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Abstract of PhD Thesis:

Study on the incidence, angiogenesis and histogenesis of skin tumors

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Malignant cutaneous tumors represent one of the most common forms of cancer. The incidence of basal cell carcinoma and squamous cell carcinoma is about ten times higher than melanoma, representing 20-30% of all neoplasms in Caucasians. Regards on the mesenchymal tumors, the benign types are more common than malignant ones; their incidence is reported of 3000/1.000.000 inhabitants compared to those of 30 sarcomas/1.000.000 people.

Taking into account the increasing incidence of skin tumors and the necessity of a proper individualized treatment, the two main goals of our study were, after performing a statistical correlation of the clinicopathologic features with the tumor immunophenotype, to explore their histogenesis and the posible predictive importance of some immunohistochemical markers.

In the first part of the study, a retrospective statistical analysis of 3410 cases of skin tumors and tumor-like lesions diagnosed in the Department of Pathology of the County Emergency Clinical Hospital of Tirgu Mureş, during 2006-2010, was performed.

We observed that the malignant epithelial tumors were the commonest ones, followed by benign mesenchymal and melanocytic tumors. Among epithelial tumors, squamous cell carcinoma was more common in men and basal cell carcinomas prevailed in women, both genders showing predominant localization in the head and neck region. Seborrheic keratosis was the commonest benign epidermal tumor and follicular differentiation was the commonest feature that characterized the adnexal tumors. In sun-exposed areas, actinic keratosis was the predominated type of premalignant lesions. Malignant melanoma showed a predominant localization on men's trunk and on women's lower limb. Regards on mesenchymal tumors, the predominance of tumors of the connective and adipose tissue was seen. Lipomas and liposarcomas prevailed, followed by epithelioid sarcomas, undifferentiated pleomorphic, sarcomas, fibrosarcomas and fibromyxosarcomas. In our material, we also observed that about 2-3 cases of mycosis fungoides are diagnosed every year.

In the second part of the study, the four chapters included four studies; after a very careful re-examination of the histological slides, we selected the most representative cases to perform immunohistochemical (IHC) examinations. Based on a large panel of antibodies, we aimed to study the particularities of angiogenesis in carcinomas (first study) and also in some of the cutaneous mesenchymal tumors (second study). At the same time, based on the tumor immunoprofile, exploration of histogenesis of Kaposi sarcoma (third study) and granular cell tumor (fourth study) was attempted. The results of each of the study were published and presented in extenso in the attached list of publication.

First study - Correlation of angiogenesis with other immunohistochemical markers in basal cell and squamous cell carcinoma. The angiogenic immunoprofile of the two carcinomas was explored with the antibodies VEGF-A and COX-2 and the values of endothelial area were quantified using the marker CD31. For a complex evaluation, the results were correlated with the immunoreactivity of maspin, DOG-1, p16 protein, and protein Mena. Our study proved that, in squamous cell carcinoma of the head and neck region, tumor dedifferentiation seemed to be dependent on VEGF-p16 interaction, possibly activated by ultraviolet rays. Carcinogenesis, independent of ultraviolet rays, was related on the interaction of DOG-1/Mena/COX-2. The abnormal DOG-1 expression was inconstantly observed in both squamous and basal cell carcinoma. The angiogenic

immunophenotype of tumor cells and microvascular density showed no significant differences between the two types of carcinomas. The nodular variant of basal cell carcinoma presented an increased p53 index and predominantly cytoplasmic expression of maspin while the adenoid variant expressed maspin in both cytoplasm and nuclei of the tumor cells, in parallel with a low p53 index.

Second study - Correlation of angiogenesis with other immunohistochemical markers in mesenchymal tumors. The aim of this study was to examine the particularities of some of the IHC markers less explored in soft tissue tumors. The tumor angiogenesis (explored with VEGF-A, COX-2, and CD31) was correlated with the immunoexpression of maspin, c-KIT, DOG-1 and CD34.

We observed that the angiogenic activity of soft tissue tumors depended on the tumor`s microscopic type; it was mediated by the interaction of VEGF-A/COX-2 in tumors with histiocytic differentiation and dermatofibrosarcoma, while the VEGF-A/ maspin relationship was more specific for liposarcomas. This information could be useful for a further personalized therapy of these tumors. Moreover, the concomitant DOG-1/VEGF-A/maspin positivity in liposarcomas suggests the potential pro-angiogenic role of DOG-1, this aspect being not yet reported in literature.

Third study - Histogenesis of Kaposi sarcoma. For this study, a panel of seven markers was used, as follows: CD31, CD34, c-KIT, SMA, COX-2, VEGF-A, CD105.

Based on the results obtained after quantification of the immunostains and literature data, we hypothesize that Kaposi sarcoma cannot be considered to have a pure vascular origin; it seems to be a variant of tumors with myofibroblastic differentiation, the possible origin being the viral modified-multipotent mesenchymal stem cell that express CD105. The mesenchymal-endothelial transition and differentiation of myofibroblasts may be the key-events whose understanding can influence the therapeutic management of Kaposi sarcoma.

Fourth study - Histogenesis of granular cell (Abrikosoff) tumor. The microsatellite status was determinded and immunohistochemical examinations were performed using a panel of 23 antibodies: maspin, p53, Ki67, CD31, CD34, CD105, SMA, EMA, c-KIT, RET, chromogranin, sinaptofizină protein S 100, NSE, GFAP, HER-2, calretinină, inhibin-α, MLH-1, MSH-2, CD56, CD68, HMB45. The main aim of the study was to emit a hypothesis on the histogenesis of this tumor, invalidating or confirming data from literature.

Our results, partially correlated on the literature data, showed that granular cell tumor cannot be considered a pure neural tumor, the immunoprofile suggesting an endo-mesenchymal origin. Microsatellite instability seems to not be involved in its histogenesis, no data being published in this field. The positivity of c-KIT and RET positivity in atypical forms of granular cell tumor, also not yet reported in the literature, suggests the possibility of using anti-tyrosine kinase drugs in targeted therapy of malignant forms. Another original observation was that the 'pustulo-ovoid bodies of Milian', expressed CD105, synaptophysin and HER-2.

To resume the thesis at one phrase, we conclude that, even in the extensively studied tumors, an attentively evaluation could show new original and valuable data, with possible prognostic and predictive value.

Keywords: skin tumor, carcinoma, soft tissue tumors, angiogenesis, histogenesis.

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