed in the left maxillary sinus (*Figure 4*). Based on the clinical and radiological features, a provisional diagnosis was given as benign odontogenic tumor probably ameloblastoma. Fibro-osseous lesion was kept as the differential diagnosis based on the radiological picture. DA was reported based on the incisional biopsy. The patient underwent surgical excision of the mass under general anesthesia (*Figure 5*). Post surgical course was uneventful and the patient did not report of recurrence at one year follow-up (*Figure 1b*).

Macroscopically, the resected mass had a lobulated surface, was grayish-white in color; measured 7 × 5 × 4 cm^3, and was firm in consistency (*Figure 6*). The specimen was solid at its periphery but was cystic in the centre which was suggestive of degeneration in the centre of the tumor mass.

Microscopically, the lesion gave the picture of two histotypes of ameloblastoma: a pronounced desmoplastic pattern admixed with plexiform pattern (*Figure 7*). Desmoplatic pattern was observed in the form of odontogenic epithelium seen as strands simulating cord-like structures in a densely collagenized stroma. Peripheral tall columnar ameloblast-like cells demonstrating reversed nuclear polarity were inconspicuous about the epithelial islands; however, in some of the areas, well formed peripheral ameloblast-like cells were appreciated. Extensive stromal desmoplasia with a tendency to squeeze or compress the odontogenic islands was appreciated (*Figure 8*). The plexiform pattern was seen as long anastomosing cords of odontogenic epithelium bounded by columnar to cuboidal ameloblast-like cells (*Figure 9*). The supporting stroma exhibited tendency towards cystic degeneration. Also, evidence of myxoid change around the epithelial tumor islands could be appreciated. The margin of

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Table 1. *Clinico pathologic features of 29 compiled cases of hybrid lesion of ameloblastoma.*

Authors	Number of cases	Age (years)	Sex	Region	Radiographic features	Histopathological features
Waldron et al., 1987[5]	5	25-82	2-males, 3-females	4-Posterior mandible, 1-INA	INA*	Coexistence of desmoplatic and follicular ameloblastoma
Higuchi et al., 1991[6]	2	1st case: 58; 2nd case: 70	Both cases: male	1st case: Anterior to posterior mandible; 2nd case: posterior mandible	1st case: soap bubble and multicystic; 2nd case: multicystic	Coexistence of desmoplastic and conventional ameloblastoma
Philipsen et al., 1992[7]	1	55	Male	Anterior to posterior mandible	Multilocular radiolucency with floccular radiopacities	Desmoplastic ameloblastoma with follicular and plexiform ameloblastoma
Ashman et al., 1993[4]	1	53	Male	Anterior mandible	Mixed radiolucent and radiopaque lesion	Hybrid desmoplastic ameloblastoma
Takata et al, 1999[8]	1	48	Male	Anterior to posterior mandible	Honeycomb appearance in the anterior mandible and unicystic radiolucency in posterior mandible	Desmoplastic ameloblastoma with follicular ameloblastoma, squamous metaplasia and cystic degeneration
Wakoh et al, 2002[9]	1	35	Female	Mandibular canine-oremolar region	Mixed radiolucent and radiopaque lesion with an adjacent cystic radiolucent area	Follicular-type ameloblastoma with desmoplasia
Hirota et al, 2005[10]	1	17	Female	Maxillary canine to premolar area	Well defined radiolucent lesion	Follicular, plexiform, acanthomatous, and basal cell patterns of ameloblastoma with desmoplasia
dos Santos et al, 2006[2]	1	36	Male	Mandibular canine to molar region	Ill defined radiolucency	Desmoplastic and follicular ameloblastoma
Desai et al., 2006[11]	1	32	Male	Posterior mandible	Well defined unilocular radiolucency	Desmoplastic and follicular ameloblastoma
Sivapathasundaram et al, 2009[12]	2	1st case: 31; 2nd case: 40	1st case: female; 2nd case: male	1st case: anterior to posterior mandible; 2nd case: anterior to posterior maxilla	Both cases: Mixed RL/RO, unilocular	Both cases: desmoplastic and follicular ameloblastoma
Yazdi et al,2009[13]	1	48	Female	Anterior mandible	Mixed radiolucent and radiopaque lesion with ill defined borders	Desmoplastic and follicular ameloblastoma
Gade et al., 2010[14]	1	35	Female	Anterior maxilla	Radiolucnecy with radiopaque specks	Desmoplastic and follicular ameloblastoma
Gupta et al., 2011[15]	1	35	Female	Anterior mandible	Ill-defined hazy, radiolucent lesion with flecks of radio-opacity	Desmoplastic and follicular ameloblastoma
Vardhan et al., 2011[16]	1	29	Female	Anterior and posterior mandible	Well defined irregular radiolucency	Desmoplastic and conventional ameloblastoma
Lawal et al., 2011[17]	2	1st case: 50; 2nd case: 29	1st case: female; 2nd case: male	Both cases: anterior mandible	Both cases: multilocular radiolucency	Desmoplastic and conventional ameloblastoma
Acharya et al., 2011[18]	1	50	Male	Mandible	INA	Desmoplastic and unicystic ameloblastoma (different growth patterns)
Angadi et al., 2011[19]	1	64	Female	Anterior to posterior maxilla	Ill defined radiolucent lesion with flecks of radio-opacity	Desmoplastic and follicular ameloblastoma with squamous metaplasia
Mahadesh et al., 2011[20]	1	46	Male	Right mandibular molar region	Well defined multilocular radiolucent lesion	Unicystic ameloblastoma of luminal, intraluminal, and mural type. Mural proliferation revealed follicular, acanthomatous areas coexisting with desmoplastic areas
Bavle et al., 2013[21]	1	28	Female	Anterior mandible	Ground glass appearance with small areas of radiopacity	Stromal desmoplasia with osteoplasia along with classical follicular, acanthomatous and basaloid differentiation
Effiom et al., 2013[4]	1	50	Female	Anterior and posterior mandible	Mixed radiolucent and radiopaque	Keratinizing follicular ameloblastoma and desmoplastic ameloblastoma with osteoplasia
Rastogi et al., 2013[22]	1	34	Female	Anterior mandible	Mixed radiolucent and radiopaque	Concomitant desmoplastic and follicular variant of ameloblastoma
Present case	1	50	Female	Anterior to posterior maxilla	Mixed radiolucent and radiopaque lesion	Desmoplastic and plexiform ameloblastoma

*INA: Information not available

the lesion revealed the lesional component in close proximity to the bony trabeculae. Collagen fibers of the stroma were stained with Van Giesson stain demonstrating desmoplasia (*Figure 10*).

Discussion

Odontogenesis comprises initiation, morphogenesis, and cytodifferentiation, controlled by sequential and reciprocal epithelial-ectomesenchymal interactions. Odontogenic tumors are lesions derived from epithelial, ectomesenchymal and/or mesenchymal elements that still are, or have been, part of the tooth-forming apparatus [23,24]. DA is now recognized as a distinct clinicopathologic entity and not just a histologic variant of the SMA because of the atypical morphology of the epithelial component, the marked stromal desmoplasia, the unusual radiologic appearance, and the difference in anatomic location compared to other forms of ameloblastomas [1]. HLA is an unusual variant that was first described by Waldron and El-Mofty in 1987 [3,5]. Philipsen and coworkers suggest that it is a possible "transitional" form of DA, showing microscopic features of the desmoplastic variant together with areas typical of "classic" follicular or plexiform

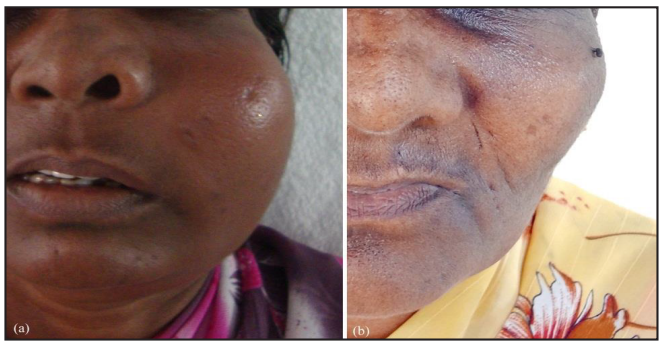

Figure 1. *(a) Extra-oral photograph showing the extent of the lesion, (b) One year follow-up photograph.*

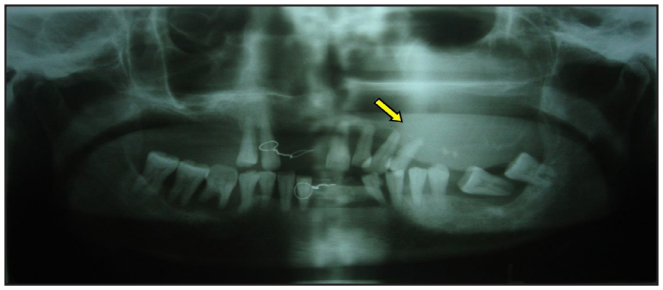

Figure 2. *Orthopantomograph showing the lesion involving the left maxilla and the left maxillary sinus.*

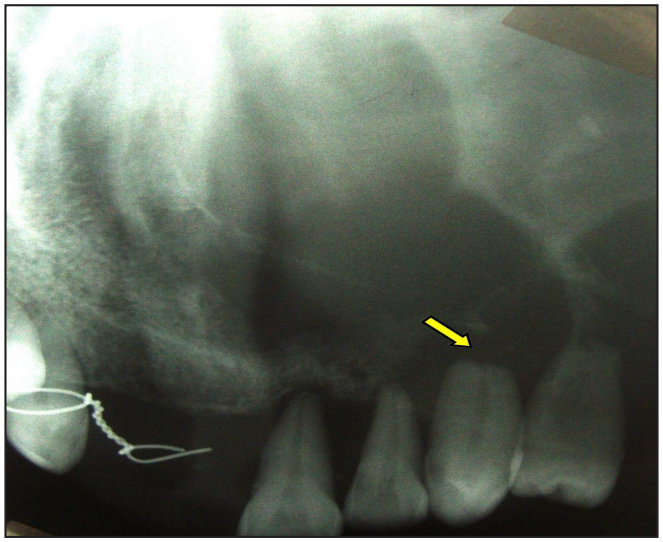

Figure 3. *Intra-oral periapical radiograph revealing the lesion with resorption of the roots of the involved teeth.*

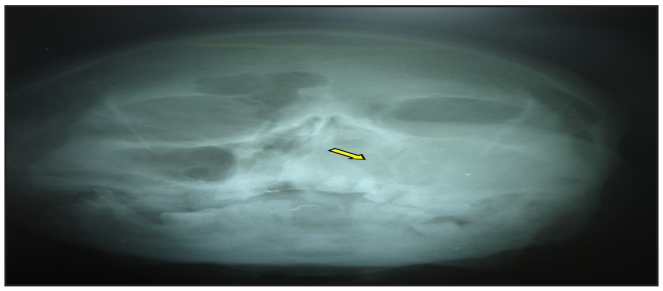

Figure 4. *Paranasal sinus view showng a mixed radiolucent and radiopaque picture with haziness.*

ameloblastoma [25]. The present case shows coexistence of DA and plexiform ameloblastoma as can be appreciated in *Figure 7***.** The insufficient number of published cases of "hybrid" ameloblastomas has not permitted establishment of any clinicopathologic correlations [26].

The present case of discussion is in agreement with the clinical and radiological features as in previous literature. Radiologically, the desmoplastic variant exhibits atypical and varied radiographic features such as: localized irregular multilocular radiolucency with indistinct borders, or a mixed radiopaque-radiolucent appearance with ill-defined

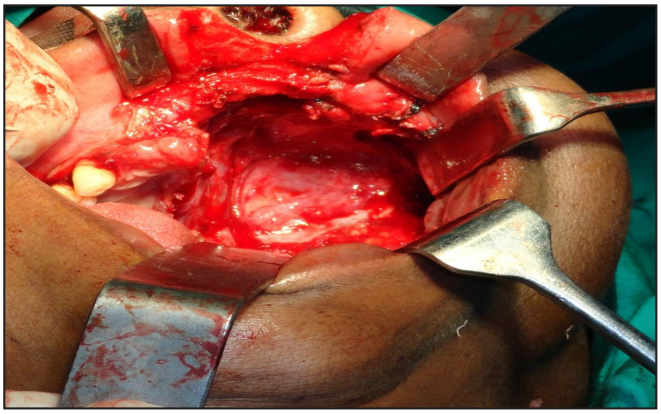

Figure 5. *Intra-operative photograph.*

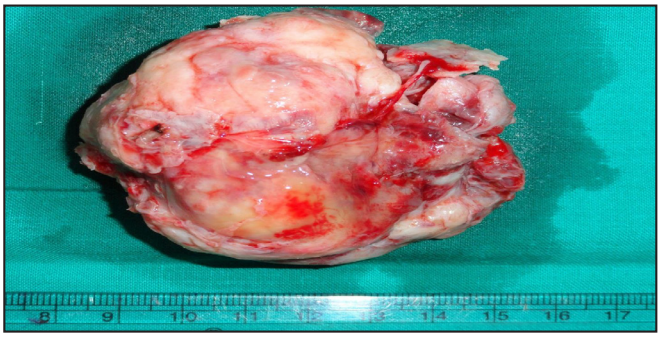

Figure 6. *Macroscopic picture of the resected specimen.*

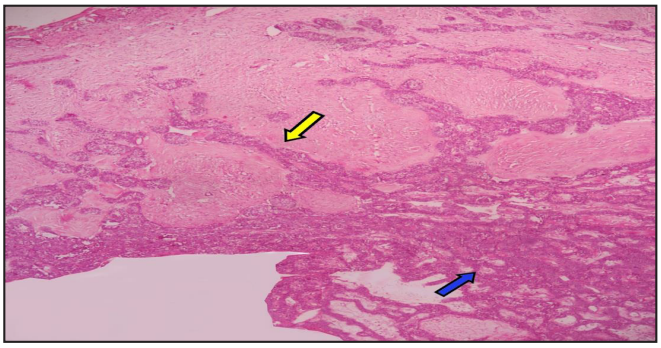

Figure 7. *Photomicrograph showing co-existence of desmoplastic ameloblastoma (yellow arrow) and plexiform ameloblastoma (blue arrow).*

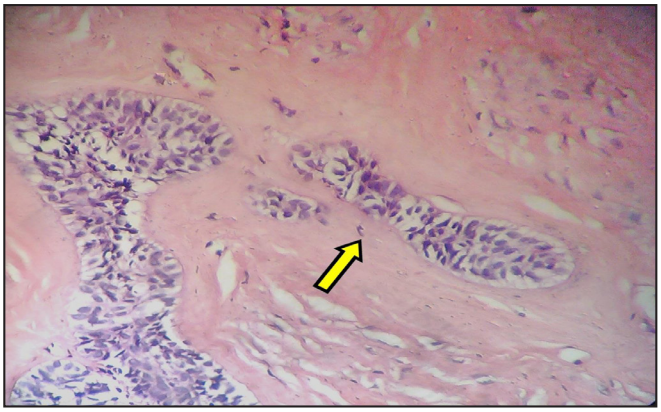

Figure 8. *Photomicrograph revealing extensive stromal desmoplasia with a tendency to squeeze the odontogenic islands (H & E, x40).*

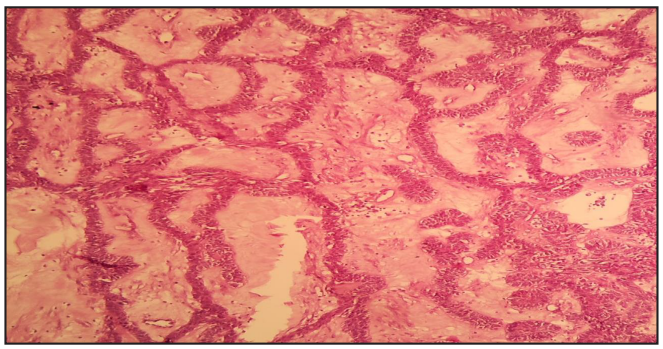

Figure 9. *Photomicrograph revealing plexiform pattern (H & E, x10).*

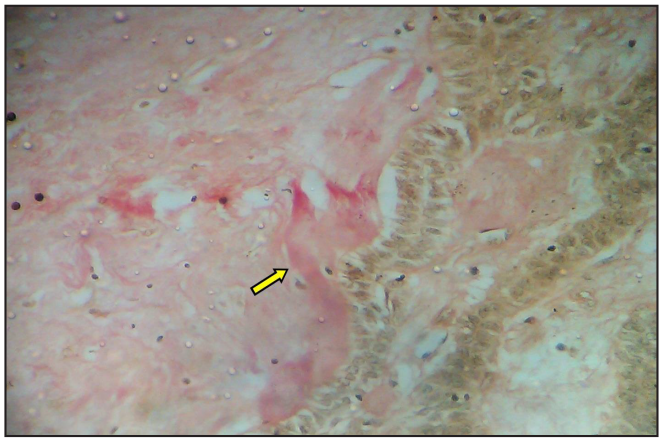

Figure 10. Photomicrograph showing collagen fibers of the stroma stained with van giesson stain demonstrating desmoplasia [Van Giesson, x40].

margins similar to fibro-osseous lesion, or a massive expansile osteolytic lesion with honeycomb, mottled or multilocular appearance [27]. In our case a mixed radiolucent and radiopaque was observed. Further, DA usually infiltrates into marrow spaces and surrounding non-neoplastic bone without a fibrous capsule. This infiltrative nature is thought to be responsible for the mixed radiolucent-radiopaque picture seen in DA [28]. Furthermore, the presence of osteoplastic bone can also present similarly [28], however no such osteoplasia was observed in our case. However, the margin exhibited lesional component in close approximation to the bony trabeculae.

The present case was reported in maxilla and it is to be emphasized that maxillary lesions are more insidious than mandibular tumors owing to the proximity of vital structures and the maxillary sinus. Also, the very thin cortical bone of the maxilla forms a weak barrier for the spread of tumors, and thus may be able to spread earlier [13].

Microscopically, the lesion consisted of small islands and cords of odontogenic epithelium in a densely collagenized stroma. Also seen was the plexiform pattern of ameloblastic proliferation. The histopathological characteristics described for the present case are in concordance with the diagnostic criteria established for a "hybrid lesion" of desmoplastic and conventional ameloblastomas according to Waldron and El-Mofty [2,5]. Futhermore, collagen fibers of the stroma stained intensely with Van Giesson stain demonstrating desmoplasia. Van Gieson stain is a simple stain which is used for selective demonstration of collagen fibers [29]. Thus, the intense staining for van gieson stain observed in our case is indicative of desmoplasia, which is basically production of an abundant collagen stroma [30].

The interpretation of simultaneous occurrence of DA and the plexiform variant in the “Hybrid” lesion is enigmatic. It constitutes a puzzling paradox since it is uncertain whether a part of primary DA transforms into conventional ameloblastoma, or whether desmoplastic change occurs secondarily in the stroma of a pre-existing SMA, or whether HLA is a kind of collision tumor [3,25].

Furthermore, the mechanism of desmoplasia in itself is baffling. It can be argued to be a maturation of SMA, as similar dense collagenization is seen during maturation of long standing tumors. This contention can be supported by the existence of hybrid tumors wherein the follicles are present in a desmoplastic background. Moreover, the location of the tumor can influence the maturity of the lesion and, hence, the tumors in anterior jaws may mature sooner than those in the posterior mandible [3,13]. Also, there may be a possible racial influence in the site predilection of ameloblastomas. It is also speculated that the majority of these ameloblastomas could turn out to desmoplastic variants if a careful histologic review is carried out. Furthermore, DA might not actually be a rare entity. Many hybrid lesions may have been misclassified, since the presence of typical ameloblastic islands in some areas could have warranted a diagnosis of SMA [12,13].

The extracellular matrix has an important role in the behavior of neoplastic cells and immunohistochemical studies on the expression of tenascin and fibronectin proteins in hybrid lesions have showed positive staining around the conventional follicles rather than the desmoplastic areas. This indicates the greater aggressive potential of conventional ameloblastoma as compared to DA as tenascin has been observed in unstable environments like neoplasia [28].

Besides, various immunohistochemical studies have reported DA tumor cells as showing high expression of caspase-3, p63 and Fas, decreased expression of cytokeratin 19 and variable expression of S-100 protein and desmin. Type IV collagen has been reported to show intense staining around tumor islands in DA indicating active synthesis of extracellular matrix proteins and that the stroma is not scar tissue. Moreover, marked expression of transforming growth factor-β has been demonstrated connoting that it may also play a part in the desmoplastic process [12,13,28].

With limited understanding of its biologic behavior and prognosis, the proper treatment strategies for HLA are not entirely defined so far [31]. Based on the present knowledge, WHO recommends to apply the same treatment modality as for SMA [1].

Conclusion

Melrose wrote that the designation hybrid tumor serves no real purpose and, if taken literally, might overstate the significance of finding a DA in combination with islands or strands of a SMA. Thus many more cases than the few published so far, with detailed clinical and radiologic data and corresponding histopathologic analysis are needed to clarify the biologic behavior of this perplexing variant [25,32].

References

1. Gardner DG, Heikinheimo K, Shear M, Philipsen HP, Coleman H, Barnes L, Eveson JW, Reichart P, Sidransky D (Editors). Ameloblastomas. Pathology and genetics of head and neck tumors. Lyon, France: *IARC Press*. 2005: 296-300.

2. Dos Santos JN, De Souza VF, Azevêdo RA, Sarmento VA, Souza LB. "Hybrid" lesion of desmoplastic and conventional ameloblastoma: immunohistochemical aspects. *Brazilian Journal of Otorhinolaryngology*. 2006; **72**: 709-713.

3. Vardhan BGH , Ingle E, Dornadula K, Gopal KS. Hybrid lesion of desmoplastic and conventional ameloblastoma – A case report. *Journal of International Oral Health*. 2011; **3**: 43-48.

4. Effiom OA, James O, Akeju OT, Salami AS, Odukoya O. Hybrid ameloblastoma in a nigerian: Report of a case and review of literature. *Open Journal of Stomatology*. 2013; **3**: 347-353.

5. Waldron CA, EL-Mofty SK. A histopathologic study of 116 ameloblastomas with special reference to the desmoplastic variant. *Oral Surgery Oral Medicine Oral Pathology*. 1987; **63**: 441-451.

6. Higuchi Y, Nakamura N, Ohishi M, Tashiro H. Unusual ameloblastoma with extensive stromal desmoplasia. *Journal of Craniomaxillofacial Surgery*. 1991; **19**: 323-327.

7. Philipsen HP, Ormiston IW, Reichart PA. The desmo- and osteoplastic ameloblastoma. histologic variant or clinicopathologic entity? Case reports. *International Journal of Oral Maxillofacial Surgery*. 1992; **2**: 68-72.

8. Takata, T, Miyauchi M, Ogawa I, Zhao M, Kudo Y, Sato S, Takekoshi T, Nikai H, Tanimoto K. So called "hybrid" lesion of desmoplastic and conventional ameloblastoma: Report of a case and review of literature. *Pathology International*. 1999; **49**: 1014-1018.

9. Wakoh M, Harada T, Inoue T. Follicular/desmoplastic hybrid ameloblastoma with radiographic features of concomitant fibro-osseous and solitary cystic lesions. *Oral Surgery Oral Medicine Oral Pathology*. 2002; **94**: 774-780.

10. Hirota M, Aoki S, Kawabe R, Fujita K. Desmoplastic ameloblastoma featuring basal cell ameloblastoma: A case report. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics*. 2005; **99**: 160-164.

11. Desai H, Sood R, Shah R, Cawda J, Pandya H. Desmoplastic ameloblastoma: Report of a unique case and review of literature. *Indian Journal of Dental Research*. 2006; **17**: 45-49.

12. Sivapathasundharam B, Einstein A, Syed RI. Desmoplastic ameloblastoma in Indians: Report of five cases and review of literature. *Indian Journal of Dental Research*. 2007; **18**: 218-221.

13. Yazdi I, Seyedmajidi M, Foroughi R. Desmoplastic ameloblastoma (a hybrid variant): Report of a case and review of the literature. *Archives of Iranian Medicine*. 2009; **12**: 304-308.

14. Gade L, Patankar S, Khot K, Korde S, Alex S. Desmoplastic ameloblastoma of maxilla- A case report. *Journal of Clinical and Experimental Dentistry.* 2010; **2**: 204-206.

15. Gupta A, Jindal C. Hybrid ameloblastoma: Report of a rare case and review of literature. *International Journal of Oral Maxillofacial Pathology.* 2011; **2**: 68-72.

16. Vardhan BGH Ingle E, Dornadula K, Gopal KS. Hybrid lesion of desmoplastic and conventional Ameloblastoma – A case report. *Journal of International Oral Health*. 2011; **3**: 43-47.

17. Lawal AO, Adisa AO, Olusanya AA, Adeyemi BF. "Hybrid" ameloblastoma: A report of two cases. *African Journal of Medicine and Medical Sciences*. 2011; **40**: 413-415.

18. Acharya S, Koneru A, Channappa NK, Krishnapillai R. Diverse growth patterns in an intraosseous ameloblastoma: A case report. *Chinese Journal of Dental Research*. 2011; **14**: 67-70.

19. Angadi PV, Kale A, Hallikerimath S, Kotrashetti V, Mane D, Bhatt P, Shukla D. 'Hybrid' desmoplastic ameloblastoma: An unusual case report with immunohistochemical investigation for TGF-β and review of literature. *East African Medical Journal*. 2011; **16**: 9-17.

20. Mahadesh J, Rayapati DK, Maligi PM, Ramachandra P. Unicystic ameloblastoma with diverse mural proliferation - A hybrid lesion. *Imaging Science in Dentistry*. 2011; **41**: 29-33.

21. Bavle RM, Thambiah LJ, Paremala K, Sudhakara M, Srinath N. Desmoplasia and osteoplasia in a hybrid ameloblastoma: A case report. *International Journal of Oral Maxillofacial Pathology*. 2013; **4**: 42-45.

22. Rastogi R, Jain H, Mohan C, Rastogi V, Rastogi K. Hybrid ameloblastoma - An unusual combination of desmoplastic and conventional ameloblastoma. *Journal of International Medical Sciences Academy*. 2010; **23**: 237-238.

23. Reichart PA, Philipsen HP, Reichart PA, Philipsen HP (Editors). Early normal Odontogenesis with special reference to the development and fate of the dental laminae. Odontogenic tumors and allied lesions. London: *Quintessence Publishing Corporation Limited*. 2004: pp.25-32.

24. Philipsen HP, Reichart P, Slootweg PJ, Slater LJ, Barnes L, Eveson JW, Reichart P, Sidransky D (Editors). Neoplasms and tumor-like lesions arising from the odontogenic apparatus and maxillofacial skeleton: Introduction. Pathology and genetics of head and neck tumors. Lyon, France: IARC Press; 2005.pp.285-286.

25. Reichart PA, Philipsen HP. Desmoplastic ameloblastoma. In: Reichart PA, Philipsen HP, editors. Odontogenic tumors and allied lesions. London: *Quintessence Publishing Corporation Limited*. 2004: pp.68-76.

26. Brooks JK, Ribera MJ, Ross DS. Diminutive, interradicular "hybrid" desmoplastic/acanthomatous ameloblastoma. *Quintessence International*. 2010; **41**: 209-212.

27. Laxmana AR, Gogineni SB, Thomas PS, Shetty SR. Desmoplastic ameloblastoma-A report of two clinical cases. *Brazilian Journal of Oral Sciences.* 2010; **9**: 137-141.

28. Savithri V, Janardhanan M, Suresh R, Kumar RBV. Desmoplastic ameloblastoma with osteoplasia: Review of literature with a case report. *Journal of Oral Maxillofacial Pathology*. 2013; 17: 298-301.

29. Joseph AP, Rajendran R. Submucosa precedes lamina propria in initiating fibrosis in oral submucous fibrosis - Evidence based on collagen histochemistry. *Journal of Oral Maxillofacial Pathology*. 2010; **1:** 1-9.

30. Kumar V, Abbas AK, Fausto N, Kumar V, Abbas AK, Fausto N (Editors). Neoplasia. Pathologic basis of disease (7th edn.) Philadelphia: Saunders; 2004: pp.269-342.

31. Sheikh S, Pallagatti S, Singla I, Kalucha A. Desmoplastic Ameloblastoma: A Case Report. *Journal of Dental Research, Dental Clinics, Dental Prospects*. 2011; **5**: 27-32.

32. Melrose RJ. Desmoplastic ameloblastoma. *Pathology Case Reviews*. 1999; **4**: 21-27.