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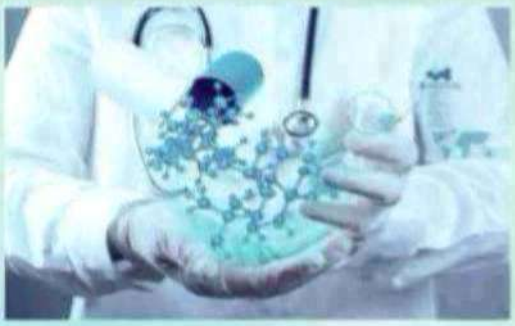

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MORPHOLOGICAL VARIANTS OF TISSUE REACTION OF THE CERVICAL EPITHELIUM IN HUMAN PAPILLOMAVIRUS INFECTION IN WOMEN OF REPRODUCTIVE AGE

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✓ ***Resume***

Women with chronic cervicitis have a high frequency of squamous cell intraepithelial lesions of the cervix (71.3%): LSIL 45.0%, HSIL 26.3%. In women with chronic cervicitis and squamous cell intraepithelial lesions of the cervix, bacterial-viral associations predominate in the microflora of the cervicovaginal discharge.

Keywords: chronic cervicitis, cervical squamous cell intraepithelial lesion.

RYePRODUKTIV YoShDAGI AYoLLARDA ODAM PAPILLOMA VIRUS INFYeKSIYaSIDA BAChADON BO‘YNI EPITYeLIYSI TO‘QIMA RYeAKSIYaSINING MORFOLOGIK VARIANTLARI

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✓ ***Rezyume***

Surunkali servitsit bilan og'rigan ayollarda bachadon bo'yni skuamoz hujayrali intraepitelial shikastlanishlarining yuqori chastotasi kuzatiladi (71,3%): LSIL 45,0%, HSIL 26,3%. Surunkali servitsit va bachadon bo'yni skuamoz hujayrali intraepitelial shikastlanishlari bilan og'rigan ayollarda serviko-vaginal ajralma mikroflorasida bakterial-virusli aloqalar ustunlik qiladi.

Kalit so’zlar: surunkali servitsit, bachadon bo‘yni, yassi xujayrali intraepitelial shakastlanish.

МОРФОЛОГИЧЕСКИЕ ВАРИАНТЫ ТКАНЕВОЙ РЕАКЦИИ ЭПИТЕЛИЯ ШЕЙКИ МАТКИ ПРИ ИНФЕКЦИИ ВИРУСОМ ПАПИЛЛОМЫ ЧЕЛОВЕКА У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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✓ ***Резюме***

Женщины с хроническим цервицитом имеют высокую частоту плоскоклеточных интраэпителиальных поражений шейки матки (71,3%): LSIL 45,0%, HSIL 26,3%. У женщин с хроническим цервицитом и плоскоклеточными интраэпителиальными поражениями шейки матки в составе микрофлоры цервиковагинального отделяемого преобладают бактериальное--вирусные ассоциации.

Ключевые слова: хронический цервицит, шейки матки, плоскоклеточный интраэпителиальный поражения.

Relevance

Inflammatory processes of the lower genital tract are the most common reason for women to consult an obstetrician-gynecologist and account for 57-79% of gynecological diseases [1,3,9,11,14]. Inflammatory diseases of the cervix in the female population occur with a frequency of up to 47% and occur predominantly in a chronic asymptomatic form [1,2,4,6]. According to modern publications, 82% of cervicitis are caused by microbial associations [1, 5, 7, 9], with Chlamydia trachomatis being the leading initiator of inflammation (31-39%). The role of bacteria of the genus Staphylococcus (53-56%), Streptococcus (33%), opportunistic flora and anaerobes (22-56%) [4,14], viruses (7-8.0%), including HPV (5-87%) [1,3] has also been determined. It is known that the violation of the morphofunctional properties of tissues due to chronic inflammatory processes is an important factor in the development of neoplasia [1, 13,14,15].

By the early nineties, it became clear that HPV is the main etiological factor of neoplastic processes and cervical cancer [1,2, 16]. As early as 1983, Harald zur Hausen demonstrated with his discovery that human papillomaviruses, which belong to the group of highly oncogenic viruses, are the etiologic factor of cervical cancer. The importance of this discovery was emphasized by the awarding of the Nobel Prize to the researcher in 2008 [1,17].

According to various authors, 15.0–40.0% of women infected with highly oncogenic human papillomaviruses (HPV) develop cervical dysplasia and carcinoma in situ, according to various authors [67]. HPV infection is an important, but not the only, condition for the development of cervical cancer [1, 7]. Numerous factors contributing to the oncogenic potential of the human papillomavirus are considered. For example, factors such as decreased immunity, early onset of sexual activity, cervical trauma, vitamin deficiency, nicotine addiction, long-term use of hormonal contraceptives, and hyperestrogenism are among the most important.

Particular attention is paid to chronic inflammatory processes in the cervix, as chronic inflammation disrupts reparative regeneration processes, leading to malignancy [14]. Due to the widespread prevalence of sexually transmitted infections (STIs), as well as the growing role of opportunistic flora in the development of chronic cervicitis [6, 15], studying the role of microbial associations (bacterial, viral, and bacterial-viral) in the induction of neoplastic diseases of the cervix is of great importance. Each woman has her own, characteristic microbial associations. Identifying patterns in microbial associations in women with chronic cervicitis infected with HPV may help in identifying the factor(s) that trigger proliferative processes in the cervix.

Thus, the results of a number of studies have shown that cervicitis associated with bacterial-viral infections contribute to the development of cervical dysplasia and Ca in situ [11, 15]. But this issue remains unresolved, since many authors are focused on recognizing only the main role of oncogenic HPV types in the pathogenesis of cervical dysplasia and cancer [1,3] and refute reports on the participation of bacterial and other viral infections in the development of neoplastic processes of the cervix [1,8,15]. Modern scientific developments and technologies allow the use of various methods for diagnosing cervical cancer (CC), such as simple cytological examination, liquid oncocytology, immunocytochemical examination, colposcopy, histological and immunohistochemical examination of cervical tissues. However, despite the widespread implementation of screening programs, the detection of cervical neoplasms in the early stages of the disease remains insufficiently effective. According to the GLOBOCAN 2018 statistical service, cervical cancer ranks fourth worldwide in the structure of malignant neoplasms in women [2,3].

At the same time, the issue of insufficient sensitivity of the diagnostic methods used is rightly debated. Thus, traditional cytology depends on the information content and quality of the obtained material [3,13], the sensitivity of the cytological method of examining the cervical epithelium is 44-96.2% [3, 5, 3], and colposcopy 48-96% [55, 123]. Liquid-based oncocytology can also produce false results [3,15], and histological examination is not devoid of subjectivity due to visual assessment [2,7]. Unfortunately, immunohistochemical (IHC) analysis of molecular biological markers, which largely underpin modern cancer early diagnosis strategies, has not yet been widely used in gynecological practice.

Therefore, it is necessary to develop approaches to an accessible and reliable set of consistent, targeted, personalized methods for assessing cervical health, which will enable timely risk prediction and early detection of squamous intraepithelial lesions (SIL) of the cervix in women with chronic cervicitis.

The aim of the study was to study the risk factors and developmental characteristics of squamous cell intraepithelial lesions of the cervix in women with chronic cervicitis, in conjunction with a personalized management strategy.

Material and methods

We included 154 patients in our clinical dataset, who were examined between 2022 and 2025. The clinical setting for the study was the gynecology department of the multidisciplinary clinic of the Abu Ali Ibn Sina

Bukhara State Medical Institute and the pathology department of the Bukhara Regional Branch of the Republican Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan.

In accordance with the aim and objectives of the study, all subjects were divided into 3 groups:

- the control group consisted of 20 (13.0%) healthy women who had no clinical, instrumental, or morphological signs of inflammatory or neoplastic pathology;
- The comparison group consisted of 71 (46.1%) patients with chronic cervical cancer without signs of precancerous changes;
- The main group consisted of 63 (40.9%) patients who were diagnosed with chronic cervical cancer accompanied by precancerous morphological changes in the epithelium.

Chronic cervicitis was diagnosed when more than 10 polymorphonuclear leukocytes were detected in endocervical discharge per field of view under a light microscope when examining more than five fields of view at 1000x magnification and when mucous-purulent discharge from the cervical canal was present for more than two months.

Immunohistochemistry was performed on 100 women included in the study and included determination of the expression of immunopositive cells and the distribution zone of p16ink4 and Ki67 markers in the cervical epithelium. p16ink4 expression was determined using monoclonal mouse antibodies clone G175-405 (BioGenex, USA), and Ki67-66 using monoclonal mouse antibodies clone MIB-1 RTU (Dako Cytomation, Denmark) according to a standard protocol. The age distribution of women included in the control group was intentionally evenly distributed across each age gradation, which was stratified according to the WHO.

Among the comparison group patients, the majority of patients were aged 30 to 44 years (35.2%). Young women were second (28.2%). The older age group (≥45 years) accounted for only 9.9%. It should be noted that among patients in the study group, we found a relative shift in age category to older ones, with the proportion of those aged 45 to 59 years equaling 38.1%. The older age category among patients in the study group was almost 2 times higher than among patients in the comparison group. Also, in the study group, a decrease in the proportion of younger women to 14.3% was observed.

Result and discussions

Women with SIL were divided into two groups: a group with high-risk oncogenic HPV (n=18) and a group without HPV (n=26). Histological and IHC studies of p16 and Ki67 expression in cervical epithelium were performed in these groups. Women with chronic cervicitis and SIL without HPV were significantly more likely to have LSIL, while women with SIL and HPV were significantly more likely to have HSIL ($p < 0.05$).

Women with SIL and chronic cervicitis associated with high-risk HPV were significantly more likely to have p16 distributed across two-thirds of the cervical epithelium compared to similar women without HPV ($p < 0.05$).

Women with SIL associated with chronic cervicitis who were not infected with HPV were 1.5 times more likely to have Ki67 distributed across one-third of the cervical epithelium compared to similar women infected with high-risk HPV ($p < 0.05$). In the compared clinical groups in Table 3.52, the Ki67 expression index of "15% and>" was significantly more common ($p>0.05$) compared to the Ki67 indexes of 5% and 10%. However, in women with SIL against the background of chronic cervicitis, not infected with HPV, the Ki67 expression index of =10% was four times more common compared to similar women, but infected with high-risk oncogenic HPV ($p>0.05$). Conversely, in women with SIL against the background of chronic cervicitis, infected with oncogenic risk HPV, the Ki67 expression index of "15% and>" was 1.4 times more common ($p<0.05$) compared to similar women without HPV. The sensitivity of IHC methods for examining cervical epithelium was calculated: the Ki67 cell proliferative activity index, the p16 and Ki67 epithelial distribution zones (PDZs) were measured in women with chronic cervicitis infected with high-risk HPV, and in a similar group of women without HPV. The sensitivity (Se) of immunohistochemical methods for examining the cervix was calculated using the formula: Se = TP : D ¬, where "TP" is the number of true positive test results and "D ¬" is the total number of cases.

In women with chronic cervicitis not infected with HPV, the p16 distribution zone method demonstrated significantly higher sensitivity ($p < 0.05$) compared to other IHC methods. In women with SIL and chronic cervicitis associated with high-risk HPV, all IHC methods for examining cervical epithelium demonstrated high sensitivity and had significantly higher sensitivity ($p < 0.05$) compared to a similar group of women without HPV. The high sensitivity of IHC markers in women with chronic cervicitis and SIL coinfected with HPV is possibly explained by the oncogenic potential of high-risk HPV.

Conclusion

Squamous intraepithelial lesions of the cervix in women with chronic cervicitis have inconsistent immunohistochemical markers. Increased epithelial proliferative activity, as measured by a Ki67 expression index of "15% and>," is demonstrated by more than 20.0% of women with NIL, and by an expression index of "15% and>" and a Ki67 expression distribution zone of two-thirds of the cervical epithelium, by more than 38.0% of women with LSIL. In women with HSIL, Ki67 expression indexes of "15% and>" and a Ki67 expression distribution zone of two-thirds of the cervical epithelium are found in 81.0% of cases.

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