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ORIGINAL ARTICALE

EXPRESSION PATTERN OF NUCLEOSTEMIN IN PLEOMORPHIC ADENOMA AND MUCOEPIDERMOID CARCINOMA OF SALIVARY GLANDS: EX-VIVO STUDY

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ABSTRACT

Background: Pleomorphic adenoma and mucoepidermoid carcinoma are the most common benign and malignant salivary gland tumors, respectively. The role of cancer stem cells and autophagy in tumor progression and aggressiveness is crucial. Nucleostemin, a stem cell-enriched nucleolar protein, plays a role in stemness, proliferation, and tumor progression however, its role in salivary gland tumorigenesis remains unexplored until now.

Materials and Methods: This study evaluated nucleostemin immunohistochemical expression in 27 samples, including normal salivary gland tissue, pleomorphic adenoma, and mucoepidermoid carcinoma. Nucleostemin immunoexpression was analyzed via Leica Qwin 500 software. Statistical analysis using ANOVA test, Bonferroni post hoc correction test, were performed to assess differences across groups.

Results: Nucleostemin nuclear expression was highest in mucoepidermoid carcinoma (27.55 ± 1.91), followed by pleomorphic adenoma (16.89 ± 1.64), and showed the least expression in normal salivary glands (0.47 ± 0.08).

Conclusion: This research revealed notable expressions of nucleostemin in mucoepidermoid carcinoma and pleomorphic adenoma suggesting its potential role in tumor biology. Further studies with larger samples and clinicopathological correlation are recommended.

Keywords: anti-GNL3, salivary gland tumors, pleomorphic adenoma, mucoepidermoid carcinoma, cancer stem cells.

INTRODUCTION

Salivary gland tumors (SGT) are a heterogeneous and complex category of neoplasms characterized by a wide range of histological features. They exhibit variability in the types of cells from which they arise, and in their underlying molecular mechanisms, making them a diverse category of neoplastic diseases. Pleomorphic adenoma (PA) is the most common type of SGTs and accounts for nearly 60% of all benign SG neoplasms. PA mostly affects the parotid gland (85%), followed by minor salivary glands then the submandibular gland. In minor salivary glands, the hard palate is the most common site. PA is typically painless, and mobile, firm swellings, and pain or facial nerve paralysis may suggest malignancy[1,2].

Histologically, PA is characterized by a mixture of epithelial and myoepithelial cells embedded in a mesenchymal-like stroma. The epithelial component can form ductal or trabecular structures, while the myoepithelial cells contribute to the myxoid and chondroid areas of the stroma. This histological diversity is a hallmark of PA and distinguishes them from other salivary gland tumors[1,3]. Mucoepidermoid carcinoma (MEC) is the most common SG malignancy in both children and adults. It represents 30%-40% of all SG malignancies (4)**.** The parotid gland is most affected, followed by minor salivary glands, especially those in the palate followed by the submandibular gland. MEC typically presents as a painless, slow-growing mass, with symptoms depending on its location and size[5]. Histologically, MEC consists of mucous cells with abundant mucin, intermediate cells, and epidermoid cells resembling squamous cells with intercellular bridges[6].

SGTs contain a small population of cancer stem cells (CSCs), which control their tumorigenic potential, recurrence, therapeutic resistance, and metastasis. Generally, stem cells play essential roles in organogenesis, tissue regeneration, aging, and cancer development. Several stem cell markers, including Nanog, Bmi1, Oct4, and CD44, have been detected in PAs and MECs. These factors correlated with their aggressiveness and poor prognosis.[3,7,8]

One of the genes enriched in stem cells is nucleostemin (NS). It is a nucleolar GTP-binding protein with significant roles in stem cell self-renewal, embryonic development, and tissue regeneration. It is also involved in ribosomal biogenesis, cell cycle regulation, and genome protection.[9,11] NS has been reported to be expressed in embryonic and adult stem cells, as well as in CSCs. Interestingly, it is abundantly expressed in many cancers and is generally associated with poor prognosis and an undifferentiated state of cancer.[12,13]

Targeting NS in cancer has been a goal in recent decades; however, it is still in its infancy. To our knowledge, no studies have investigated the immunohistochemical (IHC) expression of NS in the PAs and MECs of SGs. Therefore, this study was designed to assess the immunoexpression of NS in normal SG tissue, PAs, and different grades of salivary MEC.

Material & Methods

Specimen collection

Inclusion criteria

- PA and MEC archived tissue blocks from 2013-2023.
- PA and MEC tissue that accurately fit the histopathological criteria set by WHO classification updates (2024) of head and neck tumors.
- Normal salivary gland tissue archival blocks.
- Salivary gland origin of MECs.

Exclusion criteria

- Cases that received treatment.
- Recurrent cases
- Cases with incomplete data

Ethics approval and consent to participate

This work was approved by the Research Ethical Committee at the Faculty of Dentistry, Cairo University (No. 23 6 22), and was performed in compliance with the Helsinki Declaration. Informed consent was obtained from all the subjects and/or legal guardian(s).

The sample size was based on available tissue specimens and approved with a waiver from the Medical Biostatistics Unit, Faculty of Dentistry, Cairo University. Accordingly, 27 formalin-fixed paraffin-embedded (FFPE) specimens—pleomorphic adenomas, mucoepidermoid carcinomas, and normal salivary glands were retrieved from the Oral and Maxillofacial Pathology Department archives during the period from 2013–2023.The clinical data, such as age, sex, site of tumor, and diagnosis, were collected from the histological reports. Four-micron-thick hematoxylin and eosin (H&E)-stained sections from each specimen were re-examined by 2 experienced Oral & Maxillofacial pathologists via light microscopy to confirm the diagnosis. They classified specimens according to the 2024 WHO classification 5th edition of head and neck tumors (14)based on histopathological criteria as follows: 10 PA samples, 12 salivary MEC samples with different grades {according to Brandwein Microscopic Grading System (15)}, and 5 normal SG samples. The most representative sections were selected for immunohistochemical staining.

Immunohistochemical Staining

FFPE tissue sections 4 µm were prepared for immunohistochemical staining. The staining process was performed via iVIEW™DAB (Ventana Medical Systems, Tucson, AZ, USA), and the primary polyclonal rabbit anti-nucleostemin (NS)/GNL3 antibody (Cat. # YPA2475) was obtained from Chongqing Biopsies Company, China). Immunostaining was performed according to the manufacturer's instructions as follows: The paraffin sections were deparaffinized by descending grades of alcohol. For antigen retrieval the tissue sections were microwaved at 130°C for 10-20 minutes in 10mM citrate buffer, pH 6, followed by cooling at room

temperature for 20 minutes. Blocking the endogenous peroxidase activity was done by 0.3% hydrogen peroxidase. Additionally, the blocking of non-specific protein binding was done through incubation with 10% normal goat serum for 20 minutes at room temperature. Then, 100µ of anti-nucleostemin antibody at a dilution of (1:50)) was incubated for 44 minutes in the humidity chamber at 30℃ on each slide. Then, one drop of the amplifier was incubated for 8 minutes at room temperature. Incubation with the secondary antibody and application of diaminobenzidine was done. Mayer's hematoxylin for counterstaining was used, and then mounting with xylene was done. Negative control was performed by the omission of the primary antibody and replacing it with phosphate-buffered saline. Additionally, positive control of colon carcinoma tissue was stained to ensure the specificity of the staining.

All the prepared slides were examined under a light microscope and were considered positive if the lesion exhibited any nuclear staining. Image analysis was performed using a Leica Qwin 500 computer system at the Research Unit, Faculty of Dentistry, Cairo University, Egypt to quantify the immunoreactivity. The system was calibrated automatically to convert pixel measurements into micrometer units. The cursor was used to outline areas of positive nuclear immunoreactivity, Immunoreactivity was measured and quantified as the percentage area via light microscopy at 400x magnification. Three fields from the core of each section were selected. These areas were masked by a blue binary color to be measured by the computer system. The mean percentage area of NS nuclear immunoreactivity was measured.

Statistical analysis

SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used. All the numerically obtained data were explored for normality via the Kolmogorov–Smirnov and Shapiro–Wilk tests. Based on the normal distribution of data, a student's t-test was performed to compare the mean age values between the PA and MEC groups, and a Chi-square test was used in comparing the qualitative data (Gender and tumor site). Additionally, the IHC area percentage of NS of the examined groups were compared using a one-way analysis of variance (ANOVA) test, followed by Bonferroni post hoc correction test for pairwise comparisons between the means. The significance level was set at a P value ≤ 0.05.

RESULTS

Histopathological examination of H&E-stained sections:

Histopathological findings of H&E-stained sections of normal salivary gland tissue revealed mucous tubules of SG and striated ducts in between them (Fig. 1a). The H&E-stained sections of PAs revealed proliferating myoepithelial cells in the stroma (Fig. 1b&1c). Capsules surrounding the PAs were observed in 80% of the lesions (Fig. 1b). 20% of the cases were partially capsulated. Numerous duct-like structures formed of bi-population of cells arranged in a ductal pattern and areas of chondromyxoid differentiation were observed in 100% of cases (Fig. 1c). Additionally, histopathological examination of H&E-stained sections of MECs revealed that 50% of the cases were low-grade MEC showing proliferating malignant epidermoid, intermediate, mucous cells forming cystic spaces (Fig. 2a & 2b) and 17% of cases were classified as a high-grade tumor showing solid nests of dysplastic pleomorphic epidermoid cells with frequent mitotic figures (Fig. 2c). Clear and oncocytic cells were noted in 33% of the cases (Fig. 3a) & (Fig. 3b) respectively

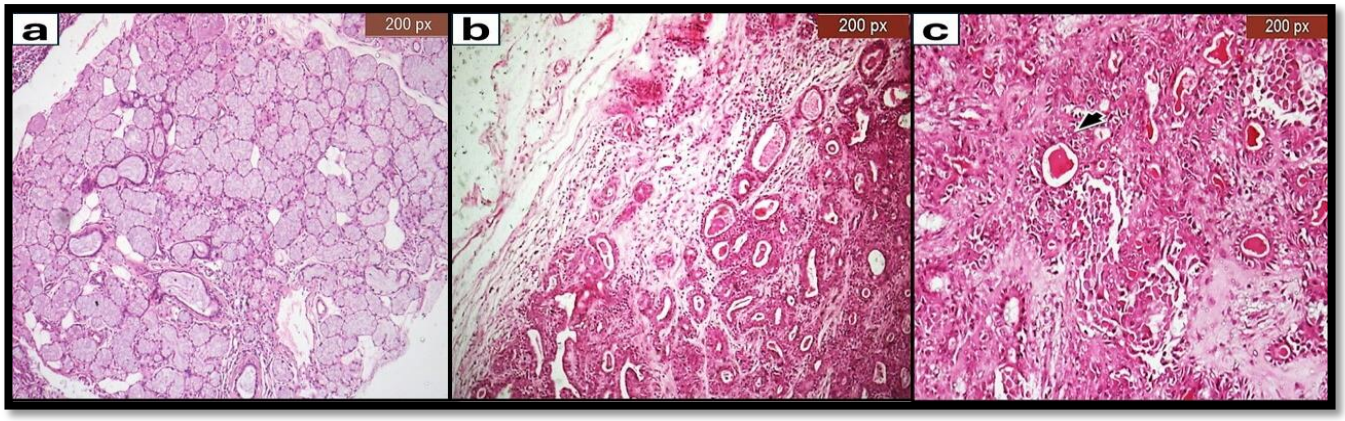

Figure 1. A photomicrograph of H&E-stained sections (x200) showing **(**a) normal SG mucous tubules with striated ducts between them, (b) PA surrounded with capsule, (c) proliferation of myoepithelial cells to the stroma of the PA (black arrow)

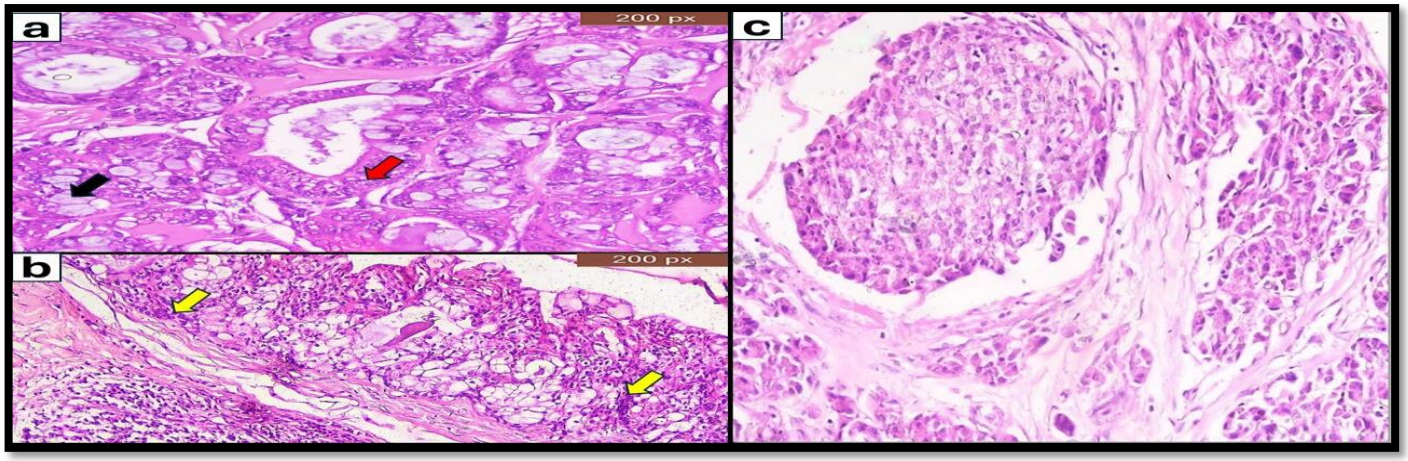

Figure 2. A photomicrograph of H&E-stained sections showing (a)&(b) MEC showing proliferating epidermoid cells (red arrow), intermediate cells (yellow arrow), and mucous cells (black arrow) forming cystic spaces, (x200) (c) a high-grade MEC showing solid nests of pleomorphic epidermoid cells with frequent mitotic figures (x400).

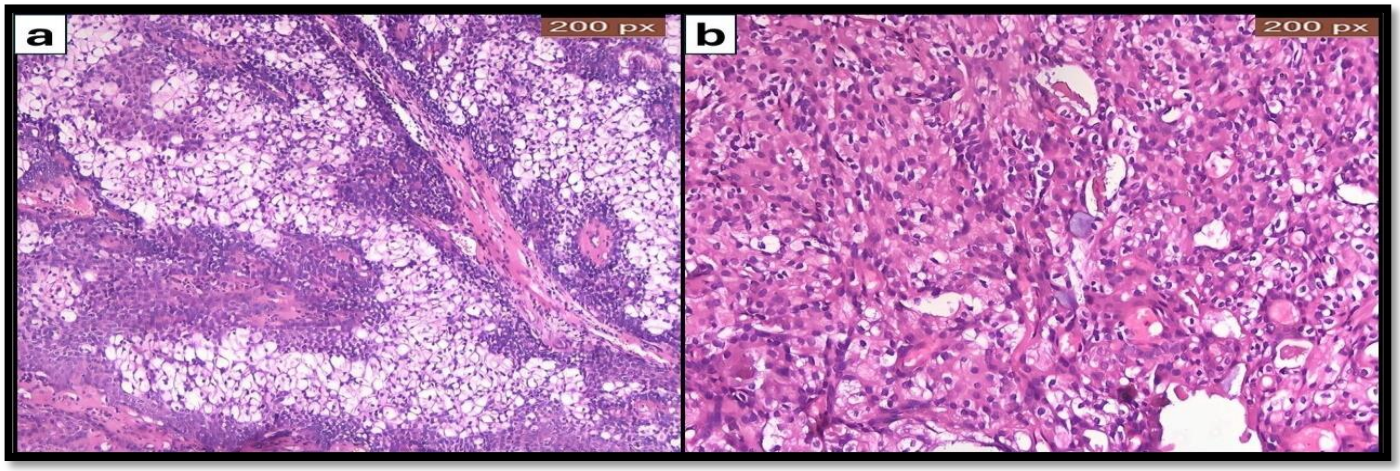

Figure 3. A photomicrograph of H&E-stained sections showing (a) MEC with predominant clear and mucous cells, (x200) and (b) MEC showing solid nests of oncocytic epidermoid cells with granular eosinophilic cytoplasm and some mucous cells (x200).

Immunohistochemical examination of NS-stained sections

The ductal cells in normal SG tissues were positive for NS staining. On the other hand, most mucous cells were NS negative (Fig. 4a). All cases of PA showed nuclear positivity for NS in both ductal cells and myoepithelial cells (Fig. 4b & 4c). The fibrous capsules were faintly positive for NS (Fig. 4b). The stromal components in PA, including stromal fibroblasts, chondroid, and myxoid tissue were positive for NS (Fig. 4c). Moreover, cytoplasmic expression was noted in most cells (Fig. 4d).

Additionally, all cases of MEC were positive for NS with nuclear and faint cytoplasmic immunoexpression in both epidermoid cells, intermediate, and mucous cells in the low-grade tumors (Fig. 5a&5b) as well as epidermoid cells in high-grade tumors (Fig. 6a&6b). The endothelial cells were faintly positive for NS in low- and high-grade tumors (Fig. 5&6). NS's nuclear expression and cytoplasmic expression were observed in clear cells and oncocytic cells of MECs variants (Fig. 7a) & (Fig. 7b) respectively.

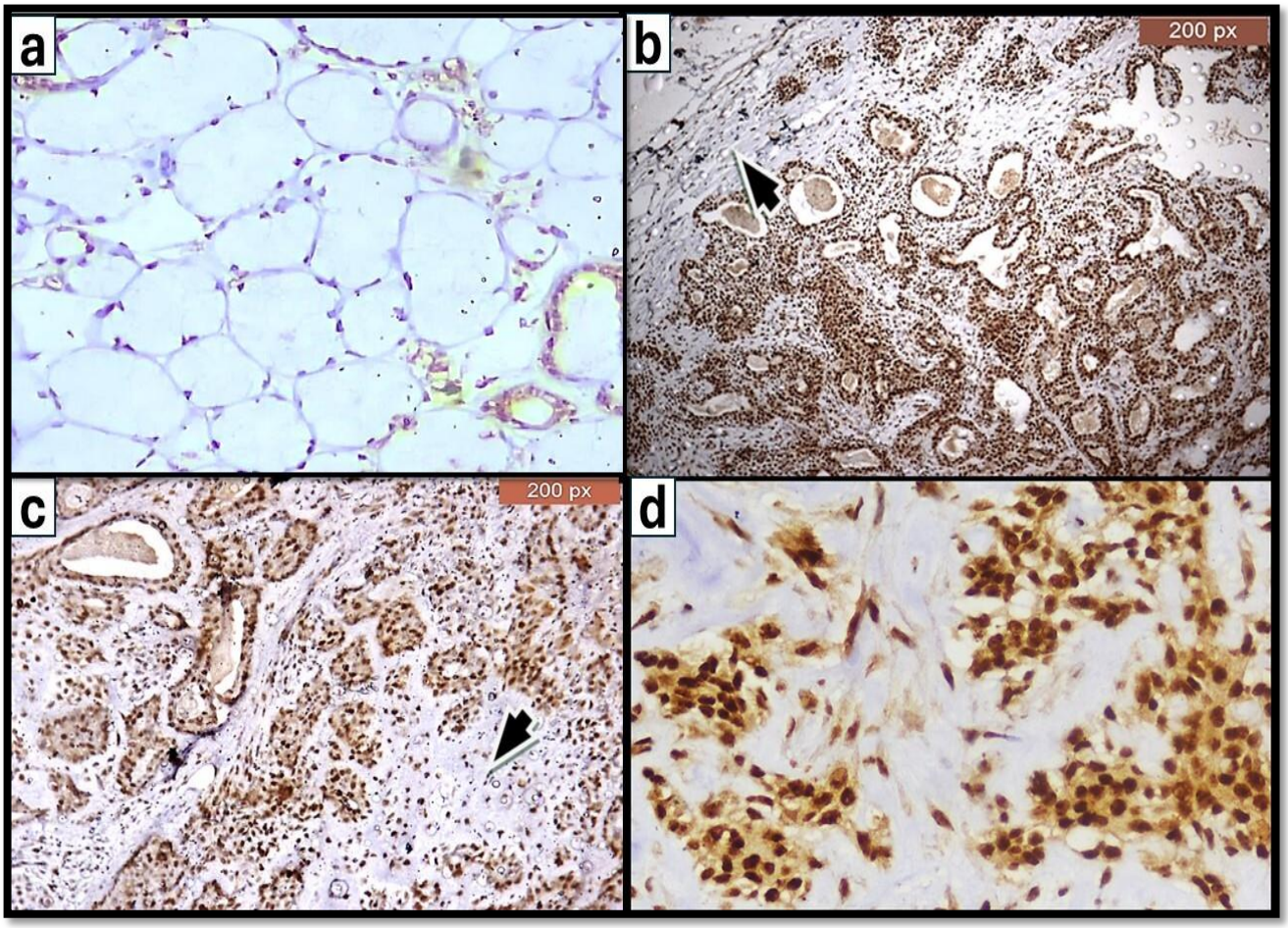

Figure 4. A photomicrograph of NS-stained sections showing (a) Normal SG tissue with most of the mucous tubules are negative, note the positivity of the ductal cells on the right (x400), (b) Faint NS expression in PA capsule (black arrow) (x200), (c) positive nuclear reaction in PA ductal and myoepithelial cells. Note the NS positivity in chondroid tissue (black arrow). (x200) and (d) nuclear and cytoplasmic expression in most cells (x400).

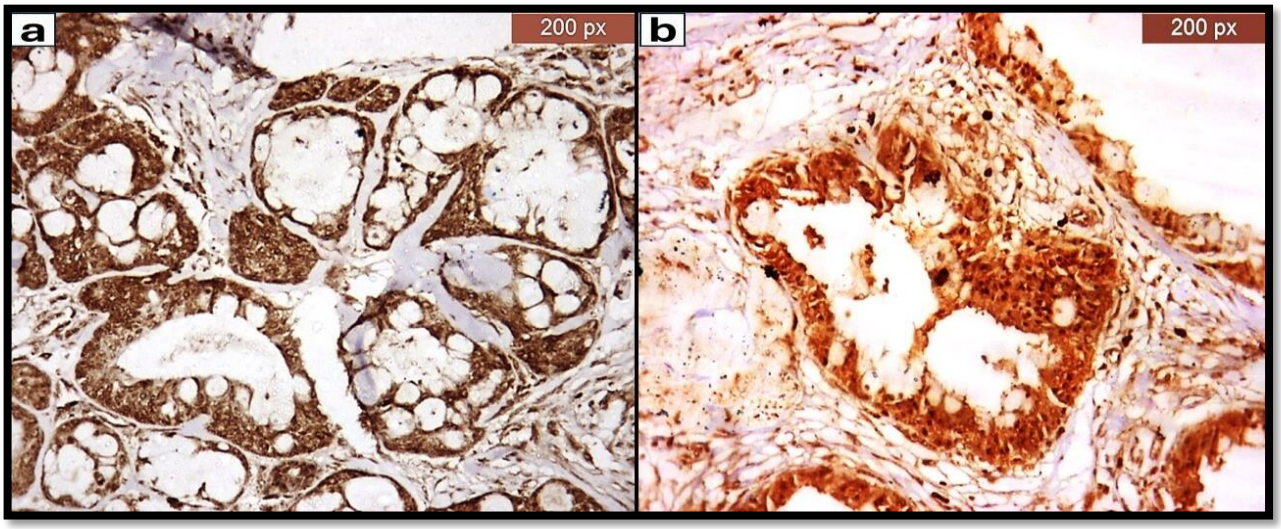

Figure 5. A photomicrograph of NS-stained MEC sections showing (a) nuclear expression in epidermoid, intermediate and mucous cells in low grade MEC (x200) (b) nuclear and cytoplasmic expression in low grade MEC (x400).

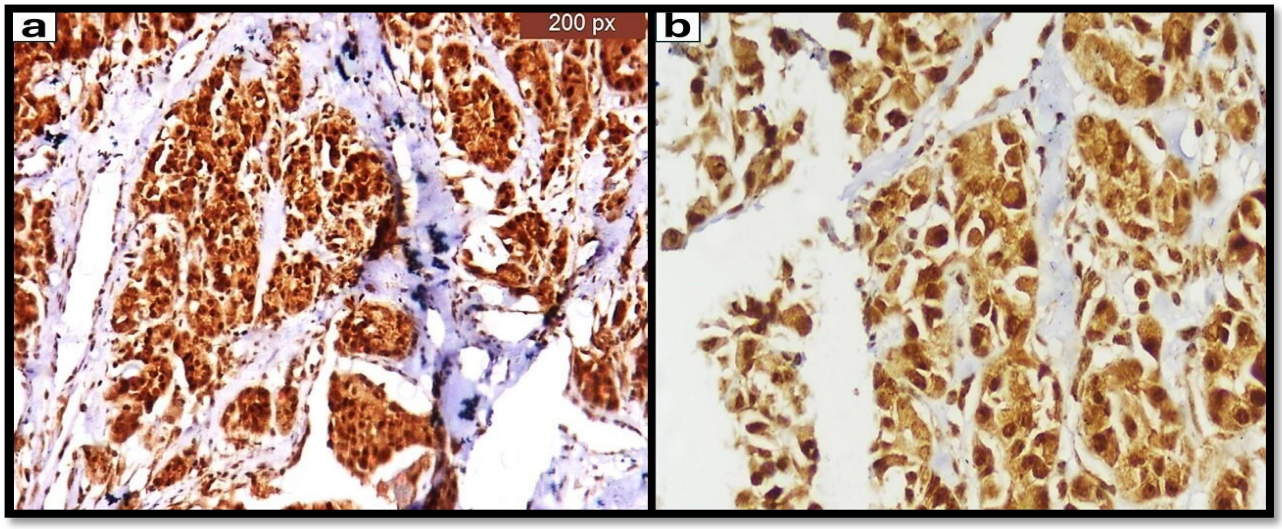

Figure 6. A photomicrograph of NS-stained MEC sections showing (a) nuclear expression in epidermoid cells in a high-grade MEC. Note the faint nuclear expression of endothelial cells (x200) and (b) nuclear and cytoplasmic expression in epidermoid of high-grade MEC (x400).

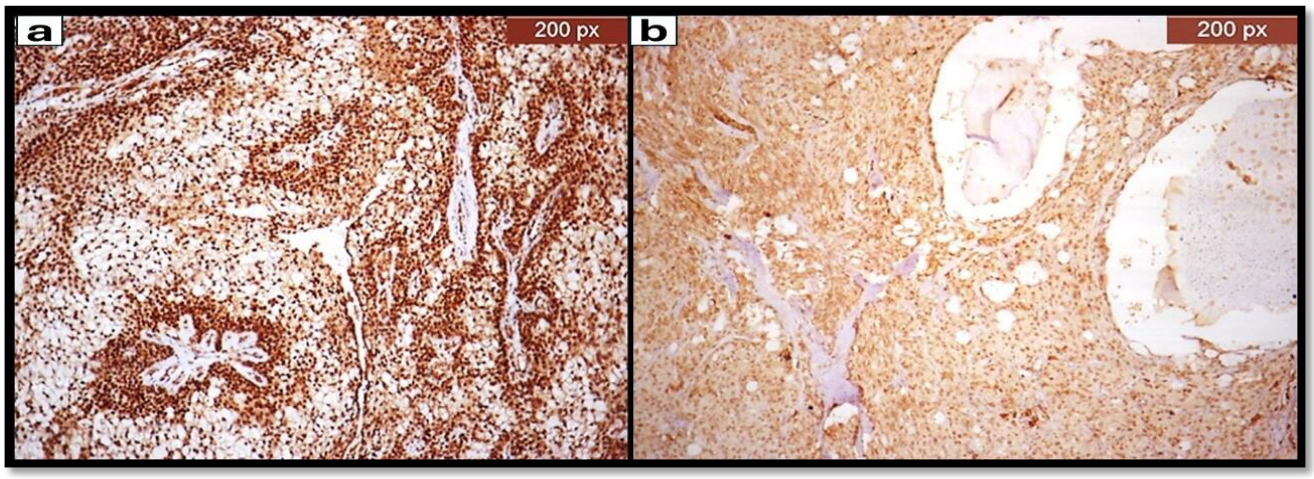

Figure 7. A photomicrograph of NS-stained sections showing (a) nuclear expression in the clear cells of MEC and (b) nuclear and cytoplasmic expression in the oncocytic cells of MEC (x200).

The clinical data of the cases studied is summarized and presented in Table 1&2. Note the drastic prevalence of the occurrence of PA in the palate. Note also the female predominance in the cases of MEC.

Table 1. Descriptive statistics of Chi-square test and student's t-test for comparisons between demographic data of the studied groups.

Demographic data	PA n=10	MEC n=12	P-Value
Sex			
Male	6(60%)	4(33%)	0.411747
Female	4(40%)	8(66%)	
Age [mean (SD)]	32.8 (8.34)	31.52 (16.67)	0.781077

Significance level p≤0.05

Table 2. Descriptive statistics of Chi-square test for comparison between tumor sites in the studied groups.

Site	PA (n=10)		MEC (n=12)		P Value
	n	%	n	%	0.08
Hard palate	9	90	4	33.3	
Labial mucosa	0	0	2	16.7	
Lower posterior gingiva	1	10	2	16.7	
Retromolar area	0	0	3	25	
Buccal mucosa	0	0	1	8.3	

Significance level p≤0.05

The data analysis of NS immunostaining revealed the highest mean NS expression in MEC cases (27.55±1.91), followed by a significantly lower value in the PA group (16.89±1.64). Normal SG tissues presented the lowest mean value (0.47±0.08). ANOVA test indicated a highly significant difference across all groups (p=0.000), and a post hoc test confirmed significant differences between each pair of groups (see Table 3&4 and Fig. 8).

Table 3. Descriptive statistics and comparison of NS area percentages of immunoexpression between groups (ANOVA test)

	Mean	Std. Dev	Std. Error	95% Confidence Interval for Mean		Min	Max	F value	P value
				Lower Bound	Upper Bound				
Normal SG tissue	.47[c]	.08	.03	.39	.56	.32	.54	526.2	.000**
PA	16.89[b]	1.64	.67	15.16	18.61	15.06	18.65		
MEC	27.55[a]	1.91	.78	25.54	29.56	25.08	30.31		

Significance level p≤0.05, ** highly significant
Post hoc test: means with different superscript letters are significantly different.

Table 4. Detailed results of Bonferroni post hoc correction test for pairwise comparisons of NS area percentage of immunoexpression

(I) Groups	(J) Groups	Mean Difference (I-J)	Std. Error	95% Confidence Interval		P value
				Lower Bound	Upper Bound	
Normal SG tissue	PA	-16.41333-*	.841	-18.68	-14.15	.000**
	MEC	-27.07500-*	.841	-29.34	-24.81	.000**
PA	Normal SG tissue	16.41333*	.841	14.15	18.68	.000**
	MEC	-10.66167-*	.841	-12.93	-8.40	.000**
MEC	Normal SG tissue	27.07500*	.841	24.81	29.34	.000**
	PA	10.66167*	.841	8.40	12.93	.000**

Significance level p≤0.05, ** highly significant

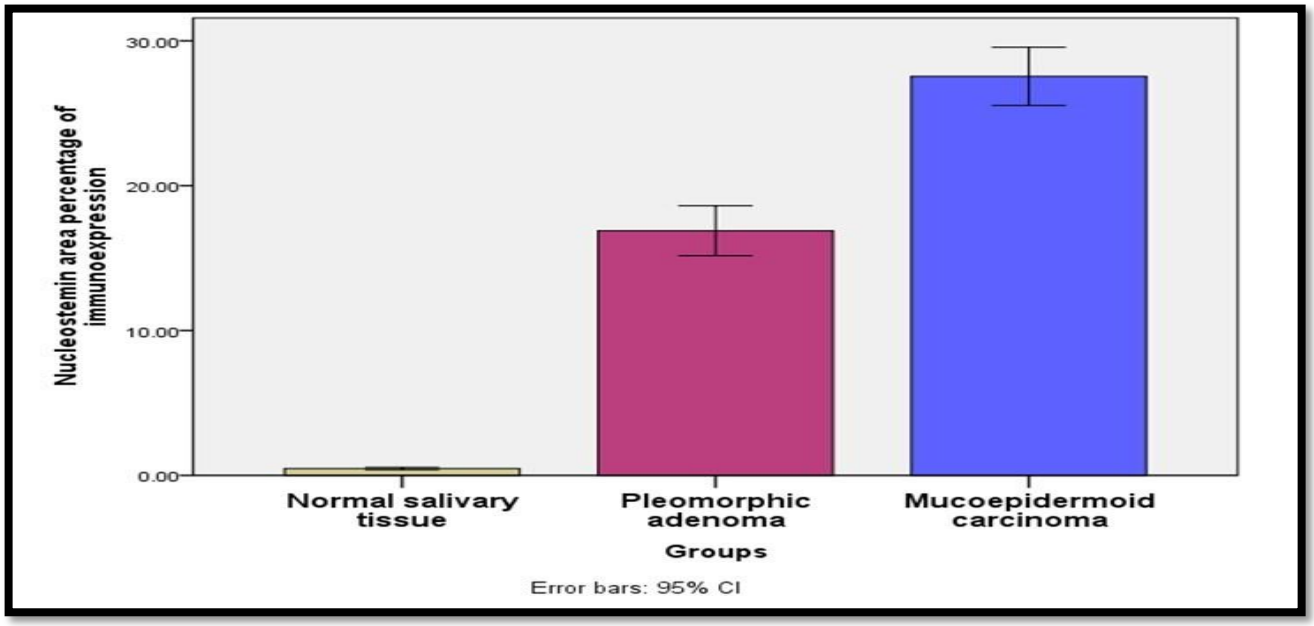

Figure 8. Bar chart illustrating mean NS area percentage immunoexpression in the study groups.

DISCUSSION

NS regulates neoplastic stem cell properties, and its overexpression is associated with tumor progression in different types of cancer[6,17]. In SGT, CSCs drive tumor growth, recurrence, resistance, and metastasis [3,8]. The differential expression patterns of NS in MECs and PAs could provide valuable insights into their pathophysiology and potential therapeutic targets. The novelty of this study lies in the investigation of NS immunoexpression in relevant SGT. In this study, the IHC analysis of NS revealed a highly significant difference in NS expression across all groups, with the highest mean NS expression in MECs, followed by PAs and then normal SGs, which is consistent with the documented function of NS in tumorigenesis[7-20]. In normal SG tissue, the predominance of NS in ductal tissues may reflect the concentration of stem cells in intercalated and excretory ducts, with fewer stem cells present in acinar tissues. Although mucous tubules are generally considered terminally differentiated, some mucous cells may retain proliferative potential. NS expressions in these cells may indicate a role in cellular maintenance or a low level of proliferative activity[21,22]. These findings provide a reasonable explanation for its expression in normal SG tissues.

In PA cases, the localization of NS in the nucleoli and nucleoplasm of both ductal and myoepithelial cells aligns with studies showing that NS shuttle between the nucleolus and nucleoplasm based on the cell cycle stage, stress conditions, and differentiation state[23]. Moreover, Bernardi and Pandolfi (2003) illustrated that when NS is expressed or localized in the nucleoplasm, it interacts with p53, inhibiting p53's growth-suppressive function, which occurs in tumorigenesis[24]. Additionally, NS expression in stromal components, including fibroblasts, chondroid, and myxoid tissues, supports its role as a marker of stemness and proliferation, as the formation of these tissues originates from stem cells or actively proliferating myoepithelial cells (1). Furthermore, the differential levels of parenchymal expression of stemness markers such as SOX2, ALDH1, and CD44 in PAs support this finding [25].

In MEC cases, NS expression is observed in the nuclei and nucleoli of both epidermoid, intermediate, and mucous cells, which is consistent with NS findings in oral squamous cell carcinoma (OSCC), where high NS expression is associated with tumor development, poor prognosis, and aggressive behavior by critically regulating CSCs[26,27] .

The cytoplasmic localization of NS in the assessed tumor sections suggests additional roles beyond proliferation, as indicated by studies on cancerous cell lines, such as the study of Kavyasudha et al., who reported that NS expression varies across normal and cancerous cells, being localized in both the nucleus and cytoplasm of cancerous cell lines but restricted to the nucleus in normal cells[28].Additionally, Yang et al.

(2005) and Fan et al. (2008) observed both nuclear and cytoplasmic NS expression in tumor cells, unlike its nuclear restriction in normal tissues This shift may reflect functional changes in malignancy, including roles in cell cycle regulation or stress response[29,30].

NS immunoreactivity was noted not only in tumor cells but also in endothelial cells within MEC tumor specimens. This observation aligns with previous evidence suggesting a role for NS in promoting the proliferation of endothelial cells in vascular biology[31,32]. The presence of NS in endothelial cells within the tumor microenvironment of MEC may reflect a response to tumor-induced stress or angiogenic signaling suggesting a broader functional role, possibly related to neovascularization or tumor-associated vascular remodeling.

CONCLUSION

In conclusion, this study demonstrates substantial NS expression in PA and MEC, indicating its potential roles in tumor biology and tumorgenesis. Further research with larger cohorts with clinicopathological correlation is recommended to provide a comprehensive understanding of these results.

DECLARATIONS

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Conflict of Interest

The authors have no conflicts of interest to declare."

Ethical approval

This work was approved by the Research Ethical Committee at the Faculty of Dentistry, Cairo University (No. 23 6 22), and was performed in compliance with the Helsinki Declaration. Informed consent was obtained from all the subjects and/or legal guardian(s).

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