Evaluation of immunohistochemical expression of E-cadherin in pleomorphic adenoma and adenoid cystic carcinoma

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Abstract

Background: Pleomorphic adenoma (PA) and adenoid cystic carcinoma (ADCC) are benign and malignant salivary gland tumors, respectively, with distinct behavior. They have similar origins and cell components. E-cadherins are the main homophilic cell adhesion molecules, which play a central role in maintaining epithelial integrity, functioning in intercellular adhesion and differentiation. Hence, changes in E-cadherin function are reflected in the morphologic events associated with the cellular arrangement, movement and wound healing.

Aim: To study and compare the expression of E-cadherin immunostaining in PA and ADCC.

Materials and Methods: Fifteen cases of each PA and ADCC were immunohistochemically stained with E-cadherin. Five cases of normal salivary gland tissues were taken as the positive control. Mann–Whitney U-test was used for statistical analysis.

Results: About 86.6% of PA cases showed homogeneous staining. 66.6% of cases of ADCC showed heterogeneous staining. PA, cribriform and tubular patterns of ADCC predominantly showed moderate immune-staining and solid patterns of ADCC exhibited predominantly mild immunostaining. Depending on the intensity of staining, we found a significant P value between PA and the solid variant of ADCC.

Conclusion: E-cadherin proved to be a better marker for epithelial phenotypes in PAs. In ADCC difference in staining intensity between different histological subtypes suggests that further studies should be done to assess the usefulness of an immuno-marker to know the aggressive behavior of ADCC.

Keywords: Adenoid cystic carcinoma, E-cadherin, immunohistochemistry, pleomorphic adenoma

INTRODUCTION

Salivary glands are the most histo-pathologically heterogeneous group of tumors and have the greatest diversity of morphologic features among their cells and tissues.[1,2] Pleomorphic adenoma (PA) and adenoid cystic carcinoma (ADCC) are benign and malignant epithelial...
Immunohistochemical (IHC) expression of E-cadherin, has been studied in a variety of carcinomas of the head and neck. Its under expression or deficiency leading to changes in cell motility, intercellular adhesion and cell morphology, has been correlated to aggressive behavior, high proliferation, dedifferentiation, invasion, metastasis, and poor prognosis. Thus, it’s considered to have a tumor suppressor function. However, its expression in human epithelial salivary neoplasms have been little studied. Few studies exist pertaining to salivary gland tumors. Studies reported that loss of E-cadherin expression in relation to the progression from an ordered polarized ductular/glandular structure to a more malignant disorganized architecture. The present study aimed at studying in detail and comparing the expression of E-cadherin in two common salivary pathologies, i.e., PAs and ADCCs.

MATERIALS AND METHODS

In the present study, buffered formalin-fixed, paraffin-embedded tissues sections of 15 cases of PA and 15 cases of ADCC were evaluated for IHC E-cadherin expression. Super Sensitive™ Polymer-HRP IHC Detection system (Bio-Genex, India), Monoclonal anti-E-cadherin and Ethylenediamine tetracetic acid (EDTA) buffer were used in the study. Two to three serial sections of 4–5 μm thickness were taken on the slide, deparaffinized and rehydrated. Antigen retrieval was done in the microwave oven (EZ-Retriever® System v. 2) and IHC staining continued. Tissue sections of normal salivary glands were used as positive controls. TBS solution was used instead of the primary antibody as negative control. Immunoreactivity for E-cadherin was assessed by two observers independently using microscope (Olympus BX 51). The mean of two observers is taken for statistical analysis. The specimens were classified according to localization (membrane or cytoplasmic), distribution of staining (homogeneous, heterogeneous or isolated foci) and intensity of staining among the various cells and stromal patterns.

The staining intensity was classified as:

- 0 – Negative/absent (no staining)
- + – Mild but definite positive staining
- ++ – Moderate staining
- +++ – Intense staining

Statistical analysis

Significant differences in the overall intensity of E-cadherin expression in PAs and ADCCs were analyzed using Mann-Whitney U-test. P < 0.05 were considered statistically significant.

RESULTS

Distribution of cases

A total of 15 cases of PA and 15 cases of ADCC were included in the study. Five normal salivary gland tissues served as positive controls.

Expression of E-cadherin was evaluated for the presence or absence of staining, all the cases of PA, ADCC and normal salivary gland, showed the presence of staining. Further, positive cases were studied with respect to localization, distribution and intensity of staining in various cells and stromal patterns, in both PAs and ADCCs and their intensity graded as mild, moderate and intense.

Expression of E-cadherin in lesional tissue and control group:

Homogeneous immunostaining was observed in all the cases of normal salivary gland tissues, 86.6% of PA and only in 20% of ADCC cases. Heterogenous immunostaining was predominantly observed in ADCC (66.6%) and only 13.3% of PA cases. 13.3% of ADCC cases exhibited immunostaining in isolated focal areas [Table 1].

All five normal salivary gland specimens, all 15 cases of PAs and all 15 cases of ADCCs exhibited diffuse mild cytoplasmic immunostaining.
Among 5 cases of normal salivary tissue, serous acini depicted predominantly moderate intensity of staining, i.e., 03/05 cases (60%), followed by one case (20%) each in mild and intense staining categories. Mucous acini showed predominant mild staining intensity in 03/05 cases (60%) and 02/05 cases (40%) moderate intensity. Ducts showed predominantly intense staining intensity (03/05 cases [60%]) [Figure 1] followed by 02 cases (40%) in the moderate category.

In PA, histologically the cells are categorized into Cohesive and noncohesive cells.[37] Among cohesive cells in the tubulo-glandular area, inner/luminal/ductal cells predominantly showed (73%) intense immunostaining and nonluminal cells predominantly showed moderate (40%) and negative (40%) immunostaining [Figure 2]. Large ducts predominantly exhibit (75%) intense immunostaining. Among cohesive nonluminal cells, islands predominantly exhibit (45%) moderate immunostaining, strands (35%) and (45%) sheets predominantly exhibit negative immunostaining. Areas of squamous metaplasia predominantly exhibit intense immunostaining and plasmacytoid areas predominantly exhibit (63%) negative immunostaining. Within the stroma chondroid (75%) and myxoid areas (87%) predominantly exhibit negative immunostaining [Table 2]. Expression of E-cadherin in ADCC was evaluated in various histological variants which include tubular, cribriform and solid types. Tubular pattern predominantly exhibited mild (40%) and moderate (40%) immunostaining, cribriform pattern predominantly exhibited moderate immunostaining (74%) and mild-to-negative staining was observed in all the cases of solid variant (100%) Both hyalinized and fibro-cellular stroma exhibited negative immunostaining [Figure 3 and Table 3].

When the overall intensity of all the cases of PA was accessed, we observed predominantly moderate staining intensity (46.6%). In ADCC combined tubular and cribriform variant exhibited predominantly moderate immunostaining (60%) and mild staining in solid pattern (100%) [Table 4].

Statistical analysis performed using Mann–Whitney U-test comparing the E-Cadherin immunostaining intensities between PA and ADCC did not yield any significant P value, when all the histologic variants of ADCC was considered as a whole [Table 5] Statistical analysis of E-cadherin immuno-stained cases between PA and combined cribriform and tubular histological patterns of ADCC did not yield any significant P value [Table 6]. However, statistical analysis showed significant P = 0.01, when the comparison of E-cadherin immunostaining intensity was analyzed between PA and more malignant solid variant of ADCC [Table 7]. Similarly, statistical analysis of E-Cadherin between the histological variants, i.e., tubular and cribriform combined as one entity and solid variant as one entity, yield a significant P = 0.03 [Table 8].

DISCUSSION

Cell adhesion molecules (CAMs) participate in cell to cell and cell–matrix interactions. By coupling such interactions to intracellular signaling mechanisms, they play an important role in tissue morphogenesis, development, integrity and maintenance. Its alternative expression is however associated with pathogenesis and progression of benign

Table 1: Distribution of E-cadherin immunostaining in normal salivary glands and in positive cases of pleomorphic adenoma and adenoid cystic carcinoma

|                      | Total number of positive cases | HM (%) | HT (%) | IF (%) |
|----------------------|-------------------------------|--------|--------|--------|
| NSG                  | 5                             | 5 (100)| Nil    | Nil    |
| PA                   | 15                            | 13 (86.6) | 2 (13.3) | Nil    |
| ADCC                 | 15                            | 3 (20.0) | 10 (66.6) | 2 (13.3) |

HM: Homogeneous, HT: Heterogeneous, IF: Isolated foci, NSG: Normal salivary gland, PA: Pleomorphic adenoma, ADCC: Adenoid cystic carcinoma

Figure 1: (a) Photomicrograph showing moderate staining of E-cadherin in the striated duct, localized on the basolateral membrane of the normal salivary gland (immunohistochemical, x400). (b) Photomicrograph showing moderate staining of E-cadherin in serous acini, localized on the basolateral membrane of normal salivary gland (immunohistochemical, x400)

Figure 2: (a) Photomicrograph showing intense staining of E-cadherin in inner ductal cells and negative staining of outer cells in pleomorphic adenoma (immunohistochemical, x200). (b) Photomicrograph showing intense staining of E-cadherin in tubuloglandular area, moderate staining in sheets and negative staining in myxochondroid areas in pleomorphic adenoma (immunohistochemical, x50)
Loss of E-cadherin seems to be related to progression from an ordered polarized ductal/glandular architecture to a more malignant disorganized architecture especially in breast and colon tumors. However studies pertaining to salivary gland neoplasm concluded that the same does not appear to exist for salivary gland neoplasm in which the diversity of architectural patterns precludes detection of any simple relationship and that E-cadherin expression

and malignant neoplasms of various tissues. E-cadherin in adherens and desmoglein-2 (the main desmoglein expressed in salivary glands) in desmosomal junctions, beta-4 integrin in alpha6 beta4 laminin receptor of hemidesmosomes, HCAM (CD44s) associated with hyaluronan and ICAM-1 – member of Ig superfamily is implicated in normal tissue epithelial architecture and/ immune responses.

| Table 2: Total number and percentage distribution of cases reflecting the pattern and staining intensities of E-cadherin immunostaining in 15 cases of pleomorphic adenoma |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Various parenchymal and stromal patterns | Total number of positive cases | Mild (%) | Moderate (%) | Intense (%) | Negative (%) |
| Cohesive cells | Tubulo - glandular | 15 | | | |
| Inner cell | Nil | 4 (27) | 11 (73) | Nil |
| Outer cell | 3 (20) | 6 (40) | Nil | 6 (40) |
| Large ducts | 8 | 1 (13) | 1 (13) | 6 (75) | Nil |
| Islands | 11 | 2 (18) | 5 (46) | Nil | 4 (36) |
| Strands | 14 | 3 (22) | 5 (35) | Nil | 6 (43) |
| Sheets | 12 | 4 (33) | 3 (25) | Nil | 5 (41) |
| Squamous metaplasia | 11 | 2 (18) | 3 (27) | 6 (55) | Nil |
| Plasmacytoid | 8 | 3 (IF) (37) | Nil | Nil | 5 (63) |
| Noncohesive/stromal cells | Chondroid | 8 | 2 (IF) (25) | Nil | Nil | 6 (75) |
| Myxoid | 15 | 2 (IF) (13) | Nil | Nil | 13 (87) |
| Stroma | Hyalinized | 10 | | | 10 (100) |
| Myxoid | 15 | | | | 15 (100) |
| Chondroid | 8 | | | | 8 (100) |

IF: Isolated foci, NL: Nonluminal cells, L: Luminal cells

| Table 3: Total number and percentage distribution of cases reflecting the pattern and staining intensities of E-cadherin immunostaining in 15 cases of adenoid cystic carcinoma |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Histological patterns in adenoid cystic carcinoma | Total number of positive cases | Mild (%) | Moderate (%) | Intense (%) | Negative (%) |
| Parenchymal patterns | Tubular | 10 | 1 (10) | 4 (40) | 4 (40) | 1 (10) |
| Cribriform | 15 | 2 (13) | 11 (74) | 2 (13) | Nil |
| Solid | 5 | 5 (100) | Nil | Nil | Nil |
| Stromal patterns | Fibro cellular | 15 | | | 15 (100) |
| Hyalinized | 15 | | | | 15 (100) |

Table 4: Distribution of cases based on the intensity of immuno-staining in pleomorphic adenoma cases and adenoid cystic carcinoma cases

| Table 5: Comparison of the intensity of E-cadherin immunostaining between pleomorphic adenoma (PA) and adenoid cystic carcinoma using Mann-Whitney U-test |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Tumors | Sum of ranks | Mann-Whitney U-value | Z | P | Significance |
| Benign | 249 | 96.0 | -0.734 | 0.463 | Not significant |
| Malignant | 216 | | | | |

Figure 3: (a) Photomicrograph showing intense staining of E-cadherin in the cribriform pattern of adenoid cystic carcinoma (immunohistochemical, ×200). (b) Photomicrograph showing mild-to-negative staining of E-cadherin in the solid pattern of adenoid cystic carcinoma (immunohistochemical, ×100)
should be studied in detail to know its importance in diagnosis or prognosis of salivary neoplasm in general. Only a limited number of researchers have focussed in the role of CAMs in salivary gland architecture and their neoplasm with conflicting results.\cite{22}

PA, the commonest salivary gland tumor is noted for its cytologic and histomorphological variations. Histomorphologically, the cells (both inner/luminal/ductal and outer/nonluminal) of tubulo-glandular areas and nonluminal cells of islands, sheets and strands remained cohesive or loosely cohesive and were grouped under the category of “cohesive cells.” Some of the nonluminal cells were widely separated amidst lots of stroma and these were grouped under the category of “non-cohesive cells.” Since squamous metaplastic cells and plasmacytoid cells also remained cohesive they were also grouped under “cohesive cells.” Thus, the cells in the parenchymal areas were considered as cohesive cells as they were grouped/linked together. Whereas the cells in the stromal areas were considered as noncohesive cells as they were separated from each other.\cite{27} Thus, its an admixture of epithelial and myoepithelial cells consisting of gland-like structures, ducts, sheets, cell nests, cords, spindle and plasmacytoid cells and mesenchymal-like chondromyxoid tissue. ADCC is an uncommon malignant salivary gland tumor, most commonly involving the minor salivary glands. It is characterized by locally invasive growth and has affinity for perineural and perivascular invasion. It exhibits a high tendency of local recurrence and metastasis to distant site.\cite{38} Ko et al. in their study observed that patients with solid histological patterns showed a significant ($P = 0.026$) correlation with local recurrence compared to distant metastasis.\cite{39}

**Expression of E-Cadherin in normal salivary gland tissues**

E-cadherin expression was noted in all five samples of normal salivary gland tissues and homogeneously, immuno-localized to the cell membranes. The baso-lateral membranes showed a more distinct staining which was in accordance with Furuse et al.\cite{26} The serous acini displayed predominantly moderate intensity of staining, i.e., 03/05 cases (60%), followed by one case (20%) each in mild and intense staining categories. On the contrary mucous acini showed predominant mild and moderate staining intensity in 03/05 cases (60%) and 02/05 cases (40%) respectively. Moderate intensity of staining was noted in the emptied serous acini compared to mild or absent staining in acinar cells with abundant cytoplasm and secretory granule which was similar to that of Furuse et al.\cite{26} Both the striated and excretory ducts showed predominant intense staining intensity 03/05 cases (60%) followed by 02 cases (40%) in mild category which was similar to Shibuya et al. and Ekarat study.\cite{59,64} In Sudeendra prabhu et al.'s observation only intense staining in normal salivary gland epithelium was reported without any details.\cite{25} All the myoepithelial cells were immuno-stained in Shibuya et al.’s study,\cite{16} contrary to our’s and that of Economopoulou et al.’s\cite{28} observation.

**Expression of E-cadherin in pleomorphic adenoma**

All 15 cases of PAs showed positive E-cadherin immuno-staining with the immune-stain localized to the membranes (especially the basolateral surfaces).\cite{22,23} Two cases also displayed diffuse mild cytoplasmic immuno-staining which was not reported earlier and probably could be due to methodological error. However cytoplasmic expression of E-cadherin was reported in the cytoplasm of thyroid cells according to Mitselou et al.’s study.\cite{41} Majority of our cases 07 (46.6%) showed moderate, followed by intense and mild staining (04, 26.6% each) which was in contrast to intense staining (05/10, 50%) followed by moderate (03/10, 30%) and mild staining (02/10, 20%) in Sudeendra et al.’s study. However, the differences were not by large.\cite{25}

**Expression of E-cadherin in adenoid cystic carcinoma**

In ADCC all 15 (100%) cases of ADCC’s displayed positive E-cadherin immunostaining, closer to the observation of positive staining in 21/24 (87.5%) cases in Prabhu et al.’s study\cite{24} and in contrast to the finding of only (37/60) 62% positivity Zhang et al.\cite{31} The immuno-stain was localized predominantly to the basolateral membranes similar to the findings of Economopoulou et al., Furuse et al., Shibuya et al.’s study (plasma membranes at interdigitations).\cite{23,24,40}

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**Table 6: Comparison of the intensity of E-Cadherin immunostaining between benign pleomorphic adenoma and malignant combined predominantly cribriform and tubular variants of adenoid cystic carcinoma by Mann-Whitney U-test**

| Tumors                              | Sum of ranks | Mann-Whitney U-value | Z   | P       | Significance |
|-------------------------------------|--------------|----------------------|-----|---------|--------------|
| Pleomorphic adenoma                 | 184          | 64.0                 | −0.669 | 0.503   | Not significant |
| Combined predominantly cribriform and tubular | 141          |                      |     |         |              |

**Table 7: Comparison of the intensity of E-cadherin immunostaining between benign pleomorphic adenoma and the malignant solid variant of adenoid cystic carcinoma**

| Tumors                              | Sum of ranks | Mann-Whitney U-value | Z   | P       | Significance |
|-------------------------------------|--------------|----------------------|-----|---------|--------------|
| Pleomorphic adenoma                 | 185.0        | 10                   | −2.588 | 0.01   | Significant  |
| Solid variant                       | 25.0         |                      |     |         |              |
Table 8: Comparison of the intensity of E-cadherin immunostaining between combined predominantly cribriform and tubular variant and the solid variant of adenoid cystic carcinoma

| Tumors                                      | Sum of ranks | Mann-Whitney U-value | Z    | P     | Significance |
|---------------------------------------------|--------------|----------------------|------|-------|--------------|
| Combined predominantly cribriform and tubular | 102.5        | 2.5                  | −2.958 | 0.003 | Significant |
| Solid variant                               | 17.5         |                      |      |       |              |

Majority showed moderate and mild intensity (12/15) followed by intense (03/15) in contrast to Prabhu et al.'s observation of majority (10/24) in intense followed by 4/24 in moderate and 07/24 in mild. This could be attributed to the varying proportions of the histological patterns as solid areas stain mild or negative as seen in our cases and that of Prabhu et al.'s, Zhang et al.'s and Franchi et al.'s [25,27,31] observations or conflicting as in Daa et al.'s observation. [30]

In predominantly combined cribriform and tubular variants (10 cases), majority, i.e., six (06) showed moderate, three (03) showed intensely and one (01) showed mild staining. In predominantly solid pattern all five (05) cases showed mild staining. Studies on ADCCs have grouped the total number of cases based on the intensity of staining but have not done the same with respect to each histologic variant of ADCCs though they have discussed about the variations in the intensity of staining. Hence, no comparisons could be made in each histologic variant.

In our study, we couldn't find statistical significance of staining intensities between PA and ADCC (all histological patterns combined). Our results were similar to the findings of Prabhu et al.'s [25] Similarly, we couldn’t find any statistical significance when only combined cribriform and tubular variants of ADCC were compared with PA. However, a P = 0.01 was noticed on comparing PAs with the solid variant of ADCCs and a P = 0.03 was noticed on comparing within the histologic variants of ADCCs. This clearly showed that E-cadherin expression got downregulated in the solid variant of ADCCs similar to the observations of Franchi et al.'s [27] who also correlated the downregulation of E-Cadherin staining with the histological grade of the tumor. However, in contrast Wu et al.'s study the expression of combined E-cadherin catenin complex was found not to correlate with the histological grade of the tumor. [28] Thus, its better to classify the ADCCs based on the predominant variant and then to assess the statistical significance as it’s a known fact that the solid type is more malignant with more potential for recurrence and metastases and is associated with poor prognosis.

SUMMARY AND CONCLUSION

In the present study, IHC expression of E-cadherin between PAs and ADCCs (all the variants combined) did not show any statistical significance. When the comparison is done considering all the histological subtypes of ADCCs individually, we observed a significant loss of E-cadherin expression in solid growth pattern. It helps to correlate decreased E-cadherin expression along with the decrease in cellular differentiation and thus signifies its role in the complex mechanism of progression of salivary gland pathologies. Hence, all future studies aiming to assess the usefulness of an immuno-marker should aim at classifying the ADCCs depending on the predominant histologic pattern.

Financial support and sponsorship
Self-supported.

Conflicts of interest
There are no conflicts of interest.

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