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(Article begins on next page)

19 May 2024

DIFFERENTIAL EXPRESSION OF NICOTINAMIDE N-METHYLTRANSFERASE IN CUTANEOUS KERATOACANTHOMA AND SQUAMOUS CELL CARCINOMA: AN IMMUNOHISTOCHEMICAL STUDY.

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Key words: keratoacanthoma; immunohistochemistry; Nicotinamide N-methyltransferase; non-melanoma skin cancer; squamous cell carcinoma; tumor biomarker.

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The authors have no conflict of interest to declare.

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Nowadays, we are witnessing a worldwide increasing incidence of non-melanoma skin cancers (NMSCs), whose major types are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Although the latter is several times less common than the basal cell type, it accounts for the majority of NMSC-related metastatic disease and death. Head and neck SCCs, in particular, are more likely to metastasize[1,2].

As concerns keratoacanthoma (KA), some authors consider it as a self-resolving benign lesion, while others think that it is a precursor or a well-differentiated variant of SCC[2,3]. A prompt differential diagnosis between these two neoplasms represents a primary goal, since KA, unlike SCC, shows an excellent prognosis, thanks to its tendency to spontaneous involution. From a histopathological point of view, KA and well-differentiated SCC are difficult to distinguish. Nevertheless, it has been recently reported that they exhibit distinct gene expression profiles[4].

The aim of our study was to evaluate for the first time in cutaneous KA and SCC the expression of nicotinamide N-methyltransferase (NNMT), which was previously found to be upregulated in different solid tumors, including clear cell renal cell carcinoma (ccRCC), oral SCC and melanoma, in order to assess its diagnostic and prognostic potential[5-9].

This retrospective study was conducted on a total of forty-eight specimens collected from patients undergoing biopsy or excisional surgery between 2016 and 2018, in accordance with the principles of the Declaration of Helsinki. In particular, 20 KA cases (7 males and 13 females; mean age: 79.19 years; age range: 56-98 years; mean lesion diameter: 1.25±0.62 cm; diameter range: 0.4-2.5 cm), 18 SCC cases occurred on the trunk and extremities (9 males and 9 females; mean age: 75 years; age range: 54-94 years; mean lesion diameter: 0.89±0.33; diameter range: 0.5-1.6 cm), and 19 SCC cases from head and neck (17 males and 2 females; mean age: 75.35 years; age range: 57-94 years; mean lesion diameter: 1.35±0.83 cm; diameter range: 0.4-3 cm) were analyzed.

NNMT expression was evaluated by means of immunohistochemistry as previously described[9].

All analyses were independently performed by two investigators blinded to the patient group using a Nikon Eclipse E600 light microscope equipped with a Nikon DS-Vi1 digital camera. Agreement

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between observers was always >95%. Stained cells were counted in at least ten fields per sample (field: 0.07 mm^2, magnification 400×) and quantified as a percentage of the total counted cells. Each experiment was carried out three times in duplicate. Differences between groups were determined using the Kruskal-Wallis and Dunn's multiple comparison tests. Correlations with clinic-pathological parameters were assessed using the Spearman test. A p-value less than 0.05 was considered statistically significant.

No statistically significant relationship was found between protein level and age, sex and lesion size. Our results evidenced a significantly higher enzyme expression in KA, where it showed a strong cytoplasmic staining, compared to SCC. In particular, in head and neck SCC NNMT immunoexpression was moderate/good and the percentage of positive cells was significantly lower than in those of the rest of the body. Moreover, in tumors of the trunk and extremities the immunostaining was focal and faint (Figures 1 and 2). It is noteworthy that tumors with a less favorable prognosis showed decreased NNMT levels, in agreement with what was previously observed in other cancer[5-10].

Taken together, these observations lead us to hypothesize the existence of an inverse correlation between NNMT expression and tumor progression, thus suggesting a potential role of NNMT as a novel biomarker that could be used in the future for the early diagnosis and prognosis of these neoplasms, as well as for the development of targeted therapeutic strategies.

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Figure 1. Immunohistochemical expression of NNMT in tumor tissue sections. a) Keratoacanthoma. b) Squamous Cell Carcinoma of the trunk and extremities. c) Head and neck Squamous Cell Carcinoma (Immunoperoxidase, original magnification: x200).

Figure 2. NNMT immunohistochemical expression in KA, SCC of the trunk and extremities, and head and neck SCC. Values represent the mean percentage ± standard deviation of stained cells with respect to total counted cells. $p<0.0001$.

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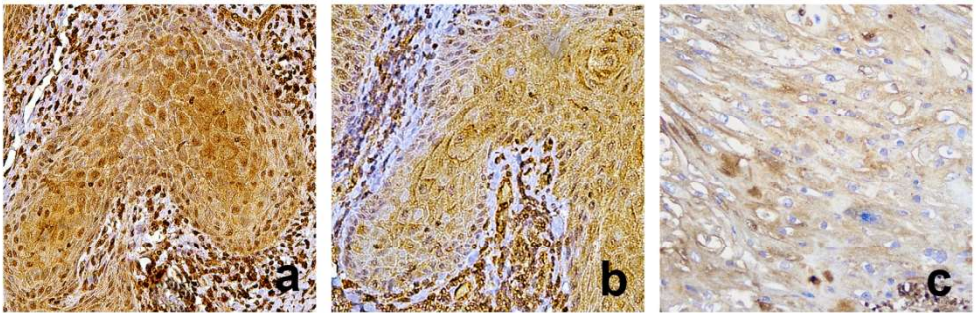

Figure 1. Immunohistochemical expression of NNMT in tumor tissue sections. a) Keratoacanthoma. b) Squamous Cell Carcinoma of the trunk and extremities. c) Head and neck Squamous Cell Carcinoma (Immunoperoxidase, original magnification: x200).

150x51mm (300 x 300 DPI)

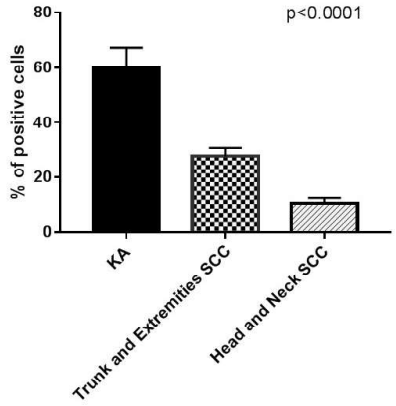

Figure 2. NNMT immunohistochemical expression in KA, SCC of the trunk and extremities, and head and neck SCC. Values represent the mean percentage ± standard deviation of stained cells with respect to total counted cells. p<0.0001.

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