EDITORIAL

Papillary thyroid carcinoma: a cancer with an extremely diverse genetic background and prognosis

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A vast majority of patients with differentiated thyroid carcinoma (DTC), especially with papillary thyroid carcinoma (PTC), live a disease-free life with good prognosis. This causes a substantial difficulty in planning the therapeutic process, as some of the patients have been overtreated (from the retrospective point of view), whereas in other patients, the same therapy does not result in the destruction of the neoplastic foci and inhibition of the natural course of the disease. Therefore, it is so important to know the factors that may indicate a more aggressive course of cancer. Having such information should affect treatment decisions and, consequently, the effectiveness of treatment to ultimately achieve remission of DTC.

Angiogenesis and lymphangiogenesis are both important for tumor progression processes and constitute basic characteristics of the tumor microenvironment.[1] However, their exact roles in the above processes are different. While angiogenesis promotes tumor growth and ability to metastasize, lymphangiogenesis is involved in the process of cancer cell dissemination to the lymph nodes, providing an alternative route for cancer spreading.[2] The methods often applied for quantifying angiogenesis and lymphangiogenesis include measuring the so called microvascular density (MVD) and lymphatic vessel density (LVD). The values of both parameters, MVD and LVD, are used to demonstrate the increased risk of tumor progression; moreover, they also facilitate prediction of disease outcome.[3]

The main purpose of the study by Sculetic et al[4] was to evaluate the angiogenic and lymphangiogenic phenotypes of different histological variants of PTC and to assess the impact of the expression of biological markers such as vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX-2), and p27 on the angiogenic and lymphangiogenic profiles in PTC. MVD was measured using the universal endothelial cell marker CD31. The assessment of LVD was performed using the highly specific lymphatic endothelium marker D2-40. The study seems to be an interesting attempt to use this method, and the results suggest that VEGF, COX-2, and p27 may be important biological markers that reveal the differences in angiogenic and lymphangiogenic potentials between the follicular and classical variants of PTC.

The major weakness of the study is the small number of cases analyzed, as pointed out also by the authors. On the basis of the obtained results, the conclusion is formulated correctly; however, it needs to be taken with caution as studies in a much larger number of patients are needed to clarify the clinical importance of the observed changes in MVD and LVD values.

When discussing some other limitations of the study, we would like to emphasize the great complexity of the various histopathological variants of PTC. We cannot quite agree with the authors that molecular profiles determining the potentially aggressive nature of various histopathological PTC variants, especially the follicular and classic ones, are not fully understood. These 2 variants of PTC that are included in the analysis are the most common histopathological variants, although they are not the most aggressive ones.[5,6] Furthermore, recently, a noninvasive follicular neoplasm with a PTC-like appearance of the cell nuclei has been distinguished from a follicular variant of PTC and recognized as a benign lesion.[7] It represents 17% of all PTC cases diagnosed on the basis of the criteria used so far for that type of cancer. The other follicular variants of PTC are characterized by only moderate aggressiveness, but they constitute a total of about 10% of all PTC cases. At this point, it should be emphasized that at the present stage of knowledge on molecular biology, it is already clear that biologically less aggressive PTC forms (mostly the follicular variant) are primarily associated with

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RAS gene mutations or with activation of *PAX8-PPARG* fusion oncogenes.[5,6] As regards the follicular PTC variant, *BRAF* gene mutations are only found in rare infiltrative follicular cases.

The classic variant of papillary cancer, although it accounts for about one-third of all cases of this tumor, is characterized by a wide range of biological behaviors, from slightly to extremely aggressive, which results from the diverse molecular basis of this subtype of cancer (most commonly *BRAF* mutations—of considerable aggressiveness; on the other hand, tyrosine kinase receptor rearrangements—less aggressive PTC). It is a pity that the authors, because of the small sample size, could not analyze the most aggressive histological variants of PTC, namely, the columnar-cell and tall-cell PTC variants, the diffuse sclerosing variant, and the newly identified hobnail variant. It appears, however, that they do not account for more than 10% of all papillary carcinomas, of which the tall-cell variant is the most frequent (7%). However, it should not be forgotten that the cited distribution of PTC into different variants (histological subtypes)[5] is—from a logical point of view—a nonstratified (blurred) classification, because belonging to particular histopathological variant is not the only criterion used in this division. The second is the diameter of the lesion—it should be less than 1 cm for a microcarcinoma. This variant can meet all histological subtypes and represents more than 30% of all PTC cases. Probably, because of the usually small size of the cancer foci, these lesions are rarely clinically relevant and, according to the American Thoracic Association guidelines, there is no need for a fine-needle aspiration biopsy, even despite intermediate or high ultrasound risk, until the onset of an extrathyroidal invasion, lymph node metastases, prior exposure to ionizing radiation, or a family history of thyroid cancer have been established.[8] In summary, the only 2 histopathological PTC variants analyzed by Sculetic et al[4] do not cover the entire problem of using MVD and LVD in predicting PTC progression and treatment outcomes.

We also have some reservations as to the selection of classification for the division of patients into high- and low-risk groups. The authors referred to the classification proposed by Sugitani et al,[9] in which the risk group was based on well-known risk factors such as local cancer invasion, distant metastasis, and patient age. The main difference in comparison to other classifications was the recognition of nodal metastasis of 3 cm or larger in size in patients aged 50 years or older as a risk factor, as well as reclassification from high to low risk after disease-free interval of more than 3 years from the initial treatment. Unfortunately, among the patients evaluated in the study by Sculetic et al,[4] there were no patients with such clinical characteristics, and the authors did not include in the classification the course of the disease after the treatment applied. Thus, the division into high and low risk was based on the age parameter and the presence of local extrathyroidal invasion. These features, however, are included in practically all prognostic schemes used for defining risk-group categories in patients with DTC (AGES: patient age, histological grade of the tumor, tumor extent, extrathyroidal invasion or distant metastases, and size of the primary tumor; AMES: patient age, presence of distant metastases, extent and size of the primary tumor; MACIS: metastasis, patient age, completeness of resection, local invasion, and tumor size; NTCTCS: National Thyroid Cancer Treatment Cooperative Study).[10] The classification by Sugitani et al[9] was established after an average follow-up period of 10.7 years, which is a shorter period than in all the above classifications. In the context of the typical DTC course, characterized by the presence of recurrences even many years after the end of treatment, it seems that it would be preferable to evaluate the association of angiogenic and lymphangiogenic phenotypes of PTC with clinical risk, using another prognostic DTC classification.

Despite all the limitations, the article of Sculetic et al[4] seems very interesting and opens a new direction for research which should be conducted on a much higher number of patients.

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