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Clinicopathologic Correlation of Cell Adhesion Molecules E-cadherin and α-catenin Expressions in Ameloblastoma

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Authors' contributions

This work was carried out in collaboration among all authors. Authors HAE designed the study, performed the statistical analysis, explained, wrote the results section and wrote the draft of the manuscript. Authors MN wrote the protocol, managed the literature searches and author SYEL designed and managed the revision of the study. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aim and Rationale: The present immunohistochemical study was carried out on 30 cases of ameloblastoma of varied histologic types. E-cadherin and α catenin expressions were investigated in relation to different clinicopathologic variables. The rationale of the study is to assess any correlations between the markers expressions and the growth, progression and invasiveness of the tumor.
Study Design: Retrospective study.
Place and Duration: Oral Pathology Department, Faculty of Dentistry, Mansoura University, Egypt, March 2020 to January 2021.
Methodology: Thirty formalin fixed paraffin embedded tissue blocks of ameloblastoma (17 of conventional type, 8 of unicystic type and 5 of ameloblastic carcinoma type) were examined for E-cadherin and α-catenin immunohistochemical expressions. Correlations between the markers` expression and different clinicopathological variables were investigated using Chi-square ($\chi 2$), Fisher's exact probability test, one way ANOVA test, LSD post hoc test and Pearson

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correlation co-efficiency test. The P-value ≤ 0.05 was considered statistically significant.

Results: Both markers revealed statistically significant differences in their expression among the study groups regarding the following parameters (tumor histologic types either benign or malignant type, localization of marker expression either diffuse or focal, size of tumor and type of tumor either primary or recurrent neoplasm, p≤ 0.05). On the other hand, both molecules revealed no statistically significant differences in their expressions regarding the variables (patient age, gender and tumor site, p> 0.05).

Conclusion: E-cadherin and α catenin expressions were related to the growth, progression and invasion of tumor. That`s suggest their involvement in epithelial mesenchymal transition process.

Keywords: Ameloblastoma; adhesion proteins; E-cadherin; α-catenin; local invasiveness; immunohistochemistry.

1. INTRODUCTION

Ameloblastomas are benign tumors whose importance lies in its potential to grow into enormous size with resulting bone deformity [1]. Histologically, ameloblastoma classified according to the new version of WHO classification of odontogenic tumors into 3 types; conventional, unicystic and peripheral. The solid/multicystic term of the old version was discarded, as it could be confused with the unicystic type. Desmoplastic ameloblastoma was also reclassified as a histological subtype and not as a clinico-pathological entity, based on the fact that it behaves like any conventional ameloblastoma, although its clinical and radiographic characteristics are peculiar [2,3]. Follicular and plexiform patterns of conventional type are the most common. Different alterations at tumor cells observed in the area of stellate reticulum like cells, such as squamous differentiation, basaloid changes, granular changes, clear cell changes, ghost cell changes and spindle cells changes. Presence of extensive changes in the tumors, the terms acanthomatous type, basal cell type, granular cell type, clear cell type, ghost cell type and spindle cell type are applied respectively [4]. The term unicystic ameloblastoma refers to those cystic lesions that show clinical, radiographic, or gross features of a jaw cyst, but on histologic examination show a typical ameloblastomatous epithelium lining part of the cyst cavity, with or without luminal and/or mural tumor growth [5]. It is a less aggressive variant and it has a low rate of recurrence, although lesions showing mural invasion are an exception [6]. The malignant counterpart of ameloblastoma is ameloblastic carcinoma (AC). In comparison with ameloblastoma, AC has a higher morbidity and distant metastatic capability [7]. Histologically, AC is characterized by anaplasia, high mitotic index, adjacent tissue infiltration, and possible necrosis [8].

Epithelial mesenchymal transition (EMT) is an essential process for early odontogenesis activation and tumor development [9]. It has been reported that signaling pathways and molecular mechanisms that are important for odontogenesis contribute to pathogenesis of ameloblastoma [10]. EMT is also an early phase during malignant transformation of epithelial cells in tumors [11].

It has been reported that multiple cytokines, growth factors, and proteins are abnormally expressed in ameloblastoma, indicating their participation in tumor progression and invasiveness [12-14]. E-cadherin is Ca^{2+} a dependent intercellular adhesion molecule belongs to the classical cadherin family [15]. It is a 120-kDa transmembrane glycoprotein essential for homotypic cell–cell adhesion and epithelial morphogenesis. E-cadherin is expressed on the epithelial cell membrane [16,17]. Cadherin and actin have an extracellular domain that binds to the intracellular proteins α-, β-, and γ-catenin to form the cytoskeleton [16]. Expressions of these intracellular proteins (α, β, and γ-catenin) have been associated with metastasis and proliferation in oral cancer [18], thyroid cancer [19], breast cancer [20] and lung cancer [21].

The association of cadherin and catenin expression has been investigated in many studies. One study illustrated the role of E-cadherin and β-catenin in ameloblastoma development. Another study explained the role of E-cadherin and α-catenin in tooth germ cell differentiation process [15,22,23]. In the light of the previous data, the present study was conducted to clarify the correlations between E-cadherin and α-catenin expressions in relation to

different clinicopathological parameters of the studied ameloblastoma cases.

2. MATERIALS AND METHODS

2.1 Materials

The current study was applied on thirty formalin fixed paraffin embedded tissue blocks of ameloblastoma cases along with its variants (17 cases of conventional solid type, 8 cases of unicystic histological type and 5 cases of ameloblastic carcinoma). All cases included to our study had complete medical records and with confirmed diagnosis. After exclusion of cases had insufficient biopsy speciemen and those with missing medical records, thirty cases were retrieved from the archival files of Oral Pathology Department, Faculty of Dentistry, Mansoura University.

Three 4 microns thick sections were prepared from each paraffin block; one section was cut for the routine hematoxylin and eosin staining to examine and confirm the diagnosis of the selected cases, while the other two sections were cut for immunohistochemical staining by the two antibodies (E-cadherin and α- catenin).

2.2 Methods

2.2.1 Clinical data retrieval

Patient`s clinical data was collected from the medical reports with emphasis upon age, gender, tumor site, tumor size and incidence of recurrence. The present study included 18 males and 12 females with 1.5:1 male to female ratio. The age of studied cases ranged from 15 to 75 years and the median was 47.8 years. Three of the studied cases had tumors aroused from the maxilla, while the rest of cases (27 cases) were from the mandible. Sixteen of cases had tumors smaller than or equal to 2 Cm in diameter. On the other hand, large sized tumors that were larger than 2 Cm in whole diameter reported in 14 cases. Six of the studied cases were recurrent tumors, while the rest 24 cases were primary tumors.

2.2.2 Immunohistochemical staining

Two 4 microns thick sections were cut from each paraffin block for immunostaining to study the expression of E-cadherin and α –catenin in the selected cases. Sections were then mounted on positive charged slides. Immunostaining was performed using the Avidin-Biotin complex (ABC) method according to the manufacturer's instructions [24]. The slides were deparaffinized by immersion in Xylene (15 minutes) then rehydrated in descending grades of alcohol and then washed in water. Blocking the endogenous peroxidase activity by treatment sections with 0.5% H_2O_2 in methanol for 30 minutes then washed in phosphate buffer saline (PBS) for 5 minutes. Pretreatment of the tissue sections by immersing in boiling citrate for 20 minutes at 94 c˚ then cooled at room temperature then washed with distilled water. Followed by incubation of the slides in a solution of protease XIV 50 mg in 100 ml of 0.1 M, PH 7.4 PBS (pre warmed to 37˚c) for 15 minutes at 37 c˚ then washed 3 times in PBS for 5 minutes to digest the proteolytic enzyme activity. Blocking of non-specific binding of antibody by incubating the slides in 4.0 % mouse serum for 30 minutes at room temperature. The primary antibody was applied and the slides were incubated with the primary antibody for overnight at room temperature then sections were washed 3 times in PBS for 5 minutes. Avidin-biotin complex peroxidase solution was applied according to manufacturer's directions. Sections were incubated for 30 minutes at room temperature then washed 3 times in PBS for 5 minutes. Application of chromogen for development of colored reaction product was done by using 3.3' diaminobenzidine-4HCL (DAB) 1mg/ml in PBS supplemented with H_2O_2 from Sigma chemical Co. St. Lo Missoure (10 µl of 50% H_2O_2 in 5 ml PBS). The DAB chromogen yielded a brown reaction end product at the site of target antigen. The sections were counter stained with Mayer's Hematoxyline and were covered using a permanent mounting media (Canada balsam). Positive controls of the used antibodies (E-cadherin and α –catenin) were performed by staining sections of tonsil and appendix respectively at the same time and under the same conditions. Negative control slides obtained by replacement of the primary antibodies by plain PBS.

2.2.3 Evaluation and scoring of immunohistochemical reaction

Assessment of tissue immunoreactivity for E-cadherin and α–catenin was made semiquantitatively by counting the positive tumor cells under ×400 magnification from five random fields and the results were expressed as percentage of immunoreactive cells from total number of tumor cells. The images were acquired utilizing a Nikon Eclipse microscope

equipped with a 5-megapixel cooled CCD camera and the Image ProPlus AMS7 software.

The positivity and intensity of E-cadherin and α–catenin immunohistochemical staining were examined, evaluated and scored using the method described by Kurioka et al. [25].

Immunostaining was evaluated for both markers by observing the intensity of the staining and their localization either diffuse expression involving both central (stellate reticulum like cells) and peripheral (basal columnar) cell layers, or focal central expression (in stellate reliculum like cells) as follow: Strong expression observed in ≥ 50% of tumor cells, Moderate expression observed in 10-50% of tumor cells, Weak expression observed in < 10% of tumor cells.

2.2.4 Statistical analysis

Results of the present study were analyzed statistically to detect the possible significant differences and correlations between the different variables.

Data analysis was conducted using Statistical Package for Social Science (*SPSS)* program version 23. Descriptive data were presented in number and percentage format. Quantitative statistics were calculated in the form of mean ± standard deviation (SD). The association between the different clinico-pathological parameters to E-cadherin and α catenin expression were tested using Chi-square ($\chi 2$) and Fisher's exact probability test. The analysis of the data was done by one way ANOVA, to test statistical significant differences in more than two groups. Pearson correlation co-efficiency test was used to test the association between the different variables. The P-value ≤ 0.05 was considered to be statistically significant.

3. RESULTS

3.1 Clinico-pathological Features of Studied Cases

Clinically, the present study included 30 cases of ameloblastoma. Male gender presented by 18 cases (60%), while females represented by 12 cases (40%). The male to female ratio was 1.5 to 1 respectively. The mean age of ameloblastoma cases was 47.8 years. The age ranged from 15 to 75 years. The majority of ameloblastomas in the present work were aroused from the mandible (27 cases, 90%). Only 3 cases (10%) were aroused from the maxilla.

Small sized tumors that were lesser or equal to 2 Cm in diameter reported by 16 cases (53.3%). On the other hand, large sized tumors that were greater than 2 Cm in whole diameter reported by 14 cases (46.7%). The greater number of cases were primary tumors (24 cases, 80%), while the rest 6 cases (20%) were recurrent ameloblastomas.

Histopathologically, the current study included 30 cases of ameloblastoma that categorized as 17 cases (56.7%) of conventional solid type. The predominant conventional histological type of the studied cases was the follicular variant (12 cases, 40%). The Plexiform histological variant observed in 5 cases (16.7%). Eight of the studied cases (26.7%) diagnosed as unicystic ameloblastoma histological type. Five cases (16.7%) showed mural histologic variant, while the luminal histological variant was presented in 3 cases. The present study includes 5 cases (16.7%) had the diagnosis of ameloblastic carcinoma. Clinicopathological findings illustrated in (Table 1).

3.2 Immunohistochemical Findings

3.2.1 E-cadherin expression in different ameloblastoma histologic types

Expression of E-cadherin was observed in the cell cytoplasm and plasma membrane. E-cadherin demonstrated differential expression in the examined ameloblastoma cases. Strong expression that involved ≥ 50% of tumor cells reported in 14 cases (46.7%), 10 cases (33.3%) revealed moderate expression (10-50% of tumor cells), and 6 cases showed weak expression (<10% of tumor cells). E-cadherin expression was significantly different in the varied histologic types of ameloblastoma (p= 0.000). Weak E-cadherin expression was observed in 6 cases (20%); all the studied ameloblastic carcinoma cases (5 cases, 100%) and in one case of follicular variant of conventional histologic type. That case was large sized recurrent tumor and microscopically of micro and macrocystic histologic variant. Moderate E-cadherin expression reported in 10 cases that categorized as 5 cases (41.7%) of conventional follicular histological type, 2 cases (40%) of conventional plexiform histological type and 3 cases (37.5%) of unicystic histological type. Strong E-cadherin expression observed in 6 cases of conventional

follicular histological type (50% within the histologic type), 3 cases of conventional plexiform histological type (60% within the histologic type) and 5 cases of unicystic ameloblastoma (62.5% within the histologic type). L.S.D post hoc test reported a high statistically significant differences in E- cadherin expression between ameloblastic carcinoma study group and the other benign forms of ameloblastoma (conventional follicular & plexiform type and unicystic type, Fig. 2, Table 2).

Equal percentages of the examined cases (14 cases, 46.7%) demonstrated either diffuse marker expression involving both central (stellate reticulum like cells) and peripheral (basal columnar) cell layers, or focal central expression (in stellate reliculum like cells). Only 2 cases (6.7%) revealed expression in peripheral or basal

Table 1. Clinicopathological data of the studied cases

Clinicopathological variables		Frequency	Percentage
Gender	Male	18	60%
	female	12	40%
Tumor site	maxilla	3	10%
	mandible	27	90%
Tumor size	≤ 2Cm	16	53.3%
	> 2 Cm	14	46.7%
Incidence of recurrence	Primary tumor	24	80%
	Recurrent tumor	6	20%
Histologic type			
Conventional solid type	follicular	12	40%
	plexiform	5	16.7%
Unicystic type	mural	5	16.7%
	luminal	3	10%
Ameloblastic carcinoma		5	16.7%
	Total	30	100%

Table 2. Multiple comparisons between E-cadherin expressions in different histologic types of ameloblastoma

(I) histologic type	(J) histologic type	Mean Difference (I-J)	Std. Error	Sig.
conventional follicular type	conventional plexiform type	-.18333-	.29511	.540
	unicystic type	-.20833-	.25305	.418
	ameloblastic carcinoma	1.41667*	.29511	.000
conventional plexiform type	conventional follicular type	.18333	.29511	.540
	unicystic type	-.02500-	.31606	.938
	ameloblastic carcinoma	1.60000*	.35064	.000
unicystic type	conventional follicular type	.20833	.25305	.418
	conventional plexiform type	.02500	.31606	.938
	ameloblastic carcinoma	1.62500*	.31606	.000
ameloblastic carcinoma	conventional follicular type	-1.41667-*	.29511	.000
	conventional plexiform type	-1.60000-*	.35064	.000
	unicystic type	-1.62500-*	.31606	.000

columnar cell layer. One way ANOVA statistical test revealed no statistically significant differences in the studied different histologic types of ameloblastoma regarding localization of E-cadherin expression (p=0.724).

3.2.2 E- cadherin expression in relation to different clinic-pathological variables

Tumor size: Tumors that were small in size (≤ 2 Cm) had moderate (2 cases, 12.5%) and strong (14 cases, 87.5%) E- cadherin expression. While large sized tumors (>2 Cm) demonstrated weak (6 cases, 42.8%) and moderate (8 cases, 57.2%) expression. A high statistically significant difference in E-cadherin expression was observed between the two groups using Chi square test (p=0.000, Table 3).

Primary versus recurrent tumors: When comparing E-cadherin expression in primary and recurrent tumors using one way ANOVA statistical test, a high statistically significant differences in E-cadherin expression presented between the two groups (p=0.034, chart 1). Recurrent tumors (6 cases, 100%) showed weak (2 cases, 33.3%) and moderate (4 cases, 66.7%) E-cadherin expression. On the other hand, primary tumors showed strong E-cadherin expression (14 cases, 58.3%), moderate (6 cases, 25%) and weak expression (4 cases, 16.7%).

E cadherin revealed no statistically significant differences in its expression in the studied groups of the variables; patient ages, gender and tumor site (P> 0.05).

3.2.3 α-catenin expression in different histologic types of ameloblastoma

α-catenin expression was observed in the cell cytoplasm. α-catenin revealed weak expression in 7 cases (23.3%), moderate in 10 cases (33.3%) and strong expression in 13 cases (43.3%).

There were a statistically significant differences in α-catenin expression between ameloblastic carcinoma and the other benign histologic types of ameloblastoma (p<0.05, Table 4, Fig. 3). Ameloblastic carcinomas (5 cases) revealed weak (3 cases, 60% within histologic type) and moderate expression (2 cases, 40% within histologic type), while the conventional follicular histologic type showed weak (3 cases, 25%

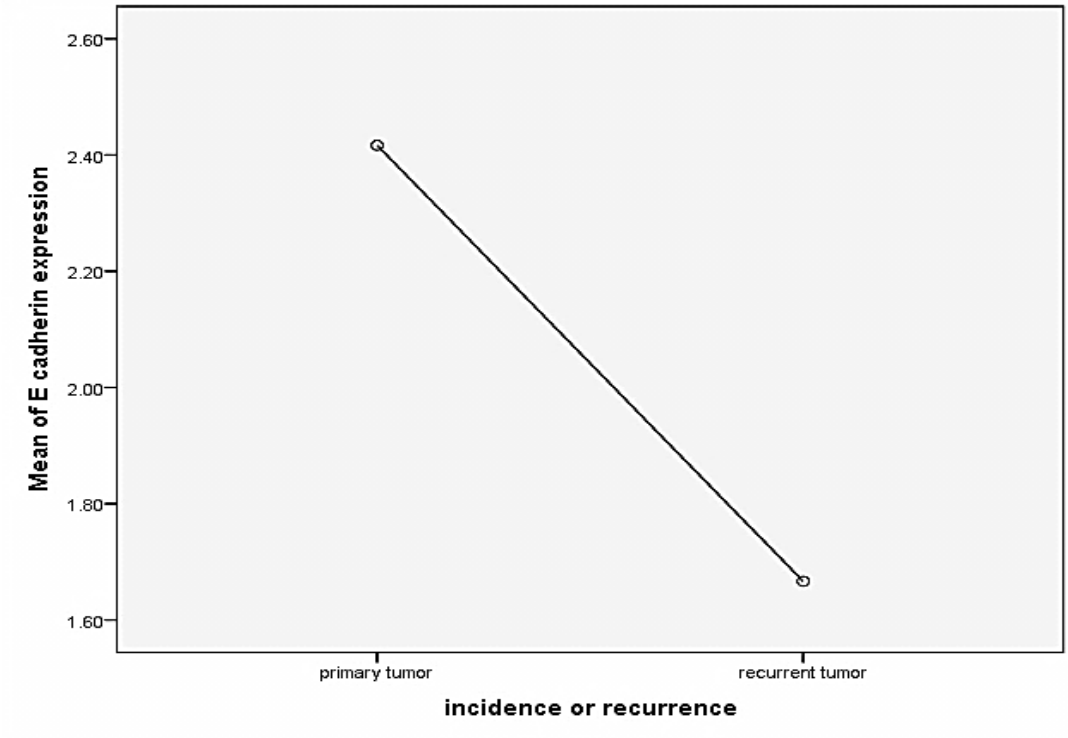

Fig. 1. E-cadherin expression in primary and recurrent tumors

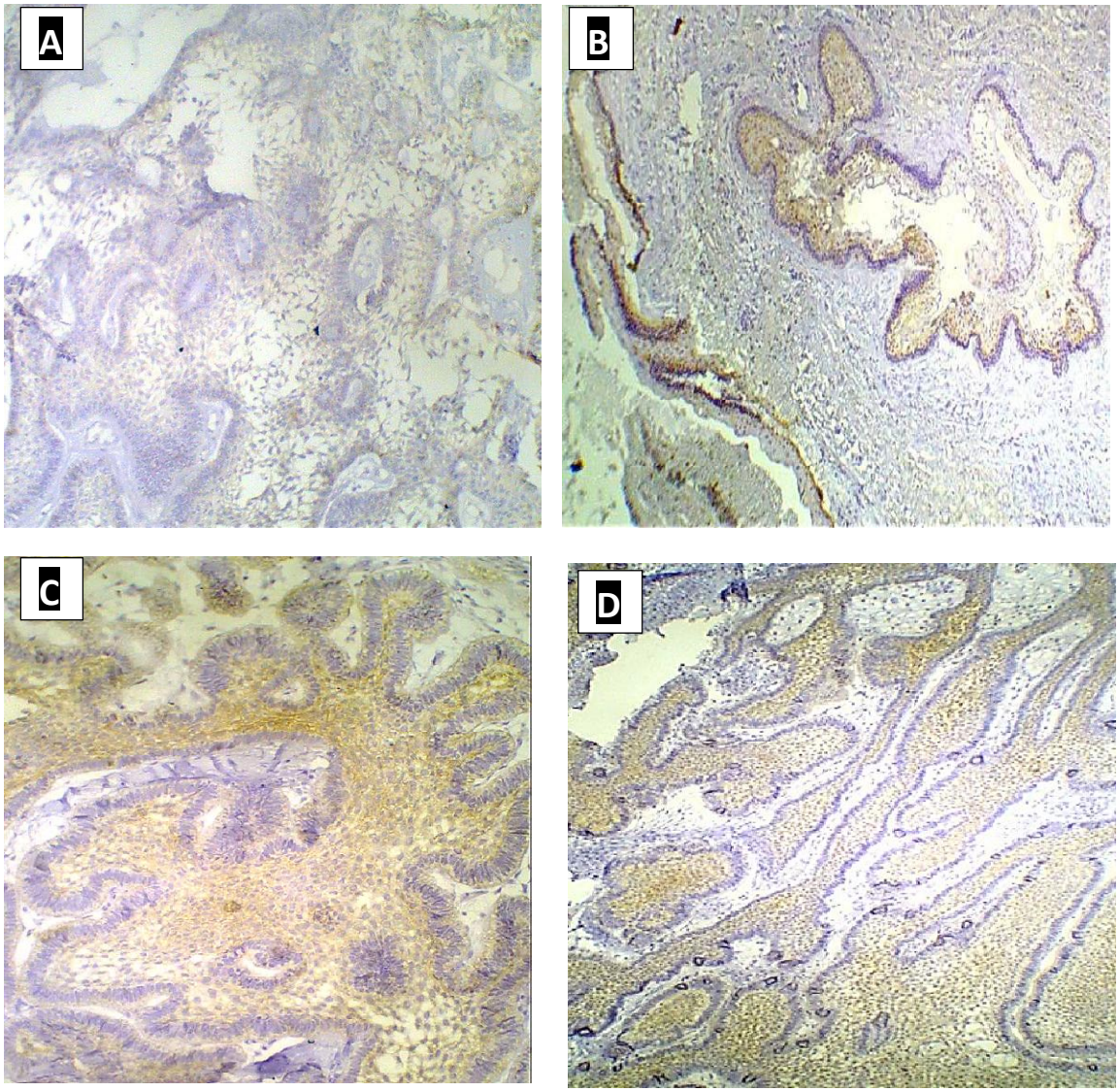

Fig. 2. E-cadherin expression; weak in ameloblastic carcinoma (A), moderate in unicystic ameloblastoma (B), strong in follicular (C) and plexiform histologic variant (D) (ABC- DAB, x250, x400)

within histologic type), moderate (3 cases, 25% within histologic type) and strong expressions (6 cases, 50% within histologic type). Plexiform histologic type demonstrated moderate expression in 3 cases (60% within histologic type) and strong expression in 2 cases (40% within histologic type). Regarding the unicystic histologic type, α- catenin demonestrated weak (one case, 12.5% within histologic type), moderate (2 cases, 25% within histologic type) and strong (5 cases, 62.5% within histologic type) expressions.

3.2.4 Localization of α-catenin expression

One half of the studied cases (15 cases, 50%) expressed α-catenin diffusely in central (stellate reticulum like cells) and peripheral (basal or columnar) cell layers of the tumor, 14 cases (46.7%) expressed α-catenin focally in the central cell layers and only one case (3.33%) showed focal peripheral (basal or columnar) cell layer expression. One way ANOVA statistical test revealed no significant differences in localization of α-catenin among the different studied groups (p= 0.676, Table 5).

Table 3. E- cadherin expression in relation to size of tumor

			Tumor size Less or equal to 2 Cm	Greater than 2 Cm	Pearson Chi-Square Asymp. Sig. (2-sided)
E cadherin expression	weak	Count	0	6	
		% within tumor size group	0.0%	42.8%	.000
	moderate	Count	2	8	
		% within tumor size group	12.5%	57.2%	
	strong	Count	14	0	
		% within tumor size group	87.5%	0.0%	
Total		Count	16	14	
		% within E cadherin expression	53.3%	46.7%	
		% of Total			

Table 4. α-catenin expression in different histologic variables

(I) histologic variant	(J) histologic variant	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
ameloblastic carcinoma	follicular acanthomatous	-.26667-	.55185	.634	-1.4083-	.8749
	follicular desmoplastic	-1.10000-*	.50691	.041	-2.1486-	-.0514-
	follicular micro & macrocystic	-1.00000-*	.47792	.048	-1.9886-	-.0114-
	plexiform	-1.00000-*	.47792	.048	-1.9886-	-.0114-
	unicystic luminal type	-1.26667-*	.55185	.031	-2.4083-	-.1251-
	unicystic mural type	-1.00000-*	.47792	.048	-1.9886-	-.0114-

**. The mean difference is significant at the 0.05 level*

Table 5. α-catenin localization of expression in different histologic types

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Sig.
					Lower Bound	Upper Bound	
periphery or columnar cell layer	1	2.0000	.	.	.	.	.676
center or stellate reliculum cells	14	2.0714	.82874	.22149	1.5929	2.5499	
both	15	2.3333	.81650	.21082	1.8812	2.7855	
Total	30	2.2000	.80516	.14700	1.8993	2.5007	

3.2.5 α-catenin expression in relation to different clinicopathologic variables

Tumor size: Large sized tumors revealed weak (7 cases, 50%) and moderate α-catenin expression (7 cases, 50%). Small sized tumors demonstrated moderate (3 cases, 18.75%) and strong α-catenin expression (13 cases, 81.25%). Chi square test revealed a high statistically significant difference in α-catenin expression between the two groups (p=0.000, Table 6).

Primary versus recurrent tumors: Recurrent tumors (6 cases, 100%) had weak (3 cases, 50%) and moderate (3 cases, 50%) α-catenin expression. The greater percentage of primary tumors demonstrated strong (13 cases, 54.2%) and moderate (7 cases, 45.8%) α-catenin expression. Only 4 cases of primary tumors had weak α-catenin expression (16.6%). Chi square and ANOVA tests revealed statistically significant differences in α-catenin expression between the two groups (p< 0.05, Table 7).

4. DISCUSSION

Ameloblastoma (AM) is the most common epithelial odontogenic tumor in the maxillofacial region. It occupies a special place, as it is considered a benign tumor that has a high risk of recurrence (90%) and even causes distant metastasis [26].

Invasion and metastasis of various neoplastic lesions have been reported to correlate with altered adhesive systems involving cell adhesion molecules [27,28]. In general, adhesion between normal epithelial cells is strong and stable. For tumor cells to dissociate, invade and metastasize, cell-to-cell association must be disrupted [29].

A major cell adhesion molecule for homophilic cell–cell adhesion of epithelial cells, E-cadherin, and its undercoat protein, *alpha*-catenin, are found in epithelial odontogenic tumors [30]. E-cadherin is responsible for epithelial cell polarity and the establishment of tissue morphology [31]. Catenins are adhesion molecules that are directly or indirectly associated with E-cadherin, forming a cadherin-catenin complex [32]. To clarify the possible role of cell adhesion molecules in local invasion of ameloblastoma, the expression of E-cadherin and α-catenin was studied by immunohistochemistry on 30 cases of ameloblastoma.

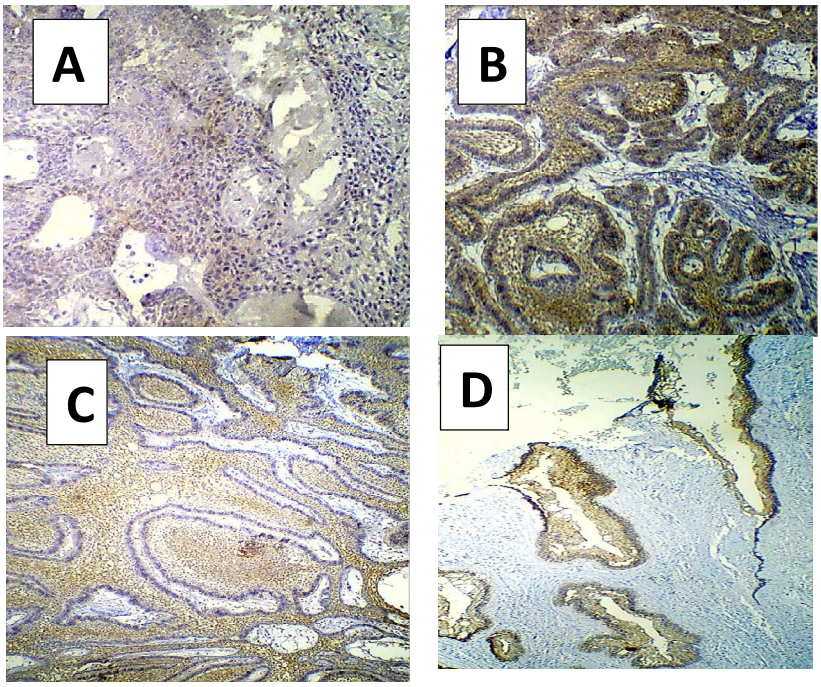

Fig. 3. α catenin expression; week in ameloblastic carcinoma (A), strong in follicular conventional type (B), plexiform conventional type (C) and mural unicystic histologic type (D) (ABC- DAB, x400)

Table 6. α-catenin expression in relation to size of tumor

			Tumor size		Asymp. Sig. (2-sided) Pearson Chi-Square
			less or equal to 2 Cm	Greate than 2 Cm	
alpha catenin expression	weak	Count	0	7	
		% within tumor size group	0.0%	50%	0.000
	moderate	Count	3	7	
		% within tumor size	18.8%	50.0%	
	strong	Count	13	0	
		within tumor size group	81.3%	0.0%	
Total		Count	16	14	
		% within tumor size	100.0%	100.0%	
		% of Total	53.3%	46.7%	

Table 7. α catenin expression in primary and recurrent tumors

			Incidence or recurrence		Total
			Primary tumor	Recurrent tumor	
α-catenin expression	Weak	Count	4	3	7
		% within incidence or recurrence	16.7%	50.0%	23.3%
		% of Total	13.3%	10.0%	23.3%
	Moderate	Count	7	3	10
		% within incidence or recurrence	29.2%	50.0%	33.3%
		% of Total	23.3%	10.0%	33.3%
	Strong	Count	13	0	13
		% within incidence or recurrence	54.2%	0.0%	43.3%
		% of Total	43.3%	0.0%	43.3%
Total		Count	24	6	30
		% within incidence or recurrence	100.0%	100.0%	100.0%
		% of Total	80.0%	20.0%	100.0%

	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	6.161	2	.046
Likelihood Ratio	8.246	2	.016
Linear-by-Linear Association	5.669	1	.017
N of Valid Cases	30		

Chi-Square Tests

In the present study, we noted that 6 of the studied cases showed weak E-cadherin expression. Normal expression and function of E-cadherin are essential for the induction and maintenance of the polarized and differentiated epithelium during embryo development [33]. Bolós et al. [34] reported that reduction of E-cadherin expression induces the detachment of the cells and the region of reduced of E-cadherin expression has been found to be related to cancer invasion. Also, Heymann et al. [35] reported that disturbances in the regulation and expression of E-cadherin can alter the mechanism of cell differentiation and trigger processes that result in tumor invasion [35].

Many studies had shown the relationship between the expression of E-cadherin and the occurrence, development, dedifferentiation, invasive growth, biological behavior and metastasis of oral tumors [36,37,38]. The E-cadherin mediated cell adhesion system is known to act as an “invasive suppressor system” [39] and the reduction of E-cadherin expression is associated with more aggressive epithelial tumors [40,41]. Down regulation in E-cadherin is mainly associated with parameters of higher biologic aggressiveness, increased invasiveness, metastases and tumor recurrence [42].

Some investigators explained the effect of reduced E-cadherin expression in the advancement and invasive biological behavior of Ameloblastoma [43,44,45]. Hakim et al. [46] suggested that decreased E-cadherin expression might explain the invasive growth of keratocystic odontogenic tumors (KOTs) [46], however, that evidence was not confirmed in other studies because most of KOT cases (>50%) showed preserved E-cadherin immunoexpression [47,48,49]. Also, Tanaka et al. [50], observed a significant relationship between reduced E-cadherin expression and invasiveness of oral squamous cell carcinomas.

Furthermore, there was a significant correlation between expression of E-cadherin-catenin complex and tumor differentiation as immunostaining for E-cadherin is more intense in well differentiated tumors and is lower in poorly differentiated tumors [51,42]. The maintenance of E-cadherin expression in well-differentiated tumors can be interpreted as the conservation of adhesion between tumor cells and the tissue architecture, which is associated with a better patient prognosis [26]. Some authors reported that benign tumors of an epithelial origin exhibit a pattern of E-cadherin expression that is similar to that seen in healthy tissue, suggesting the preservation of the function of this adhesion molecule after neoplastic transformation [9,47]. However, in poorly differentiated tumors, E-cadherin expression was diminished, which suggests a loss of adhesions between the tumor forming cells [26].

In our study, there was a highly significant difference in E-cadherin expression between ameloblastic carcinoma study group and the other benign forms of ameloblastoma indicating loss of differentiation in ameloblastic carcinoma. Additionally, [52,53] supported that reduced expression of E-cadherin is well associated with poor differentiation and a higher metastatic potential in oral squamous cell carcinoma. Conversely, [54,55] did not detect any significant association between degree of differentiation and E-cadherin expression in OSCC; however, they found that E-cadherin expression was reduced in tumors showing high invasiveness.
Another previous study suggested that reduction or loss of E-cadherin had an important role in the natural history of adenoid cystic carcinoma as it is associated with loss of differentiation [56]. Also, it was correlated with poorly differentiated or undifferentiated/anaplastic thyroid tumors and widely invasive growth [56].

Downregulation of E-cadherin had been observed in various human cancers. It had been proposed that reduced/ aberrant expression of E-cadherin is critical for the pathogenesis and biological behavior of certain thyroid carcinomas [57,58]. Another study reported that down-regulation of E-cadherin has been described in high-grade meningiomas and is associated with increased tumor cell proliferation and invasive ability of meningiomas [59]. In gastric carcinomas, mutations of the E- cadherin gene had been reported [60]. Stenner et al. [61] found that decreased expression of E-cadherin proposed to be an early event in human papilloma virus-related tumor progression.

Another notable finding in our study is the localization of E-cadherin expression , half of the examined cases demonstrated diffuse expression involving both central (stellate reticulum like cells) and peripheral cell layers, This finding is in agreement with other previous studies as Hao et al. [36], Florescu et al. [62] and Kumamoto et al. [30] who found that the immunoreactivity for E-cadherin was more obvious at the level of stellate-reticulum like cells,

and decreased in the peripheral columnar cells, as they are closer to the invasion front [9,62,63]. Some studies indicate that cells at invasive front can detach easily and changes in E-cadherin expression at this site can promote invasion and metastasis [64,65]. The other half of our examined cases demonstrated focal central expression in stellate reliculum like cells similar to what was observed by [66,47] suggesting that this neoplastic epithelial component preserves the characteristics of cyto-differentiation of the odontogenic epithelium. Our results investigated no significant differences regarding E-cadherin localization of expression between different histologic types of ameloblastoma. Conversely, Saito et al. [67] observed expression of E-cadherin in all parenchyma cells in the plexiform pattern but in the follicular pattern, the columnar cells expressed these adhesion molecules, but levels were decreased in stellate reliculum like cells (SRLC).These findings support that SRLC of the plexiform pattern had greater adhesive ability than those of the follicular one and the degree of cell differentiation might differ between the follicular and plexiform patterns.

On the other hand, we observed the expression of E-cadherin in the cytoplasm and the cell membrane in the studied cases similarly to the findings of Carreón et al. [68]. Cytoplasmic expression was suggested to be related to tumor differentiation [69].

In contrast, nuclear expression of E-cadherin was observed in cases of solid AM odontogenic carcinomas and in solid pseudo papillary tumor of the pancreas [37,70]. This nuclear staining correlate directly with increased cell proliferation and inversely with membranous staining [71].

With respect to the unicystic and solid ameloblastomas, we noticed a high significant differences in E-cadherin expression among varied histologic types. This result didn't agree with neither Mello et al. [47] nor Pereira et al. [37] as they found no difference in the E-cadherin expression between the unicystic and solid types. They illustrated that, as differences in the biological behavior of both types is determined by factors other than those directly associated with the expression of this molecule.

When comparing E-cadherin expression in primary and recurrent tumors, we noticed a high significant difference presented between the two groups. Our result is in line with a previous report by Carreón et al. [68]. This result could indicate that tumor invasion is related to alterations in cell-cell interactions, mediated by cell adhesion molecules [10].

We didn't find any association between clinical characteristics such as patient ages, gender and tumor site and the expression of E-cadherin. Previous reports on OSCC and thyroid carcinoma [72,54,73] already didn't find association with the age and gender. However, Fan et al. [74] reported that low E-cadherin expression was significantly associated with tumor location which was significantly decreased in the mucosa of oral cavity but not in tongue, mandibular, and posterior pharyngeal wall.

On the other hand, we observed a correlation between E-cadherin expression and tumor size as large sized tumors (>2 Cm) demonstrated downregulation in the expression. Our result is in agreement with previous studies as decreased E-cadherin expression occurred more frequently in tumors of larger size in OSCC, Adenoid cystic carcinoma and in gastric carcinoma [74,54,51]. conversely , in other studies there was no association between E-cadherin expression and tumor size [72,75,57] .

As catenins play a critical role in the regulation of cadherin-mediated adhesion, it was reported that normal expression of E-cadherin does not always imply the presence of a functionally normal cadherin-catenin complex [76]. Gofuku et al. [77] suggested that reduction of α-catenin is a more sensitive and useful indicator than reduction of E-cadherin. Thus, to predict tumor invasion and metastasis of carcinomas, it is useful to investigate not only the expression of E-cadherin but also the expression of α-catenin [76].

Our results revealed weak expression for α-catenin in 7 cases (23.3%) including (3 cases, 60% within the histologic type) of ameloblastic carcinoma, (3 cases, 25% within the histologic type) of follicular type and (1 cases, 12.5% within the histologic type) of unicystic variant. Vestweber et al. [78] suggested that α-catenin acts as a tumor suppressor. Thus, some studies reported that the loss of α-catenin expression might be associated with dedifferentiation, invasion and metastasis [26,79]. Reduced α-catenin expression impart invasive potential of ameloblastoma [7,45]. Further, α-catenin was involved in the metastasis of oral cancer [50] as the abnormal expression of *α*-catenin was

suggested to be valuable for diagnosis of metastasis in OSCCs [80]. In addition, there was a significant correlation between the expression of *α*-catenin and the presence of neck metastasis [50].

On the other hand, downregulation of *α*-catenin was observed in diffuse types of human cancers. α-catenin was identified by Fanjul et al. [81] as recurrently mutated in laryngeal squamous cell carcinoma patients. Also, abnormalities in α-catenin was relatively frequent and occur in both diffuse and intestinal carcinomas [82,83]. Additionally, Reduced staining was related to poor differentiation of both lung cancers and cervical carcinomas [71,84]. Nakanishi et al. [85] found high correlation between low α-catenin expression and poor prognosis in patients with esophageal squamous cell carcinomas.

Regarding the localization of α-catenin expression, Kumamoto et al. [30] noticed strong expression in central polyhedral cells and slightly in peripheral columnar cells in ameloblastomas resembling those of epithelial components in the tooth germ tissues, retaining cytodifferentiation of odontogenic epithelium [63]. In our study, we noticed half of the studied cases expressed α-catenin diffusely in central and peripheral cell layers of the tumor, the other half expressed α-catenin focally in the central cell layers and only one case focal peripheral (basal or columnar) cell layer expression. On the other hand, α-catenin expression was seen by Saito et al. [67] in all parenchymal cells of both follicular and plexiform patterns of ameloblastomas. We obtained similar results with no significant differences in localization of α-catenin expression among the different studied groups.

In the current work we noticed a high statistically significant differences in α-catenin expression between ameloblastic carcinoma and the other benign histologic variables of ameloblastoma. Moreover, there were high statistically significant differences in α-catenin expression between primary and recurrent tumors. According to the results of our study, these results agree with Tadbir et al. [45] as they observed rate of expression was lower in recurrent ameloblastomas and malignant amelobastomas, than conventional ameloblastomas.

According to our results, we revealed a high statistically significant difference in relation to tumor size which agree with Kozyraki et al. [86] who reported that alpha-catenin expression in hepatocellular carcinoma (HCC) correlated with large tumor size, conversely, findings of Tanaka et al. [50] in OSCC and Endo et al. [87] in HCC weren't compatible with previous data, illustrating that growth of the tumor may correlate not only with intercellular adhesion but also with other factors [50].

5. CONCLUSION

The present immunohistochemical study was carried out on thirty cases had the diagnosis of ameloblastoma of varied histologic types. E-cadherin and α catenin expressions were investigated in relation to different clinicopathologic variables. Both markers revealed weekend expression associated with large sized tumors, recurrent and malignant tumors. These findings proved the role of cell adhesion proteins E-cadherin and α catenin in tumor progression, invasion and acquisition of malignant behavior. E-cadherin and α catenin had vital participation in EMT process.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Our study was approved by the faculty ethics committee (approval number 03030320).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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