Microscopic and immunohistochemical researches in preneoplastic and tumor lesions of the cervix uterus

The following paper includes a retrospective study of cervical lesions biopsy diagnosed and a prospective study of cervical neoplasia, which includes a section on molecular biology of cervical neoplasia.

This retrospective study refers to the evolution rate of cervical lesions diagnosed from cervical biopsies, respectively the endocervical scrape collected from 2001 to 2008 and found its place as an introduction to a further complex study. In this period of 8 years, in our laboratory were processed a total of 1387 biopsies and endocervical scrape. All histopathological diagnoses can be classified into four categories of injury: inflammation, cervical intraepithelial neoplasia, squamous cervical carcinoma, cervical adenocarcinoma.

Following the frequency of different types of cervical intraepithelial neoplasia in two intervals (2001-2004, respectively 2005-2008) I noticed that in intraepithelial neoplasia grade 1 (CIN 1) and grade 2 (CIN 2), were not obtained statistical significant values on their frequency within the ranges studied, however intraepithelial neoplasia grade 3 (CIN 3) presents a tendency to increase in frequency in the second interval. In invasive cervical lesions, only the squamous cell carcinoma showed statistical significance in frequency, in a downward way in the second interval.

The largest part of this paper is done prospectively in 2006-2008, on a number of 265 biopsies and endocervical scrape with dysplasia and invasive cervical lesions, analyzing them from different points of view.

Microscopic examination, in usual staining, tried to specify the severity grade for intraepithelial neoplasia and in the case of carcinomas their type and microscopic grading. I studied the expression of two monoclonal antibodies: p16 protein - a marker of cell cycle and proliferation factor Ki67 in the 265 cases considered in the study, in order to determine their usefulness in a correct diagnosis of the intraepithelial neoplasia. In carcinomas we studied the expression of other immunohistochemical markers useful in the differential diagnosis.

Comparing the dysplasia diagnosed on HE staining with the ones confirmed immunohistochemical (co expression P16/Ki67) we determined the sensitivity (96.9% value) and specificity (90.45% value) of these immune reactions, confirming their high utility values.
particularly in the diagnosis of CIN 2, where the probability test shows a relative difference to CIN 1 and CIN 3.

Determination of the co expression P16/Ki67 finds its utility in the differential diagnosis of some cervical lesions that can mimic cervical dysplasia: reactive atypia in cervicitis and cervical atrophic changes. Also, in the case of quantitatively small and incomplete biopsies - when you cannot determine with certainty the degree of dysplasia in the usual coloring, using the immunomarkers P16 and Ki67, can help you classify the lesion in one of the two categories of the Bethesda classification of squamous intraepithelial lesions: L-SIL or H-SIL.

Average value of Ki67 proliferation index, which shows an exponential increase with the increasing rate for cervical intraepithelial neoplasia and positivity for P16 in cervical intraepithelial neoplasia, indicating the presence of high-risk HPV - justify the examination of protein expression P16/Ki67 in cervical biopsies and its introduction in the routine panel.

Comparing the cytological diagnosis (SIL) with the histopathological one (CIN) I have noticed a good correlation for H-SIL cytological diagnosis, relatively few cases are cytological over diagnosed, unlike L-SIL, which all are. In the cytological diagnosis of ASC-US, our findings show that 41% of cases were severe intraepithelial neoplasia on the biopsy material, compared to 10-20% in other studies.

In cervical carcinoma, the following immunohistochemical markers showed important diagnostic value: ER, PR, VIM, CEA and p63 in specifying the endocervical or endometrial location. But the safest location differential diagnosis of HPV-HR remains detection by PCR, which positive reaction excludes in all cases the endometrial location for adenocarcinoma.

Measurements of molecular biology in order to highlight and standardize HPV were performed at the National Cancer Institute in Budapest. I studied the presence of HPV type 16 in intraepithelial and invasive cervical cancer lesions by real-time PCR on an etalon of 20 cases. The results obtained with this modern research technique complete this study. The PCR method (which identifies low levels of viral DNA with the possibility to specify the HPV strain), shows evidence of active infection as a risk indicator of normal cervical epithelium transformation in dysplastic epithelium or progression of the existing dysplasia. In cases of CIN2 and CIN3 HPV16 involvement was found in all the studied cases. The presence of HPV16 is associated with high-grade cervical neoplasia, representing a potential risk marker for progression of cervical intraepithelial neoplasia. Lack of viral DNA in some invasive carcinomas should be considered as false negative, which can be explained by a significant change in HPV genome during carcinogenesis.