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ORIGINAL RESEARCH

Expression of Syndecan-1 and Cyclin D1 in Salivary Gland Tumors in Relation to Clinicopathological Parameters

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Background: Salivary tumors have various morphological features and might share some histopathological findings. They are considered a problematic area in diagnosis due to complex clinicopathological features and different biological behavior.

Objective: To identify the pathological behavior of salivary tumors immunohistochemically.

Methodology: This retrospective study involved thirty formalin-fixed paraffin-embedded blocks of salivary gland tumors. These tumors were stained immunohistochemically with syndecan-1 and cyclin D1. Chi-Square test was used to relate immunoscoring, intracellular localization, intensity, and invasion to different salivary tumors. The correlation of these two markers was done by spearman's rho test. P-value <0.05 was considered statistically significant.

Results: The mean age of the patients was 48.69 ± 17.7. The parotid gland was the most commonly reported site in benign tumors, and regarding malignant tumors, maxilla was the most prevalent site. Syndecan-1 in benign tumors showed a predominate score 3, most widely detected in pleomorphic adenoma. Malignant salivary tumors showed 89.4% positive expression with a more frequent score 3, most commonly found in adenocystic carcinoma. Cyclin D1 expressed in all benign salivary tumors, with prominent diffuse mixed intracellular localization in pleomorphic adenoma. Malignant tumors revealed an expression of 94.7%. Moderate scoring with mixed intracellular localization was recorded in adenocystic carcinoma, followed by mucoepidermoid carcinoma. There was a significant correlation between the two markers in response to the distribution of immunostaining in different cell compartments.

Conclusion: Syndecan-1 and cyclin D1 showed a significant combined role in salivary tumor progression. Interestingly notable ductal-myoepithelial cells affect epithelial morphogenesis, and growth of pleomorphic adenoma was observed. Furthermore, basophilic cells of cribriform adenocystic carcinomas might control the aggressiveness and proliferation rate of these tumors.

Keywords: syndecan-1, cyclin D1, pleomorphic adenoma, adenocystic carcinoma

Introduction

Salivary tumors have various morphological features and might share some histopathological findings. Although accurate diagnoses can be made based on routine hematoxylin-eosin staining, immunohistochemistry plays a significant role in identifying the pathological behavior and classifying these tumors appropriately. Most salivary gland tumors arise from acinar/ductal epithelial cells (luminal cells) and myoepithelial/basal cells.[1] The cell cycle-regulated markers, oncogenes, and angiogenesis markers showed various roles in salivary tumor formation and malignant transformation.[2] Salivary tumors are considered a problematic area in diagnosis due to complex clinicopathological features and various biological behavior.[3]

According to the third World Health Organization classification of head and neck tumors. Thirty-four benign and malignant salivary gland tumors are recognized. Later on, in the 5th edition is characterized by certain deletion and modifications of entities in the salivary tumors, with development in the diagnostic role of immunohistochemical markers.[4] Most salivary gland tumors are benign, and the most common detected tumor is pleomorphic adenoma.[5,6]

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Similarly, a study conducted in Sulaimani city/north of Iraq reported pleomorphic adenomas as the most prevalent salivary tumors.[7] On the other hand, adenoid cystic carcinomas, followed by mucoepidermoid carcinomas, are the most frequent salivary gland malignancy.[6,8,9]

Syndecan's family involves four cell surface transmembrane proteoglycans that have a significant role in the biological behavior of differentiation, cell adhesion, migration, cytoskeletal organization, infiltration, and angiogenesis.[10] Syndecan-1 has a vital role in tumor progression and epithelial-mesenchymal transition. The decreased expression of syndecan-1 correlates with poor prognosis and invasiveness of oral squamous cell carcinoma.[11] Studies on syndecan-1 expression in salivary tumors are limited, and its essential role in the pathogenesis and behavior of these tumors remains unknown.[12]

Cyclin D1 is a 36-kDa protein encoded by CCND1 gene, located on chromosome 11q13. It acts as a cell cycle regulator and controls cellular proliferation. It has an oncogenic role in breast, lung, and melanoma cancers.[13] Cyclin D1 is a nuclear protein that regulates the transition from G1 to S phase by activating cyclin-dependent kinase CDK4 and CDK6. Then the active Cyclin D1/CDK4 complex translocates into the nucleus, phosphorylates retinoblastoma (RB) protein, and terminates the repressive action of E2F, which modulates the transcription of other genes required for cell proliferation. Literature showed conflicting results regarding cyclin D1 expression in benign and malignant salivary tumors.[14–16] This study aimed to examine the expression of both syndecan-1 and cyclin D1 in different salivary tumors to investigate the biological behaviors of these tumors from clinicopathological, and relate the expression of these markers to available clinicopathological parameters.

Materials and Methods

This retrospective study dealt with 30 formalin-fixed paraffin-embedded blocks of previously diagnosed salivary gland tumors (11 benign and 19 malignant) collected from three major pathological centers in Sulaimani city. These tumors included 8 pleomorphic adenomas, 1 warthin's tumor, 2 canalicular adenoma. 9 adenoid cystic carcinomas (6 cribriform and 3 solid), 3 mucoepidermoid carcinomas, and 4 acinic cell carcinomas, 1 Polymorphous adenocarcinoma, 1Carcinoma ex pleomorphic adenoma, 1 Epithelial myoepithelial carcinoma, The scientific committee of the College of Dentistry / University of Sulaimani agreed with this study (code no. 110 on June 9, 2022). The available clinicopathological data were obtained from patients' reports including (sex, age, site, TNM stage and grade) from patient's reports.

These salivary gland tumors were immunohistochemically stained with syndecan-1 and cyclin D1, and immunoscoring, intracellular localization, intensity, and invasion were related to different tumors and correlated with clinicopathologic factors. Two pathologists confirmed the immunopathological results. For immunohistochemistry, Two tissue sections of 5 µm were cut and mounted on a positive charge slide from each block. Sections were deparaffinized, rehydrated, and then retrieved by boiling in citrate buffer for 15 minutes at 95◦C. Hydrogen peroxidase was applied for 10 min to block endogenous peroxidase activity. To prevent non-specific binding, sections were incubated with blocking serum for 10 min. Then sections were incubated with the primary rabbit polyclonal antibodies of syndecan-1 and cyclin D1 (Abcam®; dilution 1:100) for 45 min at 37◦C in a humid chamber. Next, the complement was added to the sections and incubated for 10 min. The detection was achieved using goat anti-rabbit HRP conjugate for 15 min. Next, the sections were incubated with DAB for 5 min and then were counterstained with hematoxylin. Negative control was gained by omitting the primary antibody. Human normal tonsil was used as a positive control for both markers. Then the slides were dehydrated, cleared, and mounted to be examined by a light microscope. Then five hot spots from each slide were captured using an AmScope auto-focus 1080p digital c-mount, and two pathologists evaluated the slide using a grid of image J software.

Immunoreactivity for syndecan-1 was judged according to the following score: 0: negative; score 1:1–10%; score 2: 11–50%, and score 3: ≥ 50.[12] While cyclin D1 was evaluated using the following scoring system: 0 = negative, focal = (1–25% of tumoral cells), moderate = (25–50% of tumoral cells), diffuse = (50–75% of tumoral cells), and very diffuse = (>75% of tumoral cells).[15]

Data were tabulated in an excel worksheet and then analyzed using a statistical software package (SPSS for Windows v.20; SPSS Inc). The frequency and percentage were measured for non-parametric variables, and the mean±SD was

calculated for the age. Data were analyzed by the Chi-Square test, and the spearman s rho test was used to correlate the two markers. P-value <0.05 will be considered statistically significant.

Results

This study involved 30 samples of salivary gland tumors. The mean age of the patients was 48.69 ± 17.7. 55.55% of benign tumors were in age group of ≥50, more prevalent in females (70%). Furthermore, the parotid gland was the most commonly affected site (66.67%) (Table 1). Regarding malignant tumors, both age groups and sex were equally involved (50%) each. The maxilla was the most detected site (25%), and showed significant relation to the malignant tumors with P-value of (0.02). Lastly, grade three was most commonly reported in archived samples of malignant tumors (50%) (Table 1). Regarding TNM staging, three cases of adenocystic carcinomas revealed lymph node involvement (N1) (33.3%). Furthermore, four adenocystic carcinomas presented with (T1), while two cases had (T2).

Regarding syndecan-1 immunoexpression. Benign tumors showed two negative cases and nine cases with positive immunoreaction with a predominate score 3 (72.7%), which was more commonly seen in pleomorphic adenoma (6/8, 75%) Figure 1A. Still, no significant relation was found (P=0.24), and 63.6% of benign salivary tumors had mixed (membranous and cytoplasmic) intracellular localizations, Figure 1B and 1C; again, no significant relation was observed (P=0.65). The strong intensity was seen in eight cases of benign tumors. However, no statistically significant association was found (P=0.24). Lastly, one pleomorphic adenoma showed capsular invasion, which was statistically insignificant (P=0.81) (Table 2).

Malignant salivary tumors demonstrated positive expression of syndecan-1 in 17 /19, 89.4%, with a predominant score 3 (63.1%), most commonly found in adenocystic carcinoma followed by mucoepidermoid carcinoma. Interestingly syndecan-1 scoring of malignant tumors illustrated significant relation to (<50) age group (P=0.01). Mixed intracellular localization was most commonly seen (78.9%) Figure 1D and E. The malignant tumors showed predominate strong intensity (47.3%). One acinic cell carcinoma showed capsular invasion, while the other revealed muscular invasion Figure 1F and G. Non-significant relations were found in response to intensity and invasion as p- values were (P=0.32). (P=0.75), respectively (Table 2). Lastly, significant relations were found between various cell compartments concerning benign and malignant salivary tumors, as p-values were 0.005 and < 0.001 (Table 3).

Cyclin D1 expression was recorded in all of the studied benign salivary tumors 100%, which more frequently showed diffuse staining (45.4%), most commonly seen in pleomorphic adenoma Figure 2A. However, non-significant relation was detected (P=0.84). High mixed intracellular localization (nuclear and cytoplasmic) was seen in pleomorphic adenoma Figure 2B, which was statistically insignificant (P=0.30). Moderate intensity was recorded in 7 cases (63.6%). Finally, non-significant relations were found in response to intensity and invasion as P-values were 0.30 and 0.81, respectively (Table 4).

Malignant salivary tumors revealed positive expression in 18/19, 94.7%. The predominant expression was moderate 36.8%. This score was recorded in adenocystic carcinoma followed by mucoepidermoid carcinoma Figure 2C and D. Still, no significant relation was found (P=0.76). High mixed intracellular localization was reported in adenocystic, mucoepidermoid, and acinic cell carcinomas in descending frequencies Table 4, Figure 2E–G. However non-significant relation was found (P=0.66). The strong intensity was detected in 52.6% of malignant tumors. Four malignant salivary tumors revealed different modes of invasion to adjacent structures (Table 4), Figure 2H–J. Cyclin D1 had significant relations in the distribution of immunostaining in different cell parts of both benign and malignant tumors, as P-values were 0.008 and < 0.001, respectively, Table 5. A significant correlation between syndecan-1 and cyclin D1 immunoscoring was found in benign tumors (P=0.012); nevertheless, a non-significant correlation was detected in the scoring of two markers in malignant tumors (P= 0.5). Lastly, significant correlations were achieved between these two markers in response to their cellular distribution in benign and malignant tumors, as P-values were 0 0.016 and 0.000, respectively.

Discussion

Salivary gland tumors are a group of rare lesions with different origins, diverse pathological behavior, and various growth pattern, with significant morphological overlapping in different subtypes.[3,17] They have a worldwide demographic diversity, with a significant impact of geographical region, socioeconomic status, lifestyle, and oral health access.[18,19]

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Table 1 Demographic Features of 30 Studied Samples of Salivary Gland Tumors

Features		Benign Tumors					Malignant Tumors							
		Pleomorphic Adenoma	Warthin Tumor	Canalicular Adenoma	Total		Adenoid Cystic Carcinoma	Mucoepidermoid Carcinoma	Acinic Cell Carcinoma	Carcinoma Ex-Pleomorphic Adenoma	Polymorphous Adenocarcinoma	Epithelial Myoepithelial Carcinoma	Total	
		n	n	n	n	%	n	n	n	n	n	n	n	%
Age*	<50	4			4	44.44	4	3	1		1		9	50
	≥50	3	1	1	5	55.55	5		2	1		1	9	50
Sex**	Male	2	1		3	30	5		3	1			9	50
	Female	5		2	7	70	4	3			1	1	9	50
Site***	Parotid	4	1	1	6	66.67	1					1	2	12.5
	Submandibular	1		1	2	22.22	2						2	12.5
	Sublingual									1			1	6.25
	Palate	1			1	11.11		1	1		1		3	18.75
	Cheek							2					2	12.5
	Tongue								1				1	6.25
	Maxilla						3		1				4	25
	Lip						1						1	6.25
Grade≠	Grade 1						3	1	1				5	31.25
	Grade 2						1	2					3	18.75
	Grade 3						5		2			1	8	50

Notes: *Age of 2 benign (1 pleomorphic adenoma and 1 canalicular adenoma) and 1 malignant SGT (Acinic cell carcinoma) were not available. **Sex of 1 benign (pleomorphic adenoma) and 1 malignant SGT (Acinic cell carcinoma) were not available. ***Site of 2 benign (pleomorphic adenoma) and 3 malignant SGT (2 adenoid cystic carcinoma and 1 Acinic cell Carcinoma) were not available. ≠Grading of 3 malignant SGT (1 Acinic cell Carcinoma, 1 Carcinoma Ex-pleomorphic adenoma and 1 Epithelial myoepithelial carcinoma) were not available. The percentages of the benign and malignant tumors were registered according to the available numbers of variables (age, sex, site and grade). The benign tumors showed non significant relations to age, sex and site as *P*-value of (0.45), (0.41) and (0.81) respectively. Malignant tumors showed non significant relations to age, sex, and grade with the *P*-value of (0.54), (0.37) and (0.09) respectively. Only malignant salivary gland tumors revealed significant relations regarding the site distribution with the *P*-value of (0.02).

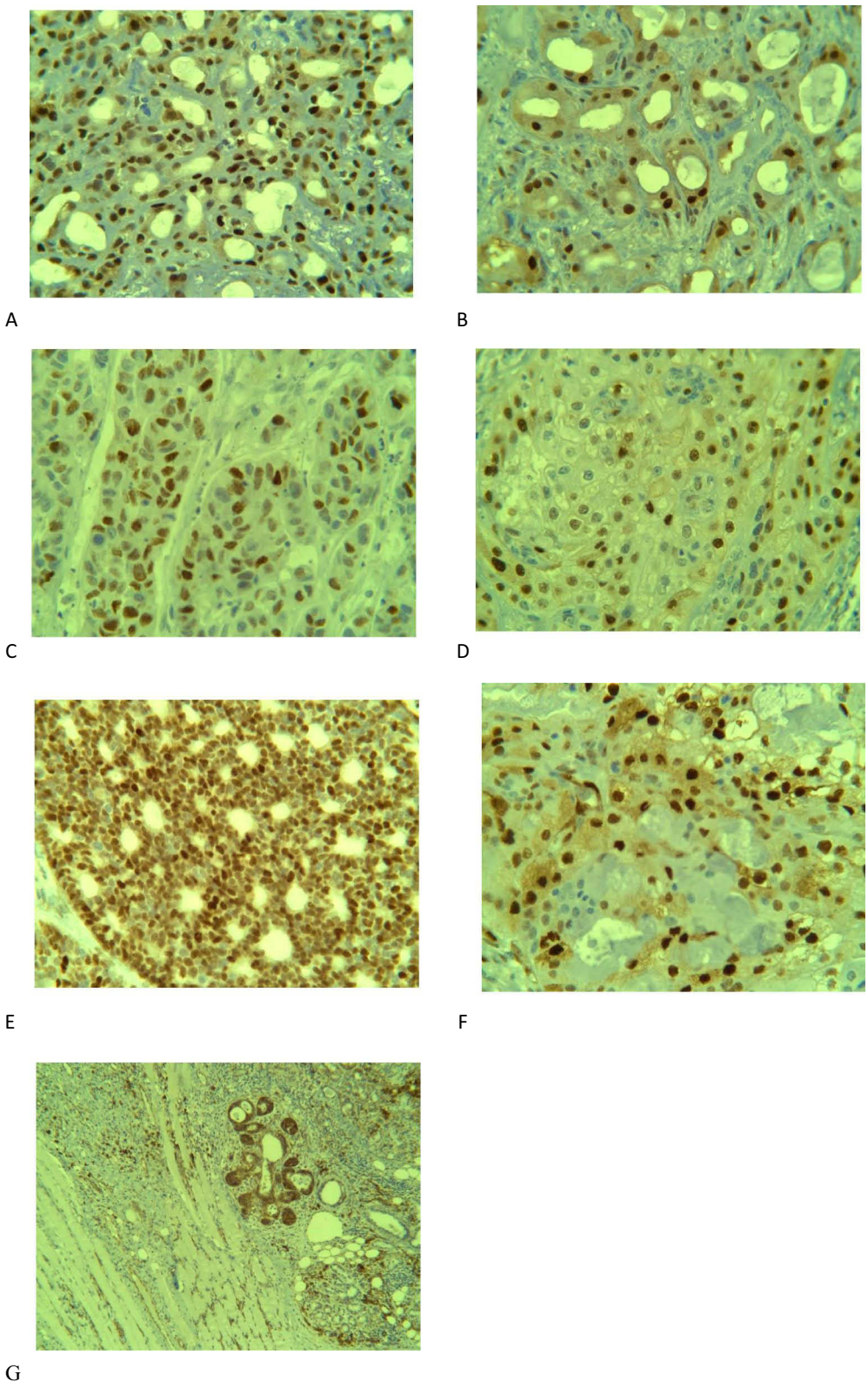

Figure 1 Syndecan-1 immunoexpression in benign and malignant salivary tumors. (**A**) Score 3 immunoexpression in ductal and myoepithelial cells of pleomorphic adenoma X40. (**B**) Mixed intra cellular localization in pleomorphic adenoma X40. (**C**) Mixed intracellular localization in bilayered epithelia of warthin tumor X40. (**D**) Score 3 expression and mixed intracellular localization in cribriform adenocystic carcinoma X40. (**E**) Score 3 immunoexpression and mixed localization of both epidermoid and mucous cells in mucoepidermoid carcinoma X40. (**F**) Capsular invasion of both acinar and ductal cells in acinic cell carcinoma X10. (**G**) Muscle invasion of acinar and ductal cells in acinic cell carcinoma X10.

Table 2 Syndecan-1 Immunohistochemical Expression in Salivary Gland Tumors

		Benign Tumors						Malignant Tumors								
		Pleomorphic Adenoma	Warthin Tumor	Canalicular Adenoma	Total		P-value	Adenoid Cystic Carcinoma	Mucoepidermoid Carcinoma	Acinic Cell Carcinoma	Carcinoma Ex-Pleomorphic Adenoma	Polymorphous Adenocarcinoma	Epithelial Myoepithelial Carcinoma	Total		P-value
		n	n	n	n	%		n	n	n	n	n	n	n	%	
Score	0	2			2	18.2	P=0.240			2				2	10.53	P=0.184
	Score 1				0	0								0	0	
	Score 2			1	1	9.09		3				1	1	5	26.32	
	Score 3	6	1	1	8	72.7		6	3	2	1			12	63.16	
Cellular localization	Negative	2			2	18.2	P=0.653			2				2	10.53	P=0.604
	Cytoplasmic							1						1	5.26	
	Membranous	1		1	2	18.2		1						1	5.26	
	Mixed	5	1	1	7	63.6		7	3	2	1	1	1	15	78.95	
Intensity	Negative	2			2	18.2	P=0.240			2				2	10.53	P=0.324
	Faint							1						1	5.26	
	Moderate			1	1	9.09		2	2	1		1	1	7	36.84	
	Strong	6	1	1	8	72.7		6	1	1	1			9	47.37	
Invasion	No invasion	7	1	2	10	90.9	P=0.814	9	3	2	1	1	1	17	89.47	P=0.755
	Capsular invasion	1			1	9.09				1				1	5.26	
	Muscular invasion									1				1	5.26	

Table 3 Syndecan-1 Immunoreactivity in Various Cellular Compartment of Studied Salivary Gland Tumors

		Benign Tumors						Malignant Tumors									
		Pleomorphic Adenoma	Warthin Tumor	Canalicular Adenoma	Total		P-value	Adenoid Cystic Carcinoma Cribriform	Adenoid Cystic Carcinoma Solid	Mucoepi dermoid Carcinoma	Acinic Cell Carcinoma	Carcinoma Ex-Pleomorphic Adenoma	Polymorphous Adenocarcinoma	Epithelial Myoepithelial Carcinoma	Total		P-value
		n	n	n	n	%		n	n	n	n	n	n	n	n	%	
Positive cells	Negative	2			2	18.2	p=0.005				2				2	10.5	P < 0.001
	Ductal			2	2	18.2							1		1	5.26	
	Myoepithelial	1			1	9.09											
	Basophilic							6	3						9	47.4	
	Epithelial		1		1	9.09											
	Epidermoid									1					1	5.26	
	Mixed-duct /myo/epi	5			5	45.5						1			1	5.26	
	Mixed-myo /epi													1	1	5.26	
	Mixed-ductal /acinar										2				2	10.5	
	Mixed-mucous / epidermoid									2					2	10.5	

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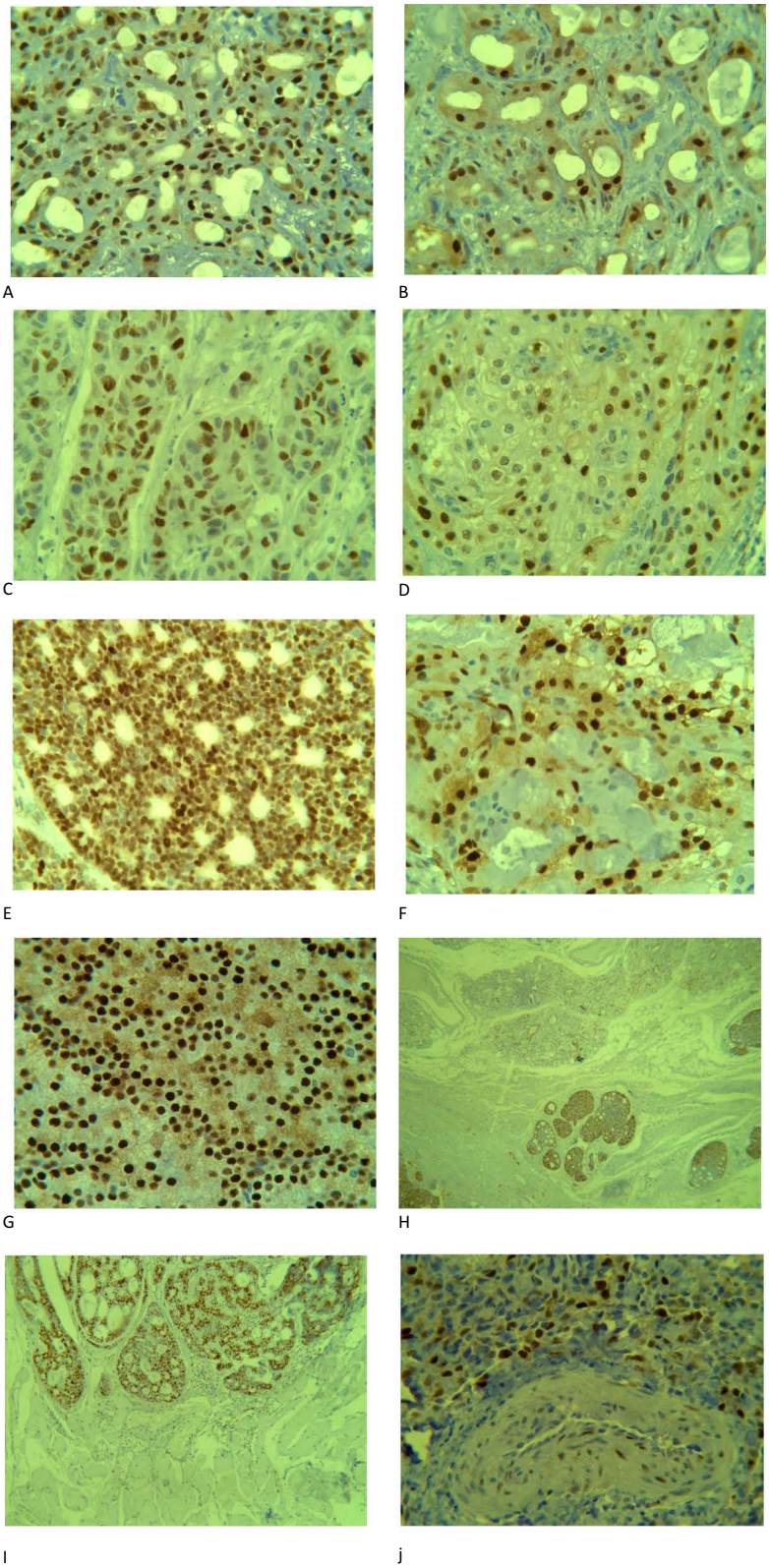

Figure 2 Cyclin D1 expression in benign and malignant salivary tumors. (**A**) Diffuse expression in pleomorphic adenoma X40. (**B**) Mixed intracellular localization in ductal and myoepithelial cells of pleomorphic adenoma X40. (**C**) Moderate immunoscoring in solid adenocystic carcinoma X40. (**D**) Moderate immunoscoring in mucoepidermoid carcinoma X40. (**E**) Mixed intracellular localization of cribriform adenocystic carcinoma X40. (**F**) Mixed intracellular localization of epidermoid cells with negative mucous cells x40. (G) Mixed intracellular localization of acinar cells in acinic cell carcinoma X40. (**H** and **I**) Capsular and muscles invasion by malignant cells in same case of acinic cell carcinoma X4, X10. (**J**) Vascular invasion by malignant cells in epithelial myoepithelial carcinoma X40.

Table 4 Cyclin D1 Immunohistochemical Expression in Different Salivary Gland Tumors

		Benign Tumors						Malignant Tumors								
		Pleomorphic Adenoma	Warthin Tumor	Canalicular Adenoma	Total		P-value	Adenoid Cystic Carcinoma	Mucoepidermoid Carcinoma	Acinic Cell Carcinoma	Carcinoma Ex-Pleomorphic Adenoma	Polymorphous Adenocarcinoma	Epithelial Myoepithelial Carcinoma	Total		P-value
		n	n	n	n	%		n	n	n	n	n	n	n	%	
Score	Negative						P=0.840			1				1	5.26	P=0.768
	Focal 1–25	2	1	1	4	36.4		1						1	5.26	
	Moderate 25–50	1			1	9.09		4	2	1				7	36.8	
	Diffuse 50–75	4		1	5	45.5		2	1		1	1	1	6	31.6	
	Very diffuse >75	1			1	9.09		2		2				4	21.1	
Cellular localization	Negative						P=0.308			1				1	5.26	P=0.660
	Nuclear	2	1	1	4	36.4		5		1				6	31.6	
	Mixed	6		1	7	63.6		4	3	2	1	1	1	12	63.2	
Intensity	Negative						P=0.308			1				1	5.26	P= 0.485
	Moderate	4	1	2	7	63.6		4	3	1				8	42.1	
	Strong	4			4	36.4		5		2	1	1	1	10	52.6	
Invasion	No invasion	7	1	2	10	90.9	P=0.814	8	3	2	1	1		15	79	P=0.110
	Capsular invasion	1			1	9.09										
	Muscular invasion									1				1	5.26	
	Vascular invasion												1	1	5.26	
	Capsular and mascular									1				1	5.26	
	Muscular and vascular							1						1	5.26	

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Table 5 Cyclin D1 Immunoreactivity in Various Cellular Compartments of 30 Different Salivary Gland Tumors

		Benign Tumors						Malignant Tumors									
		Pleomorphic Adenoma	Warthin Tumor	Canalicular Adenoma	Total		P-value	Adenoid Cystic Carcinoma Cribriform	Adenoid Cystic Carcinoma Solid	Mucoepi dermoid Carcinoma	Acinic Cell Carcinoma	Carcinoma Ex-Pleomorphic Adenoma	Polymorphous l Adenocarcinoma	Epithelial Myoepithelial Carcinoma	Total		P-value
		n	n	n	n	%		n	n	n	n	n	n	n	n	%	
Positive cells	Negetive						P=0.008				1				1	5.26	P < 0.001
	Ductal	1		2	3	27.3							1		1	5.26	
	Myoepithelial	1			1	9.09											
	Basophilic							6	3						9	47.4	
	Epithelial		1		1	9.09											
	Epidermoid									2					2	10.5	
	Mixed-duct /myo/epi	6			6	54.6						1			1	5.26	
	Mixed-myo /epi													1	1	5.26	
	Mixed-ductal /acinar										2				2	10.5	
	Mixed-mucous / epidermoid									1					1	5.26	
	Acinar										1				1	5.26	

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The mean age of patients was 48.69 ± 17.7, similar to the finding of Demet et al[18] but more than that detected by the other two studies.[19,20] While Iraqi research and further international multicentre study illustrated high prevalence in old age groups.[21,22]

In the current study, pleomorphic adenomas were more prevalent in females. The most commonly affected site was the parotid gland. Meanwhile, a similar result was found in other clinicopathological records.[18,21,23]

Regarding malignant tumors, both sexes were equally affected. The maxilla was the most detected site. Conflicting findings were reported by other research that showed female preference, with different site distributions, which were the parotid region,[23] and minor salivary glands.[21,22] This difference could be attributed to the large sample size, and more histological subtypes were included in these epidemiological studies. Lastly, grade three was most commonly conveyed in archived samples of malignant tumors, a similar result was found by,[24] but this was dissimilar to the finding of,[15] in which low-grade was the most frequent one.

Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells lose their adhesion and gain cell motility and exhibit mesenchymal features with spindle cell morphology. It displays an essential role in cancer development and progression.[25]

Syndecans have a critical role in the epithelial-mesenchymal transition through modulation and activation of specific growth factors. They showed a different pattern of expression in epithelial and mesenchymal tumors, which affect their differentiation and biological behaviors.[26]

In benign tumors, syndecan-1 revealed a high score 3 with mixed intracellular localization in pleomorphic adenoma, which was in line with the finding of Alaeddini et al.[12] Interestingly, in this study, one pleomorphic adenoma showed capsular invasion, which may give rise to recurrence due to capsule seeding of the tumor. No previous studies evaluated the cellular compartment distribution of syndecan-1. Therefore, we assessed this distribution to determine the cellular pattern effect on tumor behavior. The prominent significant mixed (ductal-myoepithelial cells) expression in pleomorphic adenoma could indicate the combined role of both compartments in the tumor's various epithelial morphogenesis and growth by stimulating other growth factors.

All the nine adenocystic carcinomas (100%) showed syndecan-1 expression in the current study. Conflicting the findings reported by other research conducted on adenocarcinoma; as they showed various expressions of this marker which was high in the lung (82.9%) and colorectal (85.3%), low in the pancreas (73.3%), stomach (54.2%), and prostate carcinomas (16.3%).[27] This difference could be attributed to different organ selection and technical procedures applied. Meanwhile, the finding of other research indicated that loss of syndecan-1 played a role in the progression of colon carcinoma.[28]

Adenocystic carcinoma displayed a predominant score 3 with mixed intracellular localization of syndecan-1. Interestingly this high scoring might be associated with aggressive behavior of the tumor as 33.3% cases from total adenocystic carcinomas samples reported N1 lymph node involvement. On the other hand, Alaeddini et al reported high scoring with cytoplasmic intracellular localization. This study showed significant positive basophilic cells in the cribriform pattern of adenocystic carcinoma, indicating that even the secretory form might have an essential role in migration and aggressive tumor behavior by activating vascular growth factors and angiogenesis.[29] All mucoepidermoid carcinomas were detected within score 3, of which two of them had mixed mucous-epidermoid patterns of expression. Although Alaeddini et al[12] found high scoring of expression, the mucus cells showed negative expression. However, a clear conclusion for this finding can not be obtained from this limited number of archived mucoepidermoid carcinomas.

One acinic cell carcinoma showed capsular invasion, while the other revealed muscular invasion, which may be related to local recurrence and or the aggressive nature of the tumor.

All studied benign salivary tumors expressed cyclin D1 (100%), frequently showed diffuse scoring and were most commonly detected in pleomorphic adenoma. Another study by Tenorio et al[14] revealed only 60.5% positivity with mild scoring of pleomorphic adenoma. On the other hand, Jour et al[15] study displayed cyclin D1 expression in 93% of benign tumors, with predominant moderate scoring in both pleomorphic adenoma and warthin tumors. This difference might be related to the difference in sample size and inclusion of other benign nonsalivary lesions in these studies. Our result expressed cyclin D1 concurrently in both ductal and myoepithelial cells of pleomorphic adenoma. This observation was in line with the previous two studies.[15,30] Furthermore, this prominent diffuse distribution in pleomorphic adenoma

demonstrates the role of cyclin D1 in the rapidly expanding growth of even benign-looking tumors. High mixed nuclear and cytoplasmic intracellular localization was seen in pleomorphic adenoma, similar to the study of Tenorio et al.[14]

Increased expression of cyclin D1 presented in various malignant tumors, including esophageal, hepatocellular, lung, and head and neck carcinoma.[31] Our study revealed positive expression in 94.7% of malignant salivary tumors. This result was in agreement with other previous studies that showed high expression of cyclin D1 in malignant salivary tumors, which were 96.6% and 100% immunopositivity.[14,15,32]

A prominent moderate score of cyclin D1 was observed in adenocystic carcinoma, followed by mucoepidermoid carcinoma. The current study findings point to the role of this marker in the destabilization of cell division, with a significant impact of a cribriform variant of basaloid cell arrangements in the aggressive behavior of this tumor. While jour et al detected a more frequent score 1 in mucoepidermoid carcinoma followed by polymorphous adenocarcinoma and acinic cell carcinoma. Similarly Tenorio et al indicated predominant score 1 but with a different distribution, which was mucoepidermoid carcinoma, followed by adenocystic carcinoma. Lastly significant correlation between syndecan-1 and cyclin D1 in response to staining distribution in the different cellular compartment that was noted in the current study support author finding in colon carcinoma that showed that loss of syndecan could induce activation of cyclin D1, and promote tumor growth.[28]

Conclusion

Both syndecan-1 and cyclin D1 have a remarkable role in determining salivary tumors' aggressiveness and growth. Furthermore, a significant influence of ductal-myoepithelial cells in pleomorphic adenoma and basaloid cells of cribriform adenocystic carcinoma was seen, which could determine tumor behavior later on. Still large sample with the clinical documentation of different histological subtypes are needed.

Ethical Approval

This retrospective research involved the archives of paraffin blocks of salivary tumors, so the informed consent was waived by the authors. The scientific committee of the College of Dentistry /the University of Sulaimani approved this study (code no. 110 on June 9, 2022). We are confirming that our study complies with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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