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ORIGINAL ARTICLE

Adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma of minor salivary glands: a comparative immunohistochemical study using the epithelial membrane and carcinoembryonic antibodies

A Epivatianos[1], S Iordanides[2], T Zaraboukas[3], D Antoniades[1]

Departments of [1]Oral Medicine and Oral Pathology, [2]Oral and Maxillofacial Surgery, [3]Histopathology, University of Thessaloniki, Thessaloniki, Greece

OBJECTIVE: The purpose of this study was to investigate immunohistochemically the expression of epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) in adenoid cystic carcinoma (AdCC) and polymorphous low-grade adenocarcinoma (PLGA) in an attempt to assess the ability of these markers to distinguish AdCC from PLGA when the histological features on routine hematoxylin and eosin are equivocal.

MATERIALS AND METHODS: Fourteen specimens of AdCC, 10 PLGA, and five normal minor salivary glands fixed in 10% formalin and embedded in paraffin, were retrieved from the files of our department and were retrospectively studied with the streptavidin-biotin complex method using the epithelial membrane and carcinoembryonic antibodies.

RESULTS: The immunoreactivities and the expression patterns of EMA and CEA in AdCC and PLGA were similar.

CONCLUSIONS: The results of this study suggest that the immunostaining of AdCC and PLGA with EMA and CEA could not offer an adjunctive aid in differential diagnosis between these two tumors.

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Keywords: adenoid cystic carcinoma; polymorphous low-grade adenocarcinoma; epithelial membrane antigen; carcinoembryonic antigen; salivary gland tumors

Introduction

Adenoid cystic carcinoma (AdCC) and polymorphous low grade-adenocarcinoma are distinct types of adenocarcinoma. AdCC occurs in minor and major salivary glands (Spiro *et al*, 1974; Perzin *et al*, 1978; Cowie and Pointon, 1984; Tomich, 1991). The tumor has a slow but relentlessly malignant natural coarse which is marked by a high incidence of local recurrence and distant metastases. The local recurrence rates vary widely from 16 to 67% (Spiro *et al*, 1974; Cowie and Pointon, 1984; Hickman *et al*, 1984; Matsuba *et al*, 1984; Nascimento *et al*, 1986) and the distant metastases from 25 to 54% and increases with time since the initial treatment lengthens (Luna, 2001).

Polymorphous low-grade adenocarcinoma (PLGA) occurs more frequently in minor salivary glands (Evans and Batsakis, 1984; Wenig and Gnepp, 1991; Vincent *et al*, 1994) and rarely as a primary neoplasm in major salivary glands (Pitland *et al*, 1993). It tends to be a low-grade malignancy with recurrences recorded up to 10 years after treatment (Merchant *et al*, 1996). The local recurrence rates vary from 10.3 to 17% (Vincent *et al*, 1994; Castle *et al*, 1999) and the distant metastases are very rare (0.6%) (Castle *et al*, 1999).

The overlapping histological features of AdCC and PLGA occasionally may result in a diagnostic pitfall (Wenig and Gnepp, 1991) and especially when small biopsies do not contribute to distinguish between these tumors (Darling *et al*, 2002). In these cases immunohistochemistry may be necessary or desirable to suggest or confirm a diagnosis (Regezi *et al*, 1991).

Gnepp *et al* (1988) studied immunohistochemically four cases of PLGA and based on their results as well as on the results of a similar study of AdCC (Chen *et al*, 1988) suggested that the detection of epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) may assist to distinguish AdCC from PLGA. Because the number of examined cases of PLGA was small further studies were suggested to confirm this possibility (Gnepp *et al*, 1988, 2001). Before and after the suggestion of Gnepp *et al* (1988) some studies (Gusterson *et al*, 1982; Caselitz *et al*, 1986; Azumi and

Correspondence: A Epivatianos, Associate Professor, Department of Oral Medicine and Oral Pathology, School of Dentistry, University of Thessaloniki, Thessaloniki 54124, Greece. Tel: 0030 + 2310 + 999521; Fax: 0030 + 2310 + 999532; E-mail: aepivati@dent.auth.gr
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Battifora, 1987; Anderson *et al*, 1990; Miliauskas, 1991; Simpson *et al*, 1991; Perez-Ordonez *et al*, 1998) demonstrated variable results without examining this possibility thoroughly.

The aim of the present study was to examine the expression patterns and immunoreactivity of a sufficient number of AdCC and PLGA to EMA and CEA with the specific goal of assessing the ability of these markers in distinguish AdCC from PLGA. Use of these tumor markers in distinguish the two lesions can prove to be useful when the histological features on routine hematoxylin and eosin (H & E) are equivocal or less than classic.

Material and methods

Fourteen cases of AdCC and 10 cases of PLGA routinely processed, formalin-fixed, paraffin-embedded samples were retieved from the files of the Pathology Laboratory of the Department of Oral Medicine and Oral Pathology at the Dental School of the University of Thessaloniki. New sections were cut and stained with H & E and were reviewed for adequacy of tissue to study and for agreement with the original diagnosis by using previously established criteria (Tauxe *et al*, 1962; Batsakis *et al*, 1983; Freedman and Lumerman, 1983). All tumors were localized in the oral cavity. Five normal minor salivary glands which were obtained from random biopsies or from non-neoplastic lesions were additionally used.

The streptavidin-biotin complex (Strept ABC) method was performed for the detection of EMA and CEA (Hsu *et al*, 1981). Four-micron sections were mounted on poly-L-lysine-coated slides, dewaxed and dehydrated. Endogenous peroxidase activity was quenched with 3% H_2O_2 for 10 min at room temperature. For the detection of EMA slides were preheated in a microwave oven for 70 s on high power and then incubated with antigen retrieval solution, 10 mM citrate buffer (pH 6), at room temperature for 60 min. After rinsing with phosphate-buffered saline (PBS), further blocking was accomplished utilizing normal goat serum at a 1:20 dilution for 20 min. Monoclonal rabbit anti-EMA (Novocastra, Newcastle upon Tyne, UK) was used at a 1:70 dilution. Incubation of the primary antibody was performed for 30 min at room temperature. Tissue sections incubated for the same time with normal rabbit serum served as negative controls. Sections from a colon adenocarcinoma were used as positive controls. After being washed with PBS, the slides were incubated with biotinylated goat anti-rabbit prediluted secondary antibody for 30 min at room temperature, washed by PBS, followed by the peroxidase-conjugated streptavidin for 30 min at room temperature and developed by diaminobenzidine reaction.

For the detection of CEA, slides were treated with 0.05% protease I (Sigma, St Louis, MO, USA) in a 0.1 M phosphate buffer at a pH 7.8 at 37°C for 10 min for antigen retrieval. After rinsing with PBS, further blocking was accomplished utilizing normal swine serum at a 1:5 dilution for 10 min at room temperature. Polyclonal rabbit anti-CEA (Dako, Glostrup, Denmark) was used at a 1:400 dilution for 30 min at room temperature. Tissue sections incubated for the same time with normal rabbit serum served as negative controls. Sections from a colon adenocarcinoma were used as positive controls. After being washed with PBS, the slides were incubated with biotinylated swine anti-rabbit secondary antibody at a dilution 1:200 for 30 min at room temperature, washed by PBS, followed by the peroxidase-conjugated streptavidin for 30 min at room temperature and developed by diaminobenzidine reaction. Slides from both detection procedures of EMA and CEA were counterstained with aqueous hematoxylin, rinsed in tap water and mounted in Soupermount (Biogenex, San Ramon, CA, USA).

The staining patterns were classified as luminal when the staining was present in the luminal border of acinar, ductal and tubular structures, as diffuse when part or whole the cytoplasm was uniformally stained and as granular when tiny dark granules were present in the cytoplasm. The staining intensity was assessed using the following brief evaluation: weak, moderate and strong. The sum of the staining intensity was used for the total immunoreactivity. The evaluation of immunoreactivity was performed after a slight modification of a previously reported method (Regezi *et al*, 1991). The evaluation of immunoreactivity was performed as follows: 500 cells from five fields of each slide were enumerated as the percentage of reactive cells. The percentage of reactive luminal and non-luminal tumor cells was also evaluated. Sections were examined by two of the authors (EA and ZT) independently of each other. The slides were then reviewed by the examiners as a group and after discussion uniform agreement was reached. The correlated *t*-test and one-way ANOVA test were applied to the values of immunoreactivity and statistical significance was determined at $P < 0.01$.

Results

Available clinical information on cases used in this study is presented in Table 1. Classical histopathologic features of AdCC and PLGA are illustrated in Figures 1–3.

In our investigation all cases of AdCC demonstrated a tumor mass that was unencapsulated and peripherally infiltrative. The tubular, cribriform and solid

Table 1 Clinical data

	AdCC (N = 14)	*PLGA (N = 10)*
Sex		
Men	8	4
Women	6	6
Age range	30–81	37–79
Location		
Palate	9	7
Buccal mucosa	3	1
Labial mucosa	2	–
Upper lip	–	2

AdCC, adenoid cystic carcinoma; PLGA, polymorphous low-grade adenocarcinoma.

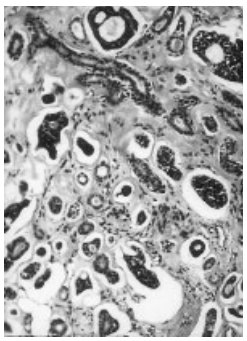

Figure 1 Adenoid cystic carcinoma with cribriform, tubular and solid histologic patterns. H & E. Original magnification ×33

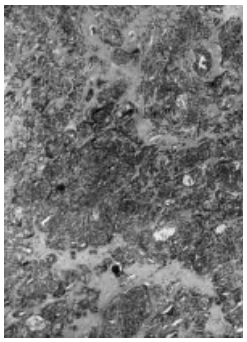

Figure 2 Polymorphous low-grade adenocarcinoma with solid, tubular and ductal histologic patterns. H & E. Original magnification ×13

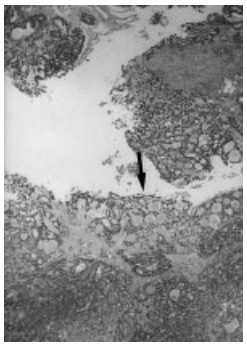

Figure 3 Polymorphous low-grade adenocarcinoma with solid and tubular histologic patterns. In an area (arrow) the eosinophilic hyalinized stroma produces a cribriform appearance. H & E. Original magnification ×13

patterns in variable proportions were present in each of our cases. Tumor cells were small and cuboidal with oval basophilic nuclei and little cytoplasm. Mitoses were infrequent and foci of necrosis in solid areas of the tumor were not observed. The stroma was collagenous and hyaline.

All cases of PLGA demonstrated a tumor mass that was unencapsulated, partially circumscribed and peripherally infiltrative. The most common patterns were solid and tubular in variable combination. A cribriform pattern was detected in three of 10 cases. Two cases contained a few areas with papillary configuration and two cases foci of mucous cells. Tumor cells were uniform

Table 2 Immunoreactivity for EMA and CEA

Tumor	*Marker*	*No. of positive cases*	*Immunoreactivity*
AdCC	EMA	14/14	21.2 ± 12.2
	CEA	14/14	24.2 ± 11.1
PLGA	EMA	8/10	20.7 ± 9.4
	CEA	9/10	20.2 ± 8.5

AdCC, adenoid cystic carcinoma; PLGA, polymorphous low-grade adenocarcinoma; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen.
Immunoreactivity is expressed in mean ± s.d.

Table 3 Immunoreactivity for EMA and CEA in luminal and non-luminal tumor cells

Tumor	*Marker*	*Luminal cells*	*Non-luminal cells*
AdCC	EMA	18.5 ± 7.4	2.7 ± 3.1
	CEA	22.1 ± 8.1	2.1 ± 2.8
PLGA	EMA	18.6 ± 5.1	2.1 ± 2.3
	CEA	18.3 ± 6.8	1.9 ± 1.6

AdCC, adenoid cystic carcinoma; PLGA, polymorphous low-grade adenocarcinoma; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen.
Immunoreactivity is expressed in mean ± s.d.

in size and shape with scant cytoplasm and absent of mitotic figures. The stroma was hyaline (six of 10), mucohyaline (five of 10) and fibrovascular (four of 10).

Epithelial membrane antigen and CEA stained all five normal minor salivary glands. Expression of EMA was observed in the luminal border and luminal cells of intercalated and excretory ducts. The mean ± s.d. of immunoreactivity was 21.5 ± 18.1. The mucous acinar and luminal cells of intercalated and excretory ducts expressed CEA. The luminal border of acini, intercalated and excretory ducts were also immunoreactive. The mean ± s.d. of immunoreactivity was 82.5 ± 49. The staining pattern was diffuse and granular. The immunoreactivity for EMA and CEA in AdCC and PLGA is presented in Tables 2 and 3.

In AdCC expression of EMA was observed in the luminal cells of tubular and ductal structures and sometimes in non-luminal cells. The luminal border of these structures and their secreted content were also positive. In the cribriform pattern the lining cells of pseudocysts did not stain. The luminal border, the luminal content and the luminal cells of small ducts which were present in cribriform areas expressed EMA. Approximately 2% of proper tumor cells of the cribriform and solid pattern were reactive. The staining pattern was diffuse and granular (Figure 4). The expression pattern of CEA was similar to that of EMA. The luminal border of most tubular and ductal structures of AdCC was positive for both EMA and CEA (Figure 5). Approximately 2% of proper tumor cells of the cribriform and solid pattern were reactive. The mean ± s.d. of immunoreactivity for CEA was similar to that of EMA. Compared with immunoreactivity of EMA, the difference was not statistically significant.

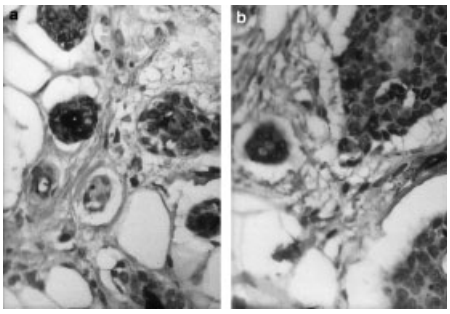

Figure 4 Epithelial membrane antigen (EMA) staining in adenoid cystic carcinoma. (**a**) Expression of EMA in luminal border, luminal and non-luminal cells of tubular and small ductal structures. (**b**) Occasional proper tumor cells in cribriform structures express EMA (arrows). Strept ABC method. Counterstain with hematoxylin. Original magnification ×132

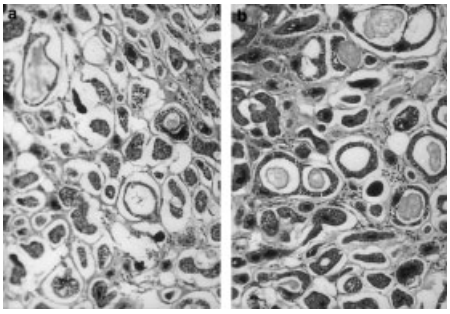

Figure 5 (**a**) Epithelial membrane antigen (EMA) staining. (**b**) carcinoembryonic antigen (CEA) staining. The expression pattern of EMA and CEA in adenoid cystic carcinoma is similar. The luminal border and content of most tubular and ductal structures are stained with the two markers. Strept ABC method. Counterstain with hematoxylin. Original magnification ×132

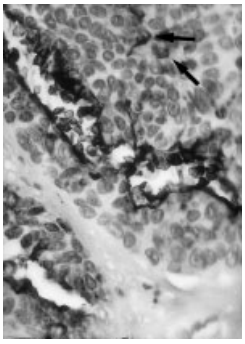

Figure 6 On the left side of the figure the luminal border and the luminal and non-luminal cells of tubular structures of polymorphous low-grade adenocarcinoma express epithelial membrane antigen (EMA). On the right side a part of solid nodule contains a narrow elongated lumen of which the luminal border and luminal and non-luminal cells are positive. Scattered proper tumor cells express EMA also (arrows). Strept ABC method. Counterstain with hematoxylin. Original magnification ×132

In PLGA expression of EMA was observed in the luminal cells of tubular and ductal structures and many times in the non-luminal cells. The luminal border of these structures and their luminal content many times were positive. In solid areas of the tumor, the luminal

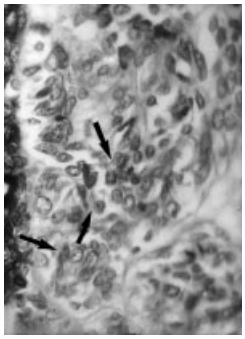

Figure 7 On the center and right of the figure a part of solid nodule contains a narrow elliptical lumen which the luminal border and luminal and non-luminal cells express carcinoembryonic antigen (CEA). Scattered proper tumor cells express CEA also (arrows). Strept ABC method. Counterstain with hematoxylin. Original magnification ×132

border and the luminal and non-luminal cells of multiple round, elliptical or narrow elongated lumens were often positive. Approximately 2% of proper tumor cells in cribriform and solid areas expressed EMA. Spindle cells arranged in a fascicular pattern were focally positive (2%). The staining pattern was diffuse and granular (Figure 6).

The expression and staining patterns for CEA was similar to that of EMA (Figure 7). The mean ± s.d. of immunoreactivity for CEA was similar to that of EMA. Compared with immunoreactivity of EMA, the difference was not statistically significant. In terms of the immunoreactivity of EMA and CEA among the two tumors, statistically no significant difference was found.

Discussion

Immunohistochemistry has been used to elucidate the origin and the differentiation of the cells of salivary gland tumors and sometimes as an adjunctive aid in differentiation one neoplasm from another. Therefore, several groups of tumor markers, including EMA and CEA, have been used to study AdCC and PLGA. In the majority of these previous studies (Azumi and Battifora, 1987; Anderson *et al*, 1990; Miliauskas, 1991; Simpson *et al*, 1991; Perez-Ordonez *et al*, 1998) except those of Chen *et al* (1988), Gnepp *et al* (1988) and Caselitz *et al* (1986), the immunoreactivity and the expression patterns of EMA and CEA have not been thoroughly examined needing further clarification to elucidate if their use could aid in differential diagnosis between AdCC and PLGA.

Gusterson *et al* (1982) referred positive staining for EMA in the luminal membranes and luminal content of true ductal structures in the cribriform and solid patterns of AdCC. Caselitz *et al* (1986) found positive staining for EMA and CEA in the luminal cells and luminal material of tubular and ductal structures present in cribriform and solid patterns of AdCC, positive staining for EMA in the luminal cells of the tubular pattern of the tumor but focal staining for CEA in the same pattern. Although their results partly agree with

Table 4 Presentative comparison of our results with previous reports

Author/tumor	*Marker*	*Immunoreactivity %*
Caselitz *et al* (1986)/AdCC	EMA	60
	CEA	32
Gnepp *et al* (1988)/PLGA	EMA	>93
	CEA	<35
Present study		
AdCC	EMA	21.2
	CEA	24.2
PLGA	EMA	20.7
	CEA	18.9

AdCC, adenoid cystic carcinoma; PLGA, polymorphous low-grade adenocarcinoma; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen.

the expression patterns observed in the present study, they evaluated a total 60% of immunoreactive tumor cells for EMA and 32% for CEA. The above-reported immunoreactivities are not in agreement with our results (Table 4). Azumi and Battifora (1987) found positive staining for EMA in the luminal border of duct-like structures present in the cribriform pattern of AdCC and negative staining in the solid pattern. Chen *et al* (1988) reported similar expression patterns for both EMA and CEA in AdCC but did not find positive staining in non-luminal cells of ductal structures and expression in proper tumor cells of the solid pattern, which were observed in the present study. Simpson *et al* (1991) referred focal and weak membranous positivity of the cells lining the lumina of ductal structures of AdCC.

With regard to PLGA, Gnepp *et al* (1988) reported expression of EMA in all cell types of the tumor, consistent with our results. They reported immunoreactivity for EMA and CEA which differ from our results (Table 4). Also diversity exists with the expression patterns of CEA. They did not find expression of CEA in non-luminal cells of tubular and ductular structures of the tumor. This finding probably led them to suggest that the dissimilar expression patterns of EMA and CEA in comparison with the similar expression patterns of these markers in AdCC (Chen *et al*, 1988) could aid in the differential diagnosis of these two tumors.

Negative results for CEA in PLGA were reported by Anderson *et al* (1990) and Perez-Ordonez *et al* (1998) and lack of expression of EMA and CEA in non-luminal cells of tubular and ductal structures in other studies (Miliauskas, 1991; Simpson *et al*, 1991; Perez-Ordonez *et al*, 1998). Simpson *et al* (1991) noticed that the staining of CEA in AdCC and PLGA was not sufficiently dissimilar to be of practical value. The differences between our results with those reported in the literature may be due to a different mode of evaluation and immunohistochemical procedures. The limits of an immunohistochemical assay vary upon factors such as the concentration of the primary and secondary antibodies, the length of incubation with such antibodies and the sensitivity of the enzymatic reaction.

Conclusively from all above-mentioned previous studies it seems that there is positive expression of EMA and CEA in AdCC and positive of EMA but variable of CEA in PLGA. This conclusion is consistent with the results of a recent report (Darling *et al*, 2002). The authors of this report reviewed all previous immunohistochemical studies in AdCC and PLGA where several markers were utilized, including EMA and CEA, and reported results consistent with our conclusion.

To our knowledge another direct comparative study of the immunoreactivity and expression patterns of EMA and CEA in AdCC and PLGA has not been reported in the literature except of that of Gnepp *et al* (1988). The equal immunoreactivities for both EMA and CEA in AdCC and PLGA that were found in the present study allow as to suggest that these tumor markers could not offer an adjunctive aid in the differential diagnosis between these two tumors. Moreover, a distinct different expression pattern for EMA and CEA was not observed. This finding could further suggest that neither the expression patterns of these tumor markers could aid in the differential diagnosis of AdCC from PLGA.

Conclusions

The results of this study suggest that the immunostaining of AdCC and PLGA with EMA and CEA could not offer an adjunctive aid in the differential diagnosis between these two tumors.

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