Original Article

Amelogenin in odontogenic cysts and tumors: An immunohistochemical study

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ABSTRACT

Background: Amelogenins are the major enamel proteins that play a major role in the biomineralization and structural organization of enamel. Aberrations of enamel-related proteins are thought to be involved in oncogenesis of odontogenic epithelium. The expression of amelogenin is possibly an indicator of differentiation of epithelial cells in the odontogenic lesions. **Aims and Objectives:** The present study aimed to observe the expression of amelogenin immunohistochemically in various odontogenic lesions. **Materials and Methods:** Paraffin sections of 40 odontogenic lesions were stained immunohistochemically with amelogenin antibodies. The positivity, pattern and intensity of expression of the amelogenin antibody were assessed, graded and statistically compared between groups of odontogenic cysts and tumors. **Results:** Almost all the odontogenic lesions expressed amelogenin in the epithelial component with the exception of an ameloblastic carcinoma. Differing grades of intensity and pattern were seen between the cysts and tumors. Intensity of expression was uniformly prominent in all odontogenic lesions with hard tissue formation. Statistical analysis however did not indicate significant differences between the two groups. **Conclusion:** The expression of amelogenin antibody is ubiquitous in odontogenic tissues and can be used as a definitive marker for identification of odontogenic epithelium.

Key words: Amelogenin, differentiation, immunohistochemistry, odontogenic cysts, odontogenic tumors

Introduction

Odontogenic lesions are a group of heterogenous lesions derived from the remnants of the tooth-forming apparatus. They range from non-neoplastic tissue proliferations to malignant neoplasms and account for between 1.0% and 30.0% of oral lesions.[1,2]

Epithelial–mesenchymal interactions between ameloblasts and odontoblasts play a pre-eminent role during odontogenesis and communication between these two is reciprocal through constructive signals.[3]

The ameloblasts produce enamel matrix that includes major protein components: Amelogenins and non-amelogenins (enamelins, ameloblastins and tuftelins).[4]

Amelogenins are the major enamel proteins that comprise 90% of extracellular matrix and have a major role in the biomineralization and structural organization of enamel. These vital molecules have been consistently demonstrated within the enamel matrix and the cytoplasm of the cells of the reduced enamel epithelium, stratum intermedium and stellate reticulum of the enamel organ.[5]

Most odontogenic tumors contain variable amounts of epithelium and findings suggest that aberrations of

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enamel-related proteins are involved in oncogenesis of odontogenic epithelium.[6,7]

The expression of amelogenin is possibly an indicator of differentiation of epithelial cells in the odontogenic lesions. The detection of amelogenin expression may thus help in the understanding of not only the pathogenesis of the lesions, but also play a part in the prediction of the histological behavior and by extension the clinical nature of the lesion.

Methods

The present study aimed to observe the expression of amelogenin immunohistochemically in rat tooth germ, odontogenic epithelium of follicular tissue, odontogenic tumors, odontogenic cysts and qualitatively evaluate the amelogenin expression in terms of sensitivity (graded as mild, moderate and intense) and specificity (graded as focal, linear or diffuse). The results were correlated statistically, between the type of expression of amelogenin in the various groups of odontogenic lesions.

Sample collection

Paraffin embedded blocks of 40 odontogenic lesions were collected from archival files. Approval from the institutional board on ethics in research was obtained before the study. Odontogenic tumors included in the study were solid/multicystic ameloblastomas (n = 7), unicystic ameloblastoma (n = 1), desmoplastic ameloblastoma (DA) (n = 2), squamous odontogenic tumor (SOT) (n = 1), adenomatoid odontogenic tumors (AOT) (n = 5), keratocystic odontogenic tumor (KCOT) (n = 6), odontomas (n = 2), calcifying cystic odontogenic tumor (CCOT) (n = 1) and ameloblastic carcinoma (n = 1). Odontogenic cysts included dentigerous cysts (n = 4) and radicular cysts (n = 10). A 4 days Wistar rat tooth germ section was used as control for odontogenic epithelium. Paraffin sections of formalin fixed tissues were used for both histological and immunohistochemical evaluation. Hematoxylin and eosin stained sections of 5 µ were used for routine histological examination. For immunohistochemical examination, 3-4 µ sections were made and loaded on positively charged slides (3-aminopropyl-tri-ethoxy-silane (Sigma Aldrich, USA).

Immunohistochemistry (IHC)

The sections were deparaffinized, washed in deionized water and subjected to antigen retrieval by pressure cooker method. Nearly 3% hydrogen peroxide was used to block endogenous peroxidase. After pre-treatment, sections were incubated with primary antibody rabbit polyclonal antibody raised against AMELX/AMELY, (Abnova, Taiwan), in a humid chamber at 4°C overnight with a dilution of 1:200. The primary antibody was diluted in antibody diluent with background reducing components (S3022, Dako, Denmark). The standard streptavidin-biotin-peroxidase complex method was performed to bind the primary antibodies (BioGenex Life Sciences Ltd., CA, USA). The reaction products were visualized by treating with diaminobenzidine solution diluted according to the manufacturer's instructions. For control studies of the antibodies, the serial sections were treated with all the mentioned reagents but omitting the primary antibody and were confirmed to be unstained.

Results

Table 1 presents a summation of the demographic data of the lesions including the positivity, pattern and intensity of their staining to amelogenin.

Tooth germ

The 4 days old Wistar rat tooth germ revealed linear expression of antibody. The secretory ameloblasts and odontoblasts showed moderately intense staining. Stellate reticulum presented less intense expression compared to ameloblasts whereas stratum intermedium was intensely positive at this stage [Figure 1].

Dental follicle (n = 2)

The follicular tissue was positive for anti-amelogenin in the epithelial component representing the odontogenic tissue. This focal expression pattern was diffuse with moderate intensity limited only to the epithelial component.

Table 1: Demographic data of cases and reaction to amelogenin antibody staining

Lesion	Number of cases (n)	Age range/sex	Site	Positivity
Ameloblastoma	10	29-55 years	Mandible = 5	All + ve
Unicystic	1	2 male/3 female		
Acanthomatous	4			
Plexiform/ follicular	3			
Desmoplastic	2			
SOT	1	58/male	Mandible	+ ve
CCOT	1	35/female	Mandible	+ ve
AOT	5	16-30 years 2 male/3 female	Maxilla = 5	All + ve
Odontoma	2	12-17 years 2 male	Maxilla = 2	All + ve
OKC/KCOT	6	17-60 years 3 male/3 female	Mandible = 5 Maxilla = 1	All + ve
Radicular cysts	10	18-65 years 4 male/6 female	Mandible = 4 Maxilla = 6	All + ve
Dentigerous cysts	4	16-24 years 2 male/2 female	Mandible = 4	All + ve
Ameloblastic carcinoma	1	70/male	Mandible	– ve

SOT: Squamous odontogenic tumor, CCOT: Calcifying cystic odontogenic tumor, AOT: Adenomatoid odontogenic tumor, KCOT: Keratocystic odontogenic tumor, OKC: Odontogenic keratocyst

Dentigerous cysts (*n* = 4)
Of the four cases studied, three presented diffuse and intense positive results, whereas one was positive with moderate intensity [Figure 2].

Radicular cyst (*n* = 10)
All ten cases of radicular cyst expressed diffuse and mild to moderate expression of amelogenin in the epithelium [Figure 3].

Plexiform ameloblastoma (*n* = 4)
Three cases showed diffuse, moderately positive in ameloblast like cells than stellate reticulum like cells. Other one presented in diffuse fashion but with more positivity in stellate reticulum than ameloblasts like cells [Figure 4].

Acanthomatous ameloblastomas (*n* = 4)
Of the four cases studied, three cases presented diffuse, moderately intense positivity of ameloblast like cells compared with stellate reticulum like cells. The other expressed minimal positivity in tumor follicles.

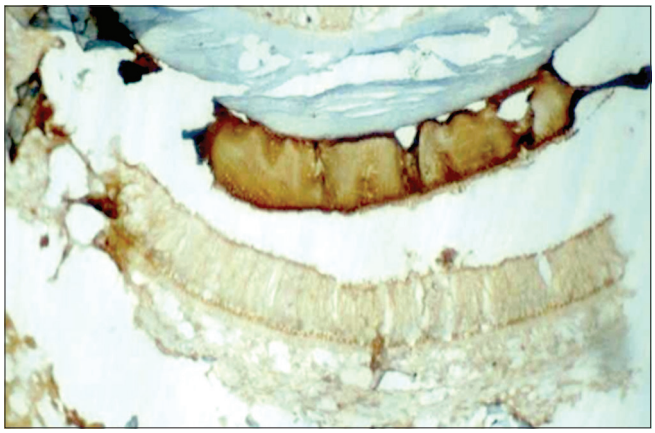

Figure 1: Tooth germ - used for positive control (4 days old Wistar rat). Note the linear intense positivity of amelogenin in the inner enamel epithelium layer (DAB, ×10)

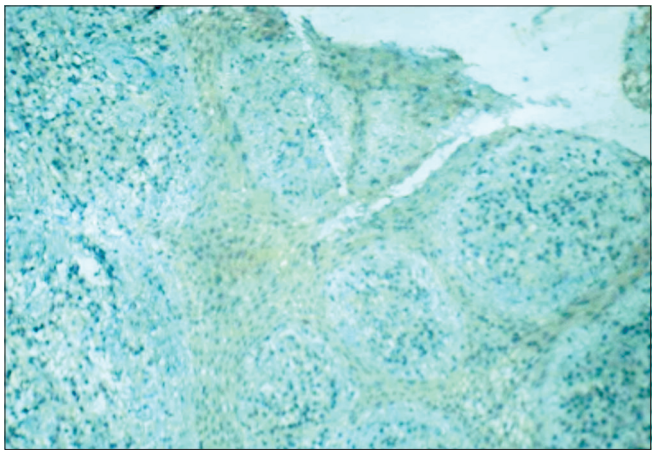

Figure 3: Radicular cyst - immunohistochemical staining with amelogenin showing a mild intensity with diffuse pattern (DAB, ×10)

Squamous metaplastic areas showed moderately positive expression [Figure 5].

DAs (*n* = 2)
One case showed diffuse moderately intense expression in the tumor islands whereas the other was less diffuse with moderately intense positivity [Figure 6].

Unicystic ameloblastomas (*n* = 1)
Linear intense expression of amelogenin was seen in the basal layer (ameloblast like cells), whereas moderately intense positivity was shown by stellate reticulum like cells.

AOT (*n* = 5)
Of five samples, two cases showed intense positivity in calcified masses in focal areas throughout the epithelium. Out of these two cases, one case showed mild intensity in the cystic epithelium. Rest of the epithelium showed very faint positivity. It was noted that the epithelial cells adjacent to the calcified masses expressed intensely positivity. Two cases showed faint positivity in the epithelium with intense positivity in calcified areas. One case expressed focal faint positivity in epithelial components but moderately intense reaction for calcified masses. The expression

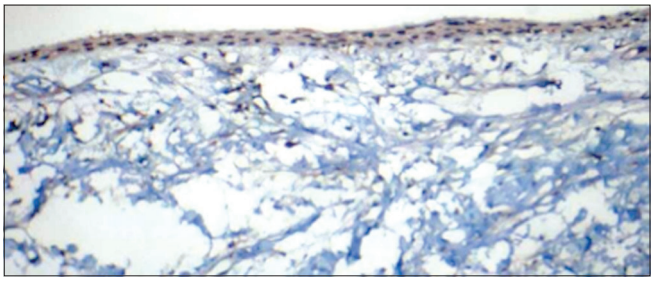

Figure 2: Dentigerous cyst - amelogenin showing an intense well defined linear pattern (DAB, ×10)

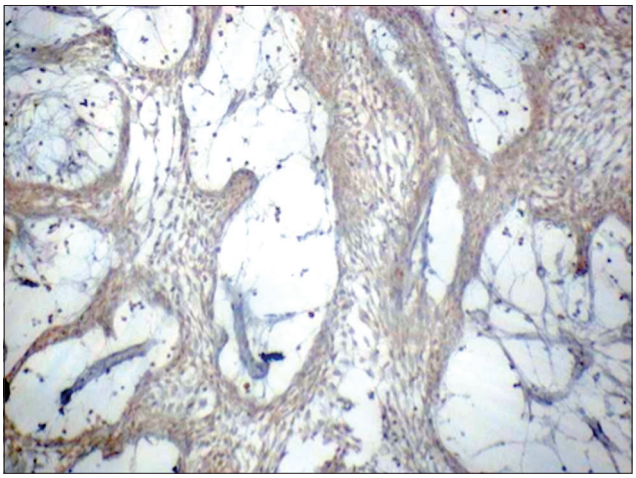

Figure 4: Plexiform ameloblastoma - immunohistochemical staining with amelogenin showing a diffuse pattern. Note intense staining of basilar layers and mild staining of stellate reticulum-like cells (DAB, ×10)

of focal positivity in the calcified globules was a predominant finding in this group [Figure 7].

SOT (*n* = 1)
Single case of SOT showed diffuse and intense expression of the molecule in epithelial islands [Figure 8].

Odontomas (*n* = 2)
Diffuse, moderate to intense expression was noted in the globules of calcified areas of odontomas [Figure 9].

KCOT/odontogenic keratocyst (*n* = 6)
Diffuse, moderately intense staining of amelogenin was seen throughout the epithelium including the keratinized layers in four of the six samples studied. The other two showed moderate and patchy staining [Figure 10].

CCOT (*n* = 1)
Diffuse staining, with intense expression especially in the basal layers of the epithelium and the ghost cell areas was seen.

Ameloblastic carcinoma (*n* = 1)
Anti-amelogenin antibody was not expressed in the solitary case of ameloblastic carcinoma.

Statistical analysis
The results were computed and subjected to statistical analysis using Mann-Whitney test and Chi-square test. Table 2 lists the statistical comparison of the results using the Chi-square test. The expression was found to be statistically not significant between the groups of odontogenic cysts and odontogenic tumors as both groups expressed enough positivity between the samples to the antibody.

Discussion

Odontogenic lesions arising from the epithelium of the odontogenic apparatus or from its derivatives or remnants entrapped within the bone or the peripheral gingival tissues exhibit considerable histological variation.[8] Amelogenin isolated by Termine *et al*.[9] in 1980 is an enamel matrix protein produced by secretory ameloblasts, and plays a major role in the organization and mineralization of developing enamel. This molecule exhibits an unusual amino acid composition, and a high degree of homology in the amelogenin amino acid sequence has been established among species.[10]

The intense positivity of the tooth germ ameloblasts and variable positivity seen in the other components especially the odontoblasts in our case was consistent with previously reported studies.[11]

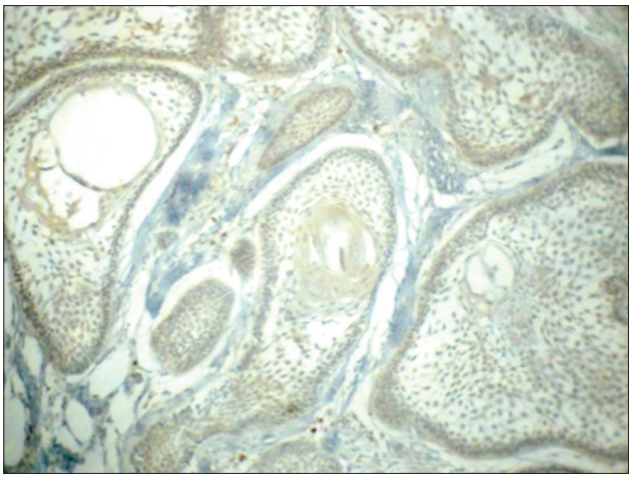

Figure 5: Acanthomatous ameloblastoma. Immunohistochemical staining with amelogenin showing a diffuse pattern (DAB, x10)

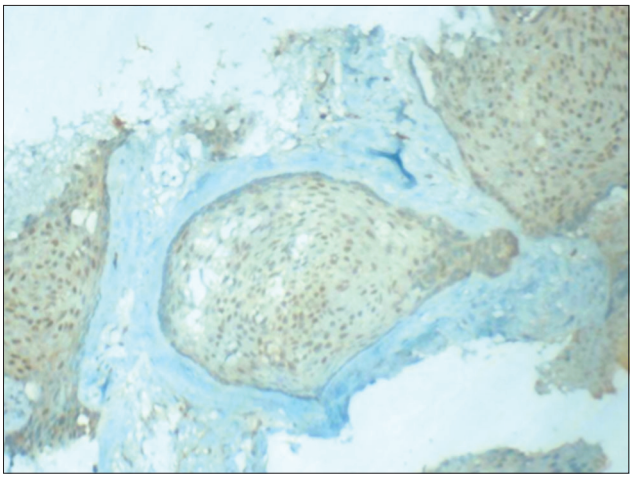

Figure 6: Desmoplastic ameloblastoma - immunohistochemical staining with amelogenin showing a diffuse pattern. Note specific staining of epithelial islands in the desmoplastic stroma (DAB, ×10)

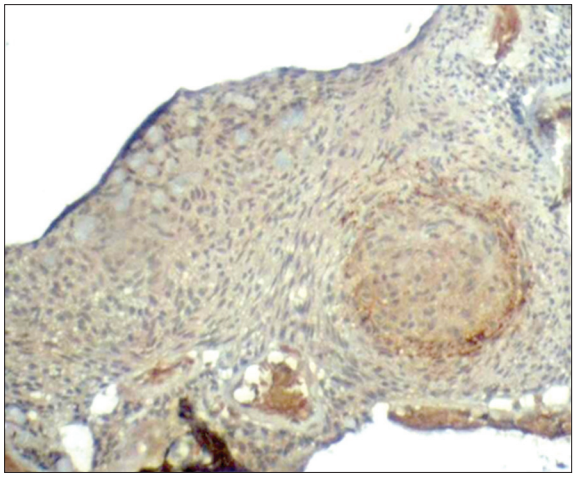

Figure 7: Adenomatoid odontogenic tumor - immunohistochemical staining with amelogenin showing a focal pattern in the whorled epithelial cells and of globular areas of calcification (DAB, ×10)

The follicular tissue was positive for the molecule in areas where odontogenic epithelium was located.

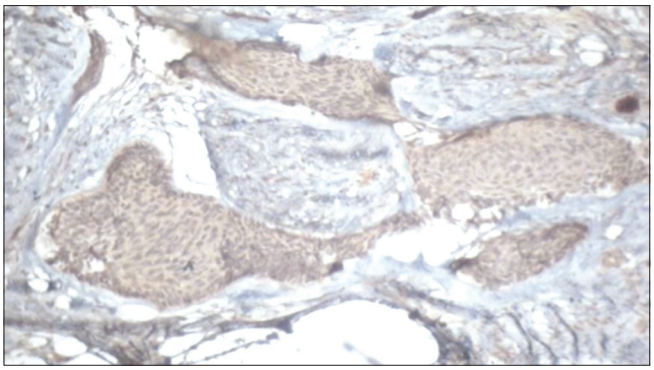

Figure 8: Squamous odontogenic tumor - immunohistochemical staining with amelogenin showing a diffuse pattern (DAB, ×10)

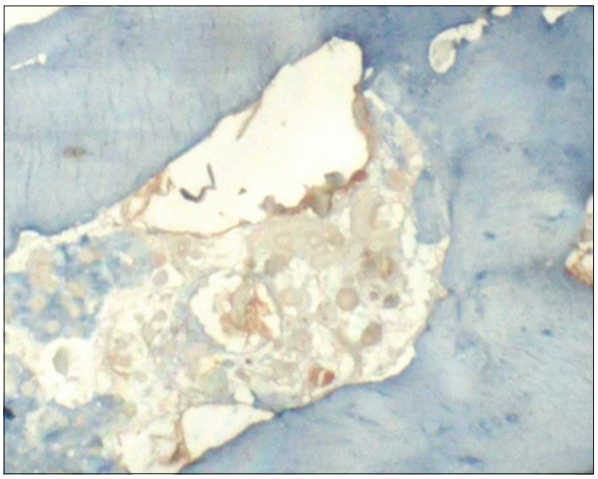

Figure 9: Odontome - immunohistochemical staining with amelogenin showing a diffuse patchy pattern only in the tissue enclosed by hard tissue (DAB, ×10)

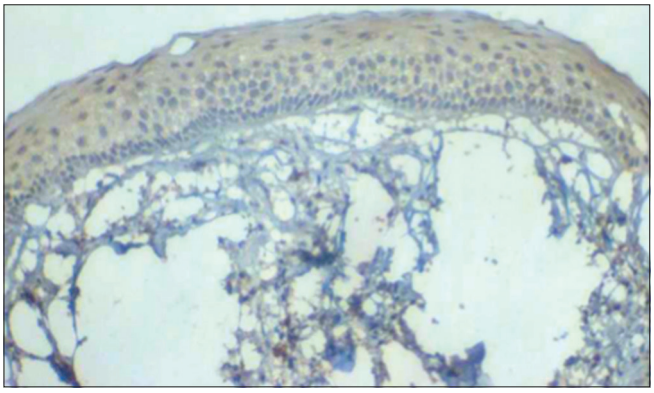

Figure 10: Odontogenic keratocyst/keratocystic odontogenic tumor - diffuse staining of epithelium including keratinized layers (DAB ×10)

This was an interesting observation especially since identification of the epithelial islands in follicular tissue was difficult in routine hematoxylin and eosin sections. This may be due to the resemblance of this tissue with the components of the lamina propria especially when there is inflammation. In such cases, the amelogenin was expressed quite focally making the epithelial islands visible. Literature reviews of amelogenin antibody in odontogenic tissues have not been reported on dental follicular tissue.

Retention of the potential for expression of amelogenin in epithelial islands of follicular tissue is proof of the fact that even senescent epithelial cells, post differentiation, possess the antigen. This would be important in considering this antibody as a marker for odontogenic epithelium.

The present study demonstrated that all the ameloblastomas reacted positively to amelogenin in the peripheral ameloblast-like cells and stellate reticulum like cells. The expression of this molecule in unicystic ameloblastoma was an interesting observation, and to the best of our knowledge has been unreported in literature. This expression was quite intense compared with the other ameloblastomas (e.g. plexiform ameloblastoma). This might explain the mature state of ameloblastoma like cells with high differentiation in unicystic ameloblastoma. This can be correlated with the less aggressive clinical behavior of unicystic ameloblastoma.

Acanthomatous ameloblastoma showed positivity in the peripheral cells, stellate reticulum like cells and also in squamous metaplastic areas. This was in contrast with a previous study.[10] This might be due to the sensitivity of the antibody used in our study and racial differences in tumors. The positive reaction for squamous metaplastic areas may suggest the retention of the antigen in the tissues in spite of further differentiation of the central cells of follicles toward maturity.

The positive expression in plexiform ameloblastomas was also in accordance with a previous study.[10] We suggest that this moderate expression in these lesions may explain the differentiation of ameloblast like cells, but the differentiation is not that of the fully differentiated ameloblasts which express intense amelogenin positive reaction as observed in our rat tooth germ.

The diffuse expression in DAs in epithelial islands was in accordance with previous studies.[10] This might explain the poor odontogenic differentiation of epithelial cells. Yet the positive expression can also be interpreted as the epithelial islands retaining potential of odontogenic differentiation thereby possibly supporting their origin from tooth bearing tissues.

In all the ameloblastomas, the positive reaction suggests that the differentiation of the ameloblast like cell toward the tooth forming stage. But the poor expression or absence of amelogenin, in many cases, in the stellate reticulum and stratum intermedium-like cells, may explain why there is no hard tissue formation in these lesions. We suggest that the role of amelogenin varies at different stages of

development of a lesion in accordance with the functional change, modulated by environment and genetics.

SOT showed results confined to the epithelial islands with no expression in other parts of the lesional tissue. Previous studies by Mori *et al*.[12] were supportive of this observation.

AOT tissues expressed amelogenin abundantly. While there was diffuse staining in the epithelial and periductal areas, islands of calcification and surrounding epithelial tissue stained focal and intense. The results were in agreement with other studies.[11,13] It has been suggested by other workers that the calcified masses adjacent to intensely expressed epithelial cells would be strong evidence for the diagnosis of an odontogenic tumor.[13] This also explains the advanced differentiation of the lesion whose recurrence is exceptionally rare according to the literature.[14-16] It is to be noted that AOT is one of the unique odontogenic lesions that expresses the whole gamut of differentiation from uncalcified epithelial tissue to calcified material associated with epithelial islands. The expression of amelogenin in all the three architectural patterns (solid, ductal and calcified) of the lesion was thus diagnostically convincing.

Odontomas were intensely positive for calcified areas. This included mild positivity of the epithelial tissues associated with the calcified masses. Consistent and similar findings have been reported by previous studies.[11,12] We suggest that the enamel matrix is positive for the amelogenin and hence the odontoma which is a highly differentiated lesion expresses the molecule in the same manner in their calcified masses.

CCOT expressed in the cystic epithelium and ghost like cells with varying intensity. The expression of amelogenin in the ghost cells would certainly seem to support an odontogenic origin for these structures. Though previous studies[11,12] have largely concurred with our findings conclusive evidence of the origin and occurrence of these structures which form diagnostic features of the cyst may need a larger sample and more studies.

Interestingly, the immunoreactivity of amelogenin in dentigerous cysts, radicular cysts and KCOT was intense. Surprisingly English language literature revealed no study done using this antibody in odontogenic cysts and KCOT. While the pattern of antibody expression was linear in the epithelial linings of the dentigerous and the KCOT, it was largely diffuse and located to the epithelial component in radicular cysts. The vascular channels of the inflammatory cyst showed background staining. This is plausible due to the fact that the antigen expressivity and retention is based on tissue architecture, development and differentiation rather than clinical and behavioral patterns.

On comparing the odontogenic tumors and odontogenic cysts for amelogenin intensity the *P* value was not statistically significant. This may be due to the fact that the origin of both cysts and tumors being odontogenic epithelial residues, expression of amelogenin was seen in varying intensities in all cases and no obvious differentiation was noticed. Whether the intensity and pattern of expression had a variance in the two groups to be statistically discernible would probably require a larger sample survey [Table 2].

When odontogenic lesions that expressed hard tissue components were compared with lesions without for amelogenin the results were found to be statistically not significant [Table 3]. The interesting observations in this comparison was the predominant increase in expression of intense staining (4/6 = 66.66%) in lesions that had hard tissue formation. The non-significant statistics may be due to two reasons. One, the number of lesions sampled were fewer and two, the generalized positivity of expression of amelogenin in all odontogenic lesions probably precluded a precise delineation of those cases with hard tissue which showed an intense expression.

This supports the observation that amelogenin is expressed quantitatively more in lesions with the

Table 2: Statistical comparison of amelogenin intensity in odontogenic tumors and cysts using Chi-square test

Lesions	+	Percentage	+ +	Percentage	+ + +	Percentage	Totals	Percentage
Odontogenic cysts	0	0.00	9	64.29	5	35.71	14	35.00
Odontogenic tumors	4	15.38	13	50.00	9	34.62	26	65.00
Total	4	10.00	22	55.00	14	35.00	40	100.00

χ^2=2.7091, df=2, *P*=0.2581

Table 3: Comparison of odontogenic lesions with or without hard tissue formation with respect to amelogenin intensity

Intensity	With hard tissue	Percentage	Without hard tissue	Percentage	Total	Percentage
Mild positivity	0	0.00	3	13.04	3	10.34
Moderate positivity	2	33.33	13	56.52	15	51.72
Intense positivity	4	66.67	7	30.43	11	37.93
Total	6	100.00	23	100.00	29	100.00

χ^2=2.9240, df=2, *P*=0.2317. Mann-Whitney U-test: *Z*=−1.5074, *P*=0.1317

potential for hard tissue formation like AOTs than in the more common odontogenic lesions which normally do not express hard tissue formation like ameloblastomas and cysts. It also supports the observation on the biologic behavior of the lesions. Lesions with odontogenic hard tissue components are thought to more differentiated and mature and by extension of less aggressive behavior as compared with lesions without hard tissue formation. Thus, the amelogenin molecule may be considered as a useful marker in the prediction of clinical and histological behavior of odontogenic lesions.

All the lesions in our study expressed amelogenin antibody varying from mild to intense positivity. We suggest based on our results that the attempt of epithelial cells of these lesions toward the ameloblastic differentiation is retained from their original tissues, but there may be other factors which restrict the epithelium from being differentiated fully. This may be due to or result in altered epithelial mesenchymal interactions leading to the pathologic process.

It was interestingly observed in our study that many connective tissue elements including erythrocytes, inflammatory cells, endothelial cells and fibroblasts showed background staining. This false positive background clutter has been reported previously.[17] This is probably due to the role of amelogenin in embryologic craniofacial development.

A recent study has demonstrated amelogenin expression in developing tissues of the developing mouse embryonic craniofacial complex such as brain, eye, ganglia, peripheral nerve trunks, cartilage and bone. Interestingly amelogenin was expressed at E10.5 in the brain and eye long before the initiation of tooth formation. Amelogenin also played a major role in the recruitment of mesenchymal cells. In an *in vivo* study recombinant human amelogenin protein (rHAM+) alone brought about regeneration of the tooth supporting tissues: Cementum, periodontal ligament and alveolar bone, in a dog model, through recruitment of progenitor cells and mesenchymal stem cells. Low molecular mass amelogenin isoforms have been suggested to have signaling activity to produce ectopically chondrogenic and osteogenic like tissue.[17] In the light of the above observations it is now well established that the amelogenin molecule leaves its blueprint in major aspects of craniofacial development including the tooth germ. Retention of this blueprint was probably reflected in the background clutter seen in our study.

The potential for identification of sensitive and specific molecules like amelogenin through IHC opens up many vistas for the average diagnostic oral pathologist in his laboratory. Use of this marker is an important step in identifying and understanding the biological behavior of odontogenic lesions including cysts and tumors.

Conclusion

The amelogenin molecule can be used as a marker for odontogenic lesions and odontogenic epithelium especially when there is difficulty in demonstration of the same in routine hematoxylin and eosin stains. Intensity of expression of amelogenin molecule in odontogenic lesions is variable and may explain the differentiation of the cells at different state of their journey in the lesions.

Intense positive reaction of calcified globular structures and adjacent lesional cells can confirm the presence of odontogenic hard tissues in a lesion. This is especially significant on two counts: (a) Apart from odontogenic hard tissues no other hard tissues, especially bone, was stained, and (b) the intense staining pattern of the amelogenin antibody in all odontogenic hard tissue containing lesions (AOT, odontomas).

Amelogenin expression in hard tissue formative lesions may indicate the advancing differentiation of the tissue. The diffuse and constant expression in the epithelium can predict the less likelihood of recurrence of the lesion. Furthermore, the aggressiveness of the lesion is likely to be moderated and treatment could be modified based on this observation.

The non-specific staining attributed in our study was due to the multifunctional role of amelogenin in many tissues during embryologic craniofacial development.

The amelogenin molecule holds abundant promise in predicting the behavior of odontogenic lesions. More studies with a large number of samples are needed to support the observation of the biologic behavior of this molecule in odontogenic lesions in detail.

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