The role of immunohistochemical markers in prognosis evaluation and carcinogenesis mechanisms of colon tumors

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A large number of studies try to clarify the etiology of colorectal carcinomas, but presently secondary prevention, early detection and removal of precancerous lesions play an important role in the management of this disease. Classification, morphologic and microscopic aspects, and the main molecular-genetic characteristics of the precancerous lesions are described in the first chapter of the general part. In the second chapter of this part I characterized the main colorectal carcinogenetic pathways, enumerating epidemiologic, histological and molecular-genetic arguments to support these mechanisms.

The aim of this work was the study of clinico-pathological parameters of colorectal adenomas/polyps and carcinomas, and their correlation with immunohistochemical parameters; the changes in expression of certain markers in adenomas and carcinomas, and their correlation with classic prognostic factors; immunohistochemical markers with a possible role in the monitoring of colorectal carcinogenesis; particular aspects of de novo CC compared to ex adenoma CC; definition of certain immunephenotypes which are able to characterize the main mechanisms of carcinogenesis.

In this retrospective study 117 colon adenomas/polyps and 149 colon carcinomas have been processed, from the Pathology Department of the Clinical County Hospital of Târgu- Mureș, localized in the cecum, ascending, transverse, descending and sigmoid colon, and rectum (the rectal ones have not been included). I followed the clinico-pathological parameters of colon adenomas and carcinomas. For immunohistochemical marker identification I used two immunohistochemistry methods: the Ultravision Labeled Polymer System and the Ventana automated method. The markers were as follows: E-cadherin, syndecan-1, Ets-1, matrix-metalloprotease-7, Bcl-2, p53, Ki-67, c-myc, APC (Adenomatous polyposis coli), MSH2. In order to quantify and compare the results of immunohistochemical reactions I performed a subjective evaluation of the number of positive cells out of 100 tumor cells, thus obtaining a percent based index subsequently used for determination of immunohistochemical score (IS) for each marker. For correlation of classic prognostic factors with immunohistochemical results I used descriptive and inferential statistical tests.

In the results and discussions chapter I described the clinico-pathological parameters and the obtained immunohistochemical results for adenomas and carcinomas for each marker, and performed a comparison with literature data. In the synthesis I compared clinico-pathological data and immunohistochemical results of adenomas and carcinomas.
Both adenomas and carcinomas develop more frequently in males between 60-70 years, bearing a similar age group distribution and in the left colon. Histologically adenomas were more frequently non-dysplastic tubular and tubulo-villous adenomas, and carcinomas were moderately differentiated adenocarcinomas, diagnosed in stage pT3N0M0 and Dukes’ B2. About a third of adenomas developed synchronously with carcinomas, and were especially of tubular type, compared to those not associated with a malignant lesion, which were especially tubulo-villous. Carcinomas developing from an adenoma were more frequently well differentiated, without lymph node and distant metastases, as compared to de novo carcinomas.

In case of carcinomas E-cadherin, syndecan-1 and APC expression showed a decrease, and Ets-1, MMP-7, p53, Ki-67, c-myc a significant increase in comparison with adenomas. In ex adenoma carcinomas compared to de novo carcinomas I observed a higher E-cadherin and syndecan-1 expression and a weaker or absent Ets-1 and MMP-7 expression. I noted a positive correlation between syndecan-1 and E-cadherin expression in case of both adenomas and carcinomas. However, Ets-1 displayed a negative correlation in adenomas, and a positive one in carcinomas expressing MMP-7.

Based on immunohistochemical changes noted in hyperplastic polyps and serrated adenomas I characterized the serrated pathway, and based on the changes demonstrated in tubular, villous and tubulo-villous adenomas and carcinomas I established the characteristics of the adenoma-carcinoma sequence. In a small number of cases I noted intermediate immunohistochemical changes between the serrated pathway and the adenoma-carcinoma sequence.

The serrated pathway is characterized by maintained E-cadherin and syndecan-1 expression, the absence of Ets-1 protein, increased expression of Ki-67, c-myc proteins, and decreased expression of MSH2. In case of the intermediate pathway I noted maintained E-cadherin and syndecan-1 expression, increased expression of Ets-1, p63, Bcl-2, Ki-67, and c-myc, and decreased expression of APC and MSH2. In case of the adenoma-carcinoma sequence E-cadherin and syndecan-1 expression decreases or disappears, Ets-1, MMP-7, p63, Ki-67, Bcl-2, and c-myc expression increases, and expression of APC and MSH2 decreases.

Our immunohistochemical study attempts to contribute to the clarification of the adenoma-carcinoma sequence and the serrated pathway in colorectal carcinogenesis, and also points out new information not yet discussed in the literature, concerning ex adenoma and de novo carcinomas.