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Original article

Diagnostic Utility of CD10 and S100 in Salivary Gland Tumors with Myoepithelial Differentiation: A Comparative Immunohistochemical Study

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Abstract

Myoepithelial differentiation is an important diagnostic feature of several salivary gland tumors and may pose a diagnostic challenge because of the considerable morphological overlap among different neoplasms. CD10 is a cell-surface metalloprotease expressed in various normal and neoplastic tissues, but its diagnostic utility in salivary gland tumors with myoepithelial differentiation remains incompletely defined. S100 is widely used as an established marker of myoepithelial differentiation; however, its expression is not entirely specific. This study aimed to evaluate the immunohistochemical expression of CD10 in various salivary gland tumors with myoepithelial differentiation and to compare its expression pattern with that of S100. The expression of CD10 and S100 was evaluated on sixty-three archival paraffin blocks of salivary gland tumors, including 22 cases of PA, 19 cases of AdCC, 13 cases of EMC, and 9 cases of MC, using immunohistochemical staining with streptavidin peroxidase. The immunopositivity of CD10 was detected in all studied cases of EMC, whereas the other current cases of PA, AdCC, and MC demonstrated a negative reaction. The mean value of CD10 area percentage in EMC was (21.8 ± 8.3). On the other hand, S100 immunoreactivity was detected in all PA, EMC, and MC cases and in 63.2% of the AdCC cases. The mean value of S100 area percentage was highest in EMC (52.2 ± 1.3) and lowest in AdCC (21.1 ± 5.1). A statistically significant difference in S100 area percentage was observed among the tumor groups ($p < 0.001$). The findings suggest that CD10 may serve as a useful adjunctive biomarker for discriminating epithelial-myoepithelial carcinoma (EMC) from other salivary gland neoplasms with myoepithelial cell differentiation. Furthermore, it is worth considering that S100 should be interpreted as a supportive marker of myoepithelial differentiation to improve diagnostic accuracy in reaching a final diagnosis.

Introduction

Tumors of the salivary glands are among the most challenging lesions in surgical pathology, due to their exceptional morphological diversity and the continual identification of new tumor forms in recent years. One of the major complicating factors is the presence of myoepithelial cells which exhibit properties of both epithelial and smooth muscle cells.

These cells frequently participate in the development of salivary gland neoplasms arising from the intercalated ducts and may exhibit varying degrees of differentiation. Tumors showing myoepithelial differentiation include benign lesions such as pleomorphic adenoma, myoepithelioma, and basal cell adenoma, as well as malignant neoplasms including carcinoma ex pleomorphic adenoma, myoepithelial carcinoma, epithelial–myoepithelial carcinoma, basal cell adenocarcinoma, and adenoid cystic carcinoma. Interestingly, many salivary gland malignancies with a myoepithelial component tend to behave as low-grade tumors and generally demonstrate less aggressive clinical behavior compared with tumors lacking myoepithelial differentiation. Therefore, the identification of these cells by immunohistochemical markers is important for diagnosis and tumor categorization [1].

S100 protein is the most often utilized marker in this setting and is regarded as a useful supportive marker for myoepithelial differentiation. It is a member of a family of calcium-binding proteins involved in several cellular processes including tumor growth and progression. S100 is expressed in myoepithelial cells, serous acinar cells and nerve tissue of normal salivary gland tissue and is a useful diagnostic aid in salivary gland pathology [2].

On the other hand, CD10 is a 90–110 kDa zinc-associated cell surface metalloprotease that enzymatically degrades numerous peptide substrates, modulating their activity and restricting their availability to interact with receptors and downstream signaling pathways. CD10 has been widely studied in hematological malignancies, lymphomas, renal cell carcinoma, cutaneous squamous cell carcinoma, endometrial stromal tumors, and breast neoplasms [3]. However, its expression pattern and diagnostic value in salivary gland tumors are not well-defined. The diagnostic utility of this biomarker warrants further investigation to address the existing gap in salivary gland pathology and to better define its potential role in identifying myoepithelial differentiation, as well as in distinguishing between benign and malignant salivary gland tumors. Such assessment can contribute to improving diagnostic precision as well as understanding tumor histogenesis and biological activity. This study aimed to assess the diagnostic value of CD10 immunoexpression as a marker for neoplastic myoepithelial cells in various salivary gland tumors, and to compare its expression with that of S100.

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Materials and Methods

Specimen Collection

A total of 63 formalin-fixed paraffin-embedded (FFPE) salivary gland tumor (SGT) blocks were retrieved retrospectively from the archives of the General Pathology Department, at the Tripoli University. The specimens included 22 pleomorphic adenomas (PA), 19 adenoid cystic carcinomas (AdCC), 13 epithelial–myoepithelial carcinomas (EMC), and 9 myoepithelial carcinomas (MC). The cases were diagnosed between September 2019 and October 2025.

Hematoxylin and eosin (H&E) were used to stain tissue samples for histopathological examination after they were cut into 4 µm sections. In addition, all previously established diagnoses were carefully reviewed and verified based on the 2022 classification criteria of the World Health Organization for salivary gland tumors [4]. Any cases showing doubtful or non-diagnostic histopathological characteristics were omitted from the study.

Immunohistochemical Staining

For immunohistochemistry, 4 µm sections from each paraffin block were mounted on positively charged slides and dried at 37 °C for 30 min. Deparaffinization and epitope retrieval were handled automatically. Staining was conducted on the Dako Autostainer Link 48 platform. After tissues were incubated with peroxidase blocking reagent for 5 min, slides were incubated for 20–30 min with primary antibodies: mouse monoclonal anti-CD10 (clone 97C5, Santa Cruz; 1:50) and mouse monoclonal anti-S100 (clone 4C4.9, Thermo Fisher; 1:100). The slides were incubated for 20 min with HRP polymer, and DAB chromogen was added for 10 min. The sections were counterstained with hematoxylin, dried via graded alcohols, and mounted for microscopic examination.

Immunostaining Analysis

The stained sections were analyzed by a conventional light microscope to confirm the presence of positive and negative immunostaining in the sections studied. Quantitative analysis was performed using Image J software (version1.41a; NIH, USA). The immunostained areas were quantitatively evaluated in terms of area and area percentage using a standardized measuring frame with an area of 465.384 μm^2. Five representative fields were examined at ×400 magnification using light microscopy, and the images were transferred to a computer monitor for analysis. Fields showing the most uniform and representative staining were selected for evaluation. The immunopositive areas were identified and masked using a red binary color, allowing their measurement by the image analysis system. The mean and standard deviation (SD) were then calculated for the examined specimens in each study group.

Analysis of Data

Statistical analysis was performed using SPSS software, version 24. The Shapiro–Wilk test was used to assess the normality of the continuous variables. Differences among the study groups were evaluated using one-way analysis of variance (ANOVA). When a statistically significant difference was detected, the Tukey–Kramer post hoc test was applied for pairwise comparisons between groups. A p-value ≤ 0.05 was considered statistically significant.

Results

Histopathological Findings (H&E Stain)

The examined cases of pleomorphic adenoma (PA) showed an admixture of epithelial and myoepithelial cells, enclosed by an incompletely formed fibrous capsule. The epithelial component is arranged in cords, nests, or duct-like structures. While the myoepithelial component was predominantly composed of plasmacytoid and spindle-shaped cells. The connective tissue stroma varied from myxomatous, myxochondroid, and fibromyxoid stroma (Figure 1, A).

The studied cases of adenoid cystic carcinoma (AdCC) exhibited cribriform, tubular, and solid growth patterns. The cribriform pattern demonstrated a characteristic “Swiss cheese” appearance, composed of basaloid tumor cells arranged around mucin-filled pseudocystic spaces. The tubular pattern was characterized by small, well-formed ducts embedded within a hyalinized stroma, lined by inner luminal epithelial cells and an outer layer of myoepithelial cells. In contrast, the solid pattern consisted of sheets and nests of basaloid cells with minimal ductal or cystic differentiation (Figures 1, B and C). In the analyzed cases of epithelial–myoepithelial carcinoma (EMC), a biphasic pattern was observed, with the presence of ductal and myoepithelial tumor cell populations in a sparse hyalinized stroma. The ductal cells, characterized by cuboidal cells and scant cytoplasm, were arranged in either solid or glandular patterns. These ductal cells were encircled by polygonal, clear myoepithelial cells (Figure 1, D). The cases of myoepithelial carcinoma (MC) were composed exclusively of malignant myoepithelial cells arranged as sheets or cords. The neoplastic cells appeared bland with varying shapes, including spindle, epithelioid, clear, and plasmacytoid cells within hyalinized stroma (Figure 1, E).

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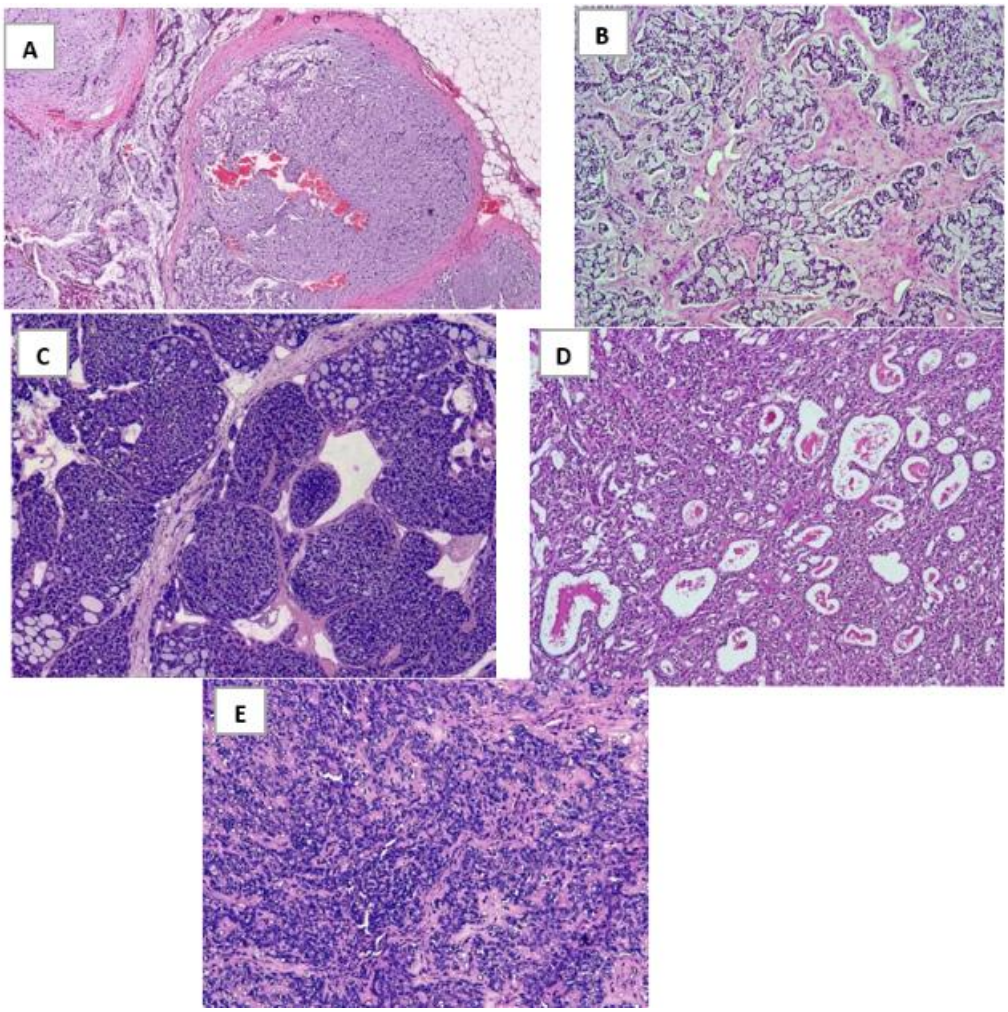

Figure (1): Photomicrograph of PA shows a biphasic appearance of epithelial and myoepithelial elements within myxochondroid stroma (H&E X100, A). Photomicrographs of AdCC show invasive malignant cells arranged around cystic spaces in a cribriform pattern within the hyalinized stroma (H&E X100, B) and solid islands of tumor cells (H&E X100, C). Photomicrograph of the EMC reveals a biphasic pattern of ductal epithelial cells and clear myoepithelial cells within a scanty hyalinized stroma (H&E X100, D). Photomicrograph of MC shows sheets of invasive cancerous cells surrounded by hyalinized stroma (H&E X100, E).

Findings of CD10 Immunohistochemical Staining

The expression of CD10 was detected as brown membranous and cytoplasmic staining in the malignant cells. Notably, the immunopositivity of CD10 was confined to all of the presented cases of EMC (100%), with a mean area percentage of (21.8 ± 8.3). Meanwhile, all examined cases of PA, AdCC, and MC were negative (0%). The immunoexpression of CD10 was concentrated in the outer myoepithelial cells of EMC as a thin, homogenous membranous reaction encircling the majority of tumor cells. A cytoplasmic reaction was observed in a minority of neoplastic cells. On the other hand, the inner ductal epithelial cells were devoid of the staining reaction (Figure 2, A and B).

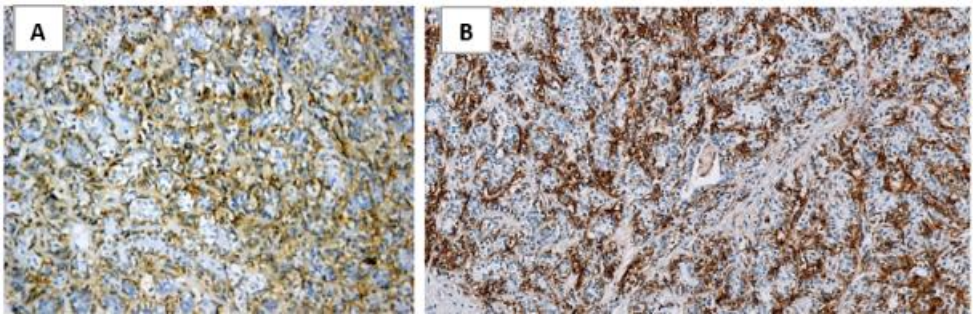

Figure (2): Photomicrographs of EMC show positive immunostaining of myoepithelial cells outlining the tumor, while the inner ductal cells reveal a negative reaction (anti- CD10, X100, A and B).

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Findings of S100 Immunohistochemical Staining

Immunohistochemical expression of S100 was observed as a nuclear/cytoplasmic brown reaction in neoplastic myoepithelial cells. The immunoreaction was detected in almost all types of the examined SGTs, while a negative response was noted only in 36.8% of the cases of AdCC. All studied cases of PA showed S100 immunoreactivity. A marked diffuse cytoplasmic and nuclear immunostain was seen in the sheets and cords of myoepithelial cells, while luminal epithelial cells were negative. Furthermore, stromal elements, including myxoid, chondroid, and myxochondroid stroma, were positive to S100 (Figure 3, A). Most of the examined cases of AdCC (63.2%) showed a positive reaction to S100. The immunopositivity among malignant cells was noticed in the cytoplasm and nucleus of myoepithelial cells, whereas the ductal epithelial cells were negative. It is noteworthy that the solid pattern expressed a negative reaction (Figure 3, B).

Regarding cases of EMC, the immunoreactivity of S100 was observed as an intense nuclear/cytoplasmic reaction among the malignant myoepithelial cells, while the inner ductal epithelial cells were negative (Figure 3, C). All examined cases of MC demonstrated diffuse S100 immunoreactivity among most of the neoplastic cells. The cytoplasmic and nuclear reactions were observed in the majority of malignant cells, while occasional tumor cells remained negative (Figure 3, D).

On the other hand, statistical analysis by using the ANOVA test revealed a significant difference in the mean S100 area percentages among the studied salivary gland tumors ($p < 0.001$). The highest mean value was observed in EMC (52.2 ± 1.3), whereas the lowest value was recorded in AdCC (21.1 ± 5.1) (Table 1).

Table (1): The mean values of S100 area percentage among the studied groups of SGTs.

SGTs	Number of cases	Positive n (%)	Negative n (%)	Mean ± SD
PA	22	22 (100%)	-	33.5 ± 4.7
AdCC	19	12(63.2%)	7(36.8%)	21.1 ± 5.1
EMC	13	13(100%)	-	52.2 ± 1.3
MC	9	9(100%)	-	39.9 ± 1.6
Total	63	56	7	-
n= number of cases,	*SD =standard deviation*	*One-way ANOVA test, p<0.001*		

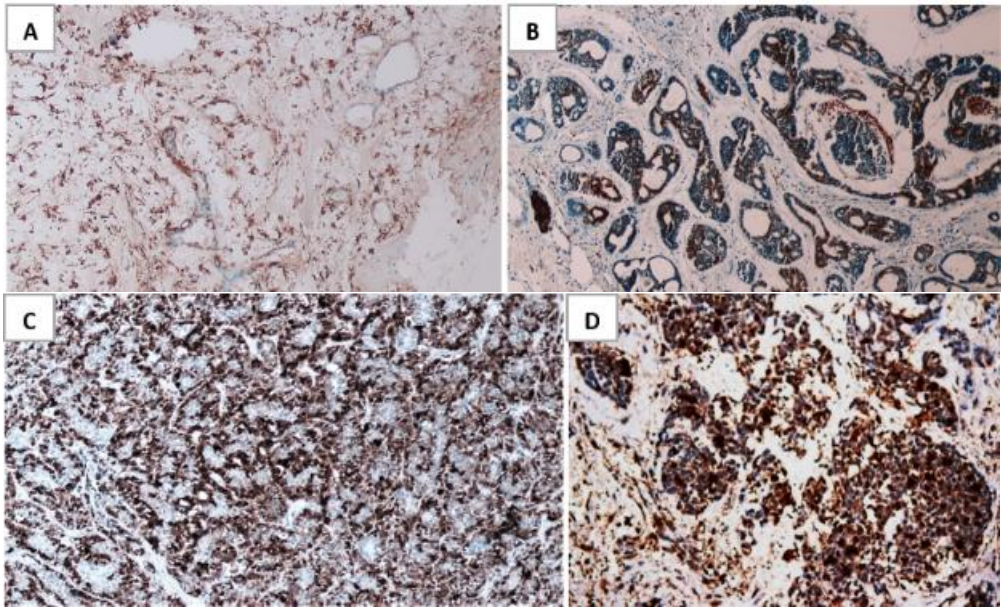

Figure (3): Photomicrograph of PA shows diffuse immunoreactivity for S100 among neoplastic myoepithelial cells, whereas luminal epithelial cells show a negative reaction (anti-S100, x100, A). Photomicrograph of AdCC shows immunoexpression of S100 among some tumor cells, while others are negative. Neural tissue displays a positive reaction (anti-S100, x100, B). Photomicrograph of EMC shows immunoexpression for S100 in the cytoplasm and nuclei of myoepithelial cells adjacent to negative-stained inner ductal epithelial cells (anti-S100, x100, C). Photomicrograph of MC shows nuclear/cytoplasmic immunoexpression for S100 among the majority of malignant myoepithelial cells. Few cells are unstained (anti-S100, x200, D).

Discussion

Myoepithelial cells are an important part of the normal structure of the salivary glands and are involved in the development of many salivary gland lesions, particularly tumors. Recognizing these cells plays a major role in reaching the correct diagnosis and selecting the most appropriate treatment for salivary gland neoplasms. Using specific markers to accurately

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identify myoepithelial cells is essential for proper histopathological evaluation, differentiating between luminal and abluminal cells, and can also provide useful information regarding the patient's prognosis.

CD10 is a cell surface peptidase expressed in a wide variety of normal and neoplastic tissues, including breast myoepithelial cells [5]. However, its role in identifying salivary gland myoepithelial counterparts remains unclear. The main finding in this study was that CD10 immunoreactivity was exclusively confined to all examined cases of EMC. This finding was supported by previous studies of Okuyama et al. [6] and Öztürk et al. [7], who observed the highest CD10 immunopositivity in this type of malignancy. Moreover, the absence of immunoexpression in the presented cases of PA, AdCC, and MC suggests that CD10 may have potential adjunctive value in distinguishing EMC from its histological mimics. This result was in accordance with the study of Neves et al. [8], who reported CD10 may be helpful in recognizing EMC, especially in diagnostically challenging specimens. However, in Neves et al.'s study, CD10 immunoreactivity was not restricted to EMC, as positive staining was also observed in PA and MC. Similarly, Terada [9] and Vencio et al. [10] showed positive reactions for CD10 in malignant myoepithelioma and AdCC, respectively. All of these findings suggest that, although CD10 expression may be prominent in EMC, it should not be considered a specific marker for this tumor. Furthermore, membranous and cytoplasmic staining of CD10 was observed only in the myoepithelial cells of the investigated EMC, while the adjacent malignant ductal cells showed a negative reaction. This pattern of immunoreactivity facilitates the identification of the dual cell population of the tumor, a distinction that is difficult to achieve at the light microscopic level by conventional H&E staining. A similar observation was reported in other biphasic lesions such as renal adenosarcoma [11] and mesonephric tumor of the vagina [12].

On the other hand, neoplastic myoepithelial cells in most of the current SGTs (63.2% of AdCC and 100% of PA, EMC, and MC) were immunopositive for S100, which was concordant with Munish et al. [2]. This observation may be explained by the well-documented role of S100 in highlighting myoepithelial cells in biphasic salivary gland tumors. Additionally, all investigated cases of PA demonstrated diffuse, intense cytoplasmic and nuclear staining, specifically in both neoplastic myoepithelial cells and stromal elements, including myxoid, chondroid, and myxochondroid stroma. However, the luminal epithelial cells displayed negative immunoreactivity. Such results were in agreement with the prior research conducted by Kalwaniya et al. [13]. This provides further evidence that S100 is utilized as a myoepithelial immunomarker for the purpose of recognizing components of PA.

Currently, negative S100 expression was detected in the solid pattern of AdCC, which represents a high histological grade of malignancy. The possible explanation for the lack of S100 expression in this tumor is the absence of myoepithelial cells. S100 is commonly expressed by myoepithelial cells, its negative expression is not unexpected in tumors devoid of these cells. Furthermore, Huang et al. [14] reported that the loss of S100 expression in AdCC could serve as a prognostic marker for aggressive behavior and reflect cellular dedifferentiation. In the current cases of EMC, S100 immunoreactivity was observed as a notable nuclear and cytoplasmic response in the neoplastic myoepithelial cells, whereas the inner ductal epithelial cells were negative. In addition, all presented cases of MC demonstrated diffuse S100 immunoreactivity among the vast majority of cancerous cells. This finding was in harmony with Xu & Katabi [15]. The authors documented that S100 protein should be always included in the immunohistochemical panel to identify MC. The statistical results of the present study showed statistically significant differences between the studied salivary gland tumors regarding the mean values of the S100 area percentage. The EMC exhibited the highest value, while the AdCC had the lowest. Such differences point out the potential diagnostic utility of S100 in differentiating between salivary gland neoplasms and providing a more accurate tumor classification.

Conclusion

The study concluded that the CD10 immunoprofile appears useful for distinguishing EMC from other salivary gland tumors sharing similar histopathological features. Combining CD10 expression alongside S100 may further improve diagnostic accuracy and increase confidence in reaching a definitive diagnosis.

Recommendations

Further studies with larger sample sizes and a wider range of myoepithelial-derived salivary gland tumors are needed to further assess the diagnostic value and specificity of CD10 in distinguishing epithelial-myoepithelial carcinoma from other salivary gland neoplasms.

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Conflict of Interests
The authors declare that they have no competing interests related to this manuscript.

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