POSSIBILITIES FOR DIAGNOSIS AND TREATMENT OF CERVICAL DISEASES

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Abstract. Women over 30 require screening to improve HPV detection and Pap smear cytology. Only a negative Pap test and negative HPV test can confirm the absence of pathology.

Keywords: Human papillomavirus, cervical intraepithelial neoplasia, liquid-based cytology, p16/Ki67 double staining, HPV testing

Relevance. Cervical pathology (CM) is one of the most common gynecological diseases, especially in antenatal clinics—25–45%. In gynecology and obstetrics, early diagnosis and adequate treatment of underlying and precancerous conditions, as well as early forms of cervical cancer, remain a major challenge [1, 3, 5, 7, 9]. Various methods are used to diagnose precancerous conditions and cervical cancer (CC), but the most readily available are clinical imaging, colposcopy, molecular biological methods for detecting HPV (polymerase chain reaction – PCR or the DIGENE test), cytological examination of smears, and histological examination of a targeted cervical biopsy. Epidemiological and molecular biological data indicate an important role of the human papillomavirus in the development of cervical intraepithelial neoplasia and cervical cancer [2,4,6,8,10]. In almost 100% of cases of cervical cancer patients confirmed by histological examination, highly oncogenic types of the human papillomavirus (HPV) are detected. Currently, it is generally accepted that HPV is one of the leading factors in the development of cervical cancer. According to C.M. Wheeler et al. (2016), 3 years after HPV infection, CIN II–III develops in every fourth woman (27%) [1,11,12]. In Russia, papillomavirus infection is diagnosed in 15.5% of women, in the USA – in 28.6%, in Europe – 2–12% [2,6]. Human papillomavirus is a DNA virus consisting of two structural genes (L1 and L2) and seven functional genes (E17). More than 200 types of HPV are known, more than 40 of which are capable of affecting the mucous membranes of the genitals [3,13]. HPV are divided into highly oncogenic (16, 18, 31, 33, 35, 39, 45, 46, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and low oncogenic (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) types of the virus. Studies by L. Giannella et al. (2018) [2] showed that in women with a histologically verified diagnosis of CIN 3, HPV type 16 was detected in 63.6% of cases, HPV type 33 in 7%, HPV type 18 in 6.2%, and HPV type 31 in 5.4%. However, the authors showed that

HPV type 16 is more common in patients under 35 years of age [15]. A number of studies have shown that invasive cervical cancer is caused by HPV types 16 and 18 in 70% of cases [1].

Cytological analysis of cervical smears is used as an initial (screening) diagnosis of tumor and precancerous lesions [3, 4]. The final conclusion determining the treatment tactics is formulated only through histological examination of biopsy or surgical material [2]. Immunohistochemical research methods play a significant role in the diagnosis and differential diagnosis of precancerous lesions of the cervix [15].

The aim of this work is to analyze the literature data on the possibilities of using immunohistochemical markers for the diagnosis and differential diagnosis of cervical lesions. According to modern guidelines on cervical oncomorphology [7], precancerous lesions of the cervix are divided into squamous cell and glandular. The former, in turn, are divided into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). Low-grade lesions correspond to CIN 1, and high-grade lesions to CIN 2 and CIN 3. The main advantages of this classification are a more accurate reflection of the processes of onco- and morphogenesis, as well as the unification of cytological and histological classifications, aimed at an unambiguous interpretation of the identified changes. It should be added that changes corresponding to CIN 1 undergo regression in 70–80% of observations, and in girls under 25 years of age – even in 90% of cases [8]. Changes of the CIN 3 type, on the contrary, are characterized by further progression to invasive forms of cancer: in 0.2–4% of cases – within 12 months [9]. The morphological diagnosis of CIN and its degree is based on the determination of the zone of the epithelial layer of the cervix occupied by atypical basal cells, during traditional histological examination of preparations stained with hematoxylin and eosin.

The most significant help in identifying and determining the degree of CIN is the immunohistochemical detection of Ki-67 and p16. Ki-67 is a cellular marker of proliferation, which is expressed at all stages of the cell cycle, with the exception of the G0 stage. In normal cervical epithelium, a positive Ki-67 reaction is observed only in the nuclei of the suprabasal cell layer [10]. In CIN observations, the localization of cells expressing Ki-67 depends on the degree of damage [10, 11]. According to R. Carreras et al. [13], the proliferation index by Ki-67 was 25%, 68% and 65.5% in LSIL, HSIL and invasive squamous cell carcinoma, respectively. Based on the determination of the number of Ki-67-stained cells in CIN 1 and CIN 2, it was concluded that it is a clear indicator of the extent of damage and a strong prognostic factor for the disease [14]. A very interesting model for determining the risk of CIN progression was

proposed by A. Kruse et al. [15]. Based on the values of the epithelial stratification index and the percentage of Ki-67-positive cells in the middle third of the epithelial layer, women were divided into groups with low and high risk of disease progression. The group of patients with low risk included CIN observations with a stratification index of less than 0.57 and a proliferation index of less than 30%, the remaining women formed a group with a high risk of CIN progression.

However, it should be added that the expression level and the number of Ki-67-positive cells depend on the level of circulating hormones. Thus, the number of stained cells increases in the parabasal layer during the secretory phase (luteal phase) of the menstrual cycle and during pregnancy [1,6]. Another widely studied marker of cervical tumor lesions is p16. The main function of p16 is considered to be the inhibition of cyclin-dependent kinase (CDK4/6), which is involved in the regulation of the cell cycle. It has been established that the expression level of p16 correlates with the presence of high-risk human papillomaviruses (HPV) in the development of cervical cancer [1,7]. Therefore, the reaction to p16 is recommended as a marker for the presence of high-oncogenic-risk HPV infection [4, 6]. Along with this, pronounced expression of p16 has been described in CIN and cervical cancer [1,8]. Moreover, the intensity of the reaction increases with the severity of the lesion [1,8]. A meta-analysis found that a positive reaction to p16 occurs in 2% of normal ectocervical specimens, 38% of CIN 1 specimens, 68% of CIN 2 specimens, and 82% of CIN 3 specimens [1,9]. It is noteworthy that nuclear staining was predominant in most specimens, although a cytoplasmic reaction was also observed.

It is believed that if a patient with a positive HPV test result is found to have atypical squamous epithelial cells of undetermined grade or LSIL during cervical cytology, the pathologist should not differentiate between reactive epithelial changes and LSIL when analyzing the biopsy material, since these changes have approximately the same risk of developing HSIL (5–10% over 2 years). The described immunohistochemical markers should be used for differential diagnosis of cervical lesions. Thus, a positive reaction to Ki-67 in superficial epithelial cells can also be observed during inflammation. Therefore, analysis of p16 expression is crucial for differentiating reactive changes from squamous intraepithelial lesions [2,3]. A high proliferation index determined by Ki-67, combined with diffuse nuclear and cytoplasmic expression of p16 in most cervical epithelial cells, indicates the presence of squamous intraepithelial lesions.

Therefore, women over 30 years of age require screening to improve HPV detection and cytological examination of cervical smears using the Papanicolaou method. Only

a simultaneous negative result of both the PAP and HPV tests can conclude that pathology is absent.

Conclusions. Unfortunately, there are currently no immunohistochemical markers to verify the invasive form of adenocarcinoma. Therefore, its diagnosis requires a thorough histological examination of serial specimens [5]. Thus, immunohistochemical examination is rightfully considered an effective method of pathohistological examination, allowing for the objective diagnosis of cervical tumor lesions, their differential diagnosis with reactive and tumor-like changes, and determining the prognosis of the disease.

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