Original Article

Expression of CK14 and vimentin in adenomatoid odontogenic tumor and dentigerous cyst

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Abstract

Background: Origin of adenomatoid odontogenic tumor (AOT) has long been a controversy, and the issue of it being a neoplasm or hamartoma was a subject of debate for a long time. Earlier it was grouped under a mixed group of odontogenic tumors considering the varying degrees of inductive changes. Recently, the WHO classification states that the presence of hard tissue within AOT was not due to induction but was rather a metaplastically produced mineralization and hence the tumor was reclassified under a group of tumors arising from odontogenic epithelium. This study is an attempt to identify if both epithelial (cytokeratin 14 [CK14]) and mesenchymal (vimentin) markers are expressed in the follicular and extrafollicular variants of AOT and to compare the expression with dentigerous cyst (DC) as this cyst is known to arise from reduced enamel epithelium which expressed CK14. This is done to possibly relate the origin of AOT with reduced enamel epithelium.

Aims and Objectives: To study, analyze and correlate the expression of CK14 and vimentin in AOT and DC.

Materials and Methods: Retrospective study on paraffin embedded tissues. Sixteen cases of AOT and 15 cases of DC were retrieved from the departmental archives and subjected to CK14 and vimentin immunostaining.

Statistical Methods: Measures of central tendency was used to analyze the results.

Results and Observations: Ninety percent of cases of follicular AOT (FAOT) and 100% cases of extra-follicular AOTs (EAOTs) showed positivity for CK14 and all cases of DC showed positivity for CK14. Vimentin was positive in 44% and negative in 56% cases of both FAOT and EAOT taken together.

Conclusion: The CK14 expression profile in AOT and DC supports its odontogenic epithelial specific nature. The possible role of reduced enamel epithelium and dental lamina in histogenesis of AOT and DC is strongly evident by their CK14 expression pattern.

Key Words: Adenomatoid odontogenic tumor, cytokeratin 14, dentigerous cyst, vimentin

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INTRODUCTION

The adenomatoid odontogenic tumor (AOT) is the third most frequent odontogenic tumor originating from odontogenic epithelium. The tumor that meets today's diagnostic criteria of AOT has been known for more than 90 years.[1] It was first reported by Harbitz in 1915 under the name of cystic

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adamantinoma. Philipsen and Birn proposed the widely accepted and currently used name AOT, a term that was adopted by the first edition of the World Health Organization classification of odontogenic tumors in 1971.[2] AOT is also popularly known as "two-third" tumor because two-third of cases occurs in females, involve maxilla and are associated with an impacted canine.

It is defined as a tumor composed of odontogenic epithelium in a variety of histoarchitectural patterns, embedded in a mature connective tissue stroma and characterized by slow but progressive growth.[3]

It is most commonly encountered in the second decade, having greatest predilection for females. It can occur both intraosseously and extraosseously. It is usually surrounded by a well-developed connective tissue capsule and may present as one large cystic space or as numerous cystic spaces. The tumor is mainly composed of spindled-shaped cells or polygonal cells forming various patterns in scanty connective tissue stroma. Some of the common histopathological patterns observed include ductal, rosette, convoluted and nodular patterns [Figure 1] and some unusual histopathological patterns of presentation of AOT include cell ball, calcifying epithelial odontogenic tumor (CEOT)-like areas, plexiform pattern and melanin pigmentation [Figure 2]. Some cases of AOT demonstrate areas resembling other odontogenic tumors such as CEOT, odontoma (and similar tumors) and calcifying odontogenic cyst (calcifying cystic odontogenic tumor). They should be classified as histologic variants of AOT, as they have been shown not to influence the biologic behavior of AOT.[2] Two types of cells are observed in AOT. Type A cells are cuboidal and occur in the form of nodules, whorls, nests and form duct-like structures and Type B cells are smaller, spindle-shaped and are present peripheral to the nodules [Table 1].[4]

The issue of its nature being neoplastic or hamartomatous and its classification has long been a subject of controversy. Furthermore, there is no consensus regarding exact histogenesis of the tumor whether it arises from the dental lamina and its remnants or reduced enamel epithelium.[5]

Earlier AOT was classified under a mixed group of odontogenic tumors considering the varying degree of inductive changes. Recently, the revised WHO classification (2005) states that the presence of hard tissue within AOT was not due to induction but was rather a metaplastically produced mineralization and hence reclassified the tumor under the group odontogenic tumors that arise from the odontogenic epithelium with mature fibrous stroma, depending partly on study showing negativity to bone morphogenetic proteins (BMPs). However, recently Kumamoto and Ooya[6] demonstrated the presence of BMP receptors and core binding factor α1 in both epithelial and mesenchymal cells in normal tooth germ and AOT and concluded that BMP and associated molecules play a role in cytodifferentiation of normal and neoplastic odontogenic epithelium through epithelial-mesenchymal interactions. This reclassification has kindled the debate once again as to the nature of the cellular events which might lead to dental matrix material deposition in this tumor.[7]

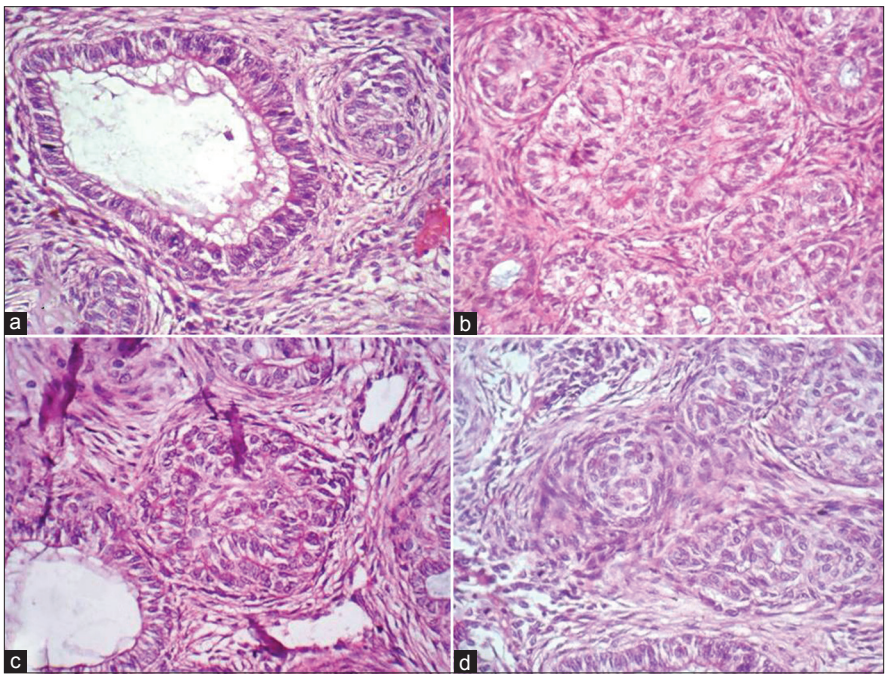

Figure 1: The common histological patterns seen in adenomatoid odontogenic tumor include (a) ductal, (b) rosette, (c) convoluted and (d) nodular pattern (H&E stain, ×400)

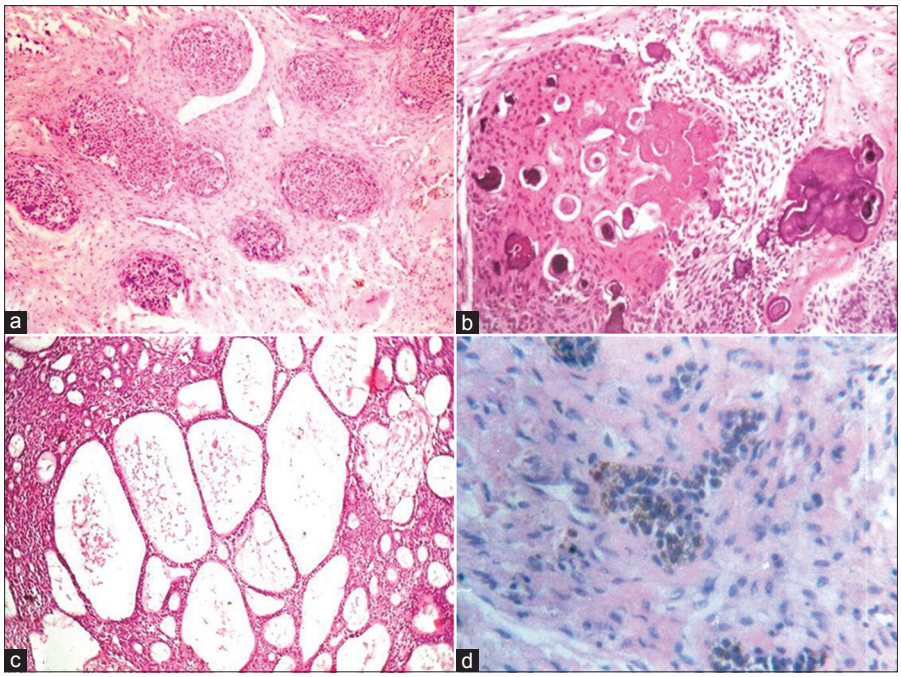

Figure 2: The unusual histological patterns in adenomatoid odontogenic tumor include (a) cell ball (H&E stain, ×40), (b) calcifying epithelial odontogenic tumor like areas (H&E stain, ×100), (c) plexiform pattern (H&E stain, ×40) and (d) cells showing melanin pigmentation (H&E stain, ×400)

Table 1: Description of Type A and Type B cells

Type A cells	Type B cells
Form solid nodules, whorls, nests and duct - like	Present periphery to Type A cells, internodularly, cribriform pattern in some parts of tumor
They were cuboidal, columnar - shaped	Usually spindled - shaped
Pale cytoplasm and nucleus - vesicular with prominent nucleoli.	Darkly stained eosinophilic cytoplasm with hyperchromatic nuclei
Nucleus placed away from basement membrane cells - duct like pattern	
Resemblance - inner enamel epithelial cells	Resemblance - stratum intermedium, stellate reticulum

Dentigerous cyst (DC) is the second most common odontogenic cyst that commonly involves impacted mandibular molar and maxillary canine. Histologically, it is known to show certain variations apart from classical histological presentations. Histogenesis of this cyst is considered to be in relation to reduced enamel epithelium of impacted tooth. Several investigations considered DC as a precursor lesion of AOT since most of the (71.6%) AOTs are follicular in relation to canine. It is generally accepted that lining of DC has the potential to develop few odontogenic and nonodontogenic tumors including AOT. Reduced enamel epithelium (REE) may be a source of origin for follicular AOT (FAOT) but fails to explain the origin of extra-follicular AOT (EAOT). Reduced enamel epithelium is considered to be a potential candidate for the origin of certain odontogenic and nonodontogenic tumors.[8]

The strong positive reactivity of cytokeratin 14 (CK14) by neoplastic cells of adenomatoid odontogenic tumor and reduced enamel epithelium suggests that reduced enamel epithelium may be another source of origin.[3,9]

Apart from CK polypeptides, few studies have shown that vimentin is also expressed in epithelial component of odontogenic neoplasms such as AOT and CEOT. Vimentin is class II intermediate filament primarily expressed in mesenchymal tissue.[10]

This project attempts to study the expression of CK14 and vimentin in adenomatoid odontogenic tumor and DC with an aim to study the histopathology, expression of CK14 (epithelial marker) and vimentin (mesenchymal marker) in adenomatoid odontogenic tumor and DC and elucidate the possible role of CK14 and vimentin in pathogenesis of adenomatoid odontogenic tumor and DC. It also attempts to identify if both epithelial and mesenchymal makers are expressed in AOT so as to associate it with the mixed origin and also to know if FAOT and EAOT express variability in markers.

MATERIALS AND METHODS

The retrospective study was carried out on tissue sections obtained from previously diagnosed 16 cases of AOT consisting both of FAOT (n=10) and EAOT (n=6) variants and 15 cases of DC retrieved from the archives of Department of Oral and Maxillofacial Pathology.

Formalin fixed paraffin embedded tissue specimens were sectioned to 4–5-micron thickness and stained with routine H and E stain.

Three-four micron thick sections were obtained on polyvinyl coated slides and stained immunohistochemically with monoclonal antibody to CK14 and vimentin using standard biotin peroxidase complex method.

All stained sections were visually assessed by three observers independently and was graded as:

1. Negative (–) – no staining
2. Weakly positive (+) faint staining, either diffuse or focal
3. Positive (++) – appreciable brown staining
4. Strongly positive (+++) – appreciable brown staining with more color intensity.

(Grading depends on color intensity)

Both Type I and Type II cells were observed for staining characteristics.

RESULTS AND OBSERVATIONS

Sections of all studied cases of follicular variant exhibited the capsule, cystic space lined by nonkeratinized stratified squamous epithelium and supporting fibrous wall. This neoplastic epithelium exhibited localized or focal proliferation into cystic lumen or wall exhibiting various histopathological patterns of AOT. The follicular variants showed 90% ($n = 9$) of ductal, 80% ($n = 8$) of nodular and tumor droplets, 70% ($n = 7$) of whorl, 60% ($n = 6$) of plexiform, 50% ($n = 5$) of eosinophilic areas, 40% ($n = 4$) convoluted and calcifications and 20% ($n = 2$) rosette and CEOT like areas.

All the extra-follicular variants, exhibited microcyst formation, where as 83% ($n = 5$) showed nodular, ductal and plexiform patterns. Sixty-six percent ($n = 4$) showed calcification, 50% ($n = 3$) of whorled pattern, 33% ($n = 2$) of convoluted, rosette and eosinophilic structures and 17% ($n = 1$) of CEOT like areas.

All these histological patterns occurred in combination with each other and exhibited both Type A and Type B cells in varying proportions in both FAOT and EAOT.

Adenomatoid odontogenic tumor - cytokeratin 14

The overall expression of CK14 in AOT (follicular and extrafollicular $n = 16$) cases showed strong positivity in 69% (11 cases), intermediate positivity in 25% ($n = 4$) and weak positive reaction with 6% ($n = 1$) of cases [Figure 3].

The 90% (9 cases) of FAOTs expressed positivity (strong and intermediate) for CK14 and negative reactivity in 10% (1 case) of cases.

The predominant expression of CK14 in FAOT was observed in Type B (80% eight cases) cells when compared to Type A (70% seven cases) cells. Negative\weakly positive reactivity was observed in Type A (30% three cases) cells and Type B (20% two cases) [Table 2].

All cases of extra-follicular variant of AOTs expressed positive CK14 expression. Wherein 66.6% (4 cases) showed strong positivity and 33.3% (2 cases) showed intermediate positivity [Table 3].

Table 2: Expression of cytokeratin 14 and vimentin by Type A and Type B cells in follicular adenomatoid odontogenic cyst

	Grading	CK14	%	Vimentin	%
Type A	–	3	30	2	20
	+	0	0	2	20
	++	3	30	5	50
	+++	4	40	1	10
	Total	10	100	10	100
Type B	–	1	10	1	10
	+	1	10	4	40
	++	3	30	5	50
	+++	5	50	0	0
	Total	10	100	10	100

CK14: Cytokeratin 14

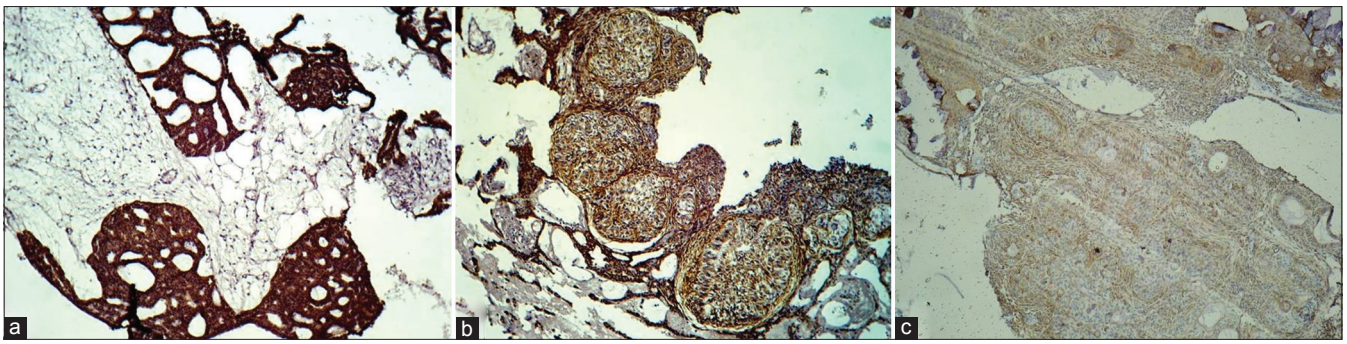

Figure 3: Expression of cytokeratin 14 in adenomatoid odontogenic tumor: (a) strong positivity, (b) intermediate positivity and (c) weak positivity (IHC stain, ×40)

Cytokeratin 14 - dentigerous cyst

The CK14 reactivity in a study group of DC was observed to be focally distributed either in basal layer or suprabasal layers or only superficial layer or in all layers of epithelium [Figure 4].

All the cases of DC showed positive reactivity for CK14 (strong and intermediate positive) except one (7%) which showed weak positivity. The distribution of expression of CK14 in different layers of epithelium is presented in Table 4.

Vimentin expression in follicular adenomatoid odontogenic tumor and extra-follicular adenomatoid odontogenic tumor

The overall expression of vimentin in both FAOT and EAOT together was found to be negative in 56% ($n = 9$) and positive in 44% ($n = 7$).

The expression pattern consisted of intermediate positivity in 38% ($n = 3$), weak positivity in 31% ($n = 5$), negativity in (25% $n = 4$) and strong positive expression in only one case (6%) [Figure 5].

In follicular variant

The negative reactive expression of vimentin was observed in 60% ($n = 6$) and positive reactivity (strong and intermediate) in 40% ($n = 4$).

The overall positive (strong and intermediate) expression of vimentin was found to be 60% ($n = 6$) of Type A and Type B 50% ($n = 5$) cells [Table 2].

In extrafollicular variant showed equal proportions of positive and negative expression of vimentin, i.e. 50% (three) of intermediate positive and 50% (three) of negativity [Table 3].

The predominant positive expression of vimentin was showed by 67% ($n = 4$) of Type B, whereas negativity expressed by 83% ($n = 5$) of Type A cells.

Table 3: Expression of cytokeratin 14, vimentin by Type A and Type B cells in extra-follicular adenomatoid odontogenic cyst

Cell	Grading	CK14	%	Vimentin	%
Type A	–	3	50	5	83
	+	0	0	0	0
	++	1	17	1	17
	+++	2	33	0	00
	Total	6	100	6	100
Type B	–	1	17	2	33.3
	+	0	0	2	33.3
	++	2	33	2	33.3
	+++	3	50	0	0
	Total	6	100	6	100

CK14: Cytokeratin 14

Table 4: Patterns of expression of cytokeratin 14 and vimentin in dentigerous cyst

Histopathology	+	%	++	%	+++	%
Focal positivity						
CK14	1	7	2	14	1	7
Vimentin	0	0	0	0	0	0
Only basal cells						
CK14	0	0	1	7	0	0
Vimentin	0	0	0	0	0	0
Suprabasal cells						
CK14	0	0	1	7	1	7
Vimentin	0	0	0	0	0	0
All epithelial cells						
CK14	0	0	3	20	4	27
Vimentin	1	7	3	20	0	0
Superficial layer only						
CK14	0	0	1	7	0	0
Vimentin	0	0	1	0	0	0

CK14: Cytokeratin 14

Vimentin-dentigerous cyst

Seventy-three percent ($n = 11$) of DC cases showed negative expression, 20% ($n = 3$) cases showed intermediate positive expression and only 7% ($n = 1$) expressed weak positivity.

Considering the individual case, in 20% ($n = 3$) all layers of epithelium expressed Intermediate positivity, and 7% ($n = 1$) expressed weak positivity only in superficial layer [Table 4].

DISCUSSION

AOT is a unique lesion of the maxillofacial skeleton (central variety) or in the soft tissue (peripheral) overlying tooth bearing areas or alveolar mucosa in edentulous regions. The categorized central (follicular or extra-follicular) and peripheral variants have common histopathological features that indicate a common origin as derived from the complex system of dental lamina or its remnants. Gubernaculum dentis (GuDe) is implicated in the development of AOT. GuDe comprises two structures, the gubernacular cord (GuCo) and the gubernacular canal (GuCa). GuCo consists of a fibrous band, containing peripheral nerves, blood and lymphatic channels and epithelial cells or cell clusters from the fragmented dental lamina running in a bony canal. GuCa connects the pericoronal follicular tissue of the successional tooth with the overlying alveolar crest

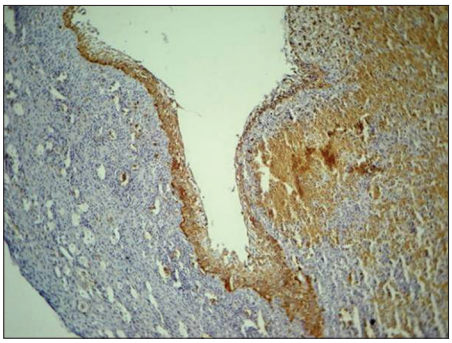

Figure 4: Expression of cytokeratin 14 in epithelial lining cells of dentigerous cyst (IHC stain, ×40)

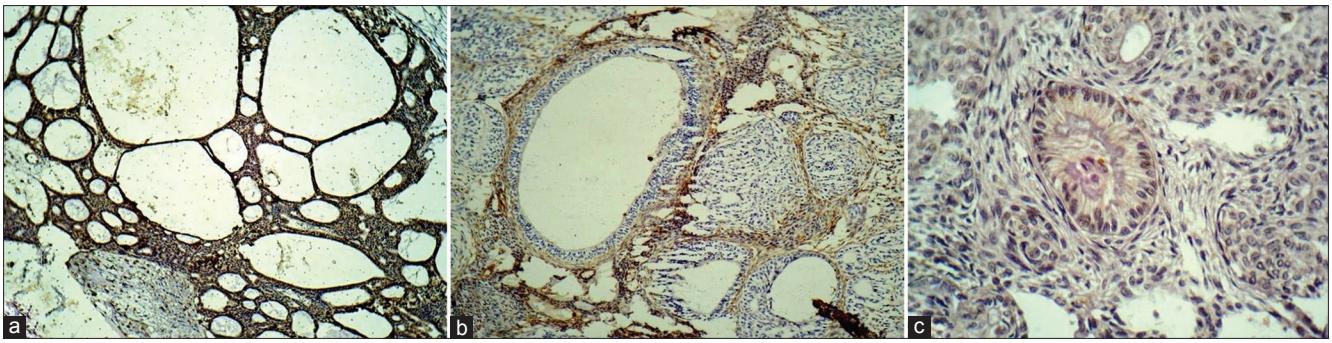

Figure 5: Expression of vimentin in adenomatoid odontogenic tumor: (a) strong positivity (IHC, ×40), (b) intermediate positivity (IHC, ×100) and (c) weak positivity (IHC stain, ×400)

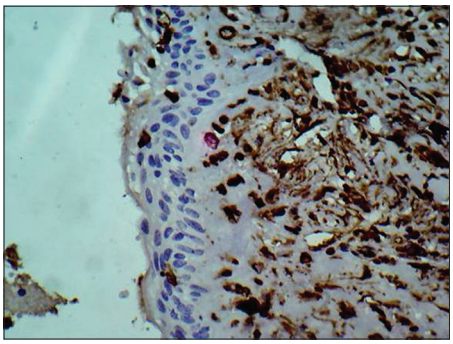

Figure 6: Expression of vimentin in connective tissue wall of dentigerous cyst (IHC stain, ×400)

and gingiva behind the deciduous predecessor. According to Philipsen *et al,* AOT is derived from odontogenic epithelium of the dental lamina complex or its cellular remnants located in the GuCo.[11] Apart from distinct histopathological features observed in this tumor, the true nature of inductive component is yet to be settled. Recently, this tumor is regrouped as an epithelial tumor considering the inductive process.[7]

This study was conducted to understand the relation between DC and AOT with respect to origin and also to analyze the immunoexpression of epithelial and mesenchymal markers in AOT (both FAOT and EAOT) and DC. The immunohistochemical expression of the cases is discussed as follows:

Cytokeratin 14 expression in adenomatoid odontogenic tumor

Crivelini *et al*.[9] have shown that the dental epithelium and epithelial odontogenic neoplasm are positive for CK14, except preameloblasts and secreting ameloblasts in which CK14 is gradually replaced by CK19.

All the cells of AOT in this study (FAOT $n = 10$, EAOT $n = 6$) expressed CK14 positivity except one which expressed weak positivity. The CK14 was predominantly expressed by Type B cells than Type A cells which was statistically not significant. This similar pattern of CK14 expression were observed by Crivelini *et al*.,[9] however, they did not mention the expression in relation to different types of cells. But, in another study by Crivelini *et al*.[12] the luminal (Type A) cells did not express CK14. In this regard, some of the authors considered the Type A and Type B cells as two distinct cell populations having different proliferation capacity and origin.[13,14] The similar pattern of CK14 positive expression by both Type A and Type B cells in this study, suggests that, though histomorphologically these appear different/distinct, histogenetically they represent common tumor cell population.

The expression of CK among FAOT and EAOT, when compared, was almost similar, although the number of EAOTs was less. In addition to Type A and Type B cells in FAOT the cystic nonkeratinized lining also showed positivity for CK14. Leon *et al*.[15] demonstrated variable expression of CK 5, 14, 13, 19 in cystic epithelium of FAOT. They concluded that cystic epithelium of AOT exhibits immense phenotypic variability.

The overall CK14 positive expression by all the AOTs in present series was similar and within the CK profile of AOT and other odontogenic lesions as previously reported in the literature. This finding further confirms the consistent and characteristic expression of CK14 confined to odontogenic epithelium, especially in AOT.

The expression of CKs by tumor cells of AOT in this study supports the view of Crivelini *et al*.[12] that CK14 labeling indicates differentiation grades for secretory ameloblasts or ameloblasts in the postsecretory stage in the adenomatoid structures of AOT. These observations may form the basis to explain the presence of enamel like areas within the tumor cells of AOT.

Vimentin expression in adenomatoid odontogenic tumor

Crivelini *et al*.[12] demonstrated the vimentin positivity mainly in the cells around calcified bodies and dark eosinophilic materials of AOT. Further, they suggested that these cells may

secrete the mineralized structure. Leon *et al*.[15] and Tatemoto *et al*.[10] have described the expression of CK14 and vimentin in epithelial components of odontogenic neoplasm, wherein AOT tumor cells at periphery of ductal, tubular or whorled structure expressed both the vimentin and CKs. However, they did not mention any significance of their observations. In the present study, vimentin negativity was shown in 56% ($n = 9$) of AOTs which is contrary to findings of the previous studies. The variable expression of vimentin by epithelial components of AOT in various studies demonstrates the nonspecific heterogeneous reactivity of vimentin. Further, we agree with Crivelini *et al*.[12] that the significance of vimentin coexpression in odontogenic tumors such as AOT and CEOT remains to be explored.

The predominant vimentin negative expression by tumor cells of AOT in this study suggests that the role of vimentin in the tumourigenesis is negligible. However, the majority of vimentin positivity expressed by Type B tumor cells does not preclude their role in genesis of mineralizing components of AOT.

Cytokeratin 14 in dentigerous cyst

The last two decades witnessed series of publications examining keratin expression by odontogenic cell rests and more common odontogenic cysts. More or less these studies attempted in determining the particular patterns of CKs staining which would provide the accurate diagnostic markers for common odontogenic cysts: Odontogenic keratocyst (OKC), DC and radicular cyst (RC). They also aimed in elucidating the pathogenesis of cysts using comparative studies with oral mucosa and odontogenic epithelium at a different stage of tooth development.[8,16,17]

The CK14 expression in this study was found to be positive in all the cases of DC, except one. The expression was either focally confined to only to basal layer or suprabasally or only superficial layer or all the layers of epithelium. Although several groups of studies have advocated the use of different CKs[7,8,12,14,17] expression in odontogenic cysts in general.[9] Only two or more studies have included CK14 in analyzing the DC in relation to OKC and RC. Their results showed that CK14 and with others CKs[7,8,12,14,17] were strongly expressed by both OKC and DC. Even in this study CK14 positive expression was noted in almost all the cases of DC. The expression of CK14 in odontogenic epithelium, dental lamina, REE and odontogenic cysts in the previous studies leads to the view that CK14 reactivity is not only confined to DC but also shared/shown by other odontogenic cysts and structures.

Vimentin in dentigerous cyst

The vimentin expression was predominantly negative in DC of the present study and only three cases expressed positivity. No data is available regarding this in the previous literature [Figure 6].

Dentigerous cyst and adenomatoid odontogenic tumor association

Agreeing with the proven fact that DC is a pathology resulting from REE and strong expression of CK14 in REE, dental lamina, DC and AOT, it can be reinforced that both DC and AOT may originate from REE and dental lamina.[1,3,8,17]

CONCLUSION

The CK14 expression profile in AOT and DC supports its odontogenic epithelial specific nature. The possible role of REE and dental lamina in the histogenesis of AOT and DC is strongly evident by their CK14 expression pattern. The heterogeneous variable expression of vimentin in AOT suggests it to be a nonspecific marker, but its partial role in histogenesis of mineralized component cannot be negated. Finally, the observations of this study concluded that the two clinico-radiographic variants exhibit similar light microscopic and immunohistochemical profile of CK14.

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Conflicts of interest

There are no conflicts of interest.

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