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Morphological Criteria for HPV-Associated Cervical Ectopy

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Impaired squamous epithelial differentiation in cervical neoplasia associated with HPV type 16 results in suppressed capsid protein synthesis, ranging from 70.93% in CIN 1 to 7.69% in invasive squamous cell carcinoma (p=0.02).

Introduction

Human papillomavirus infection (HPV) is currently one of the most significant sexually transmitted infections of viral etiology. The relevance of the HPV problem is determined by the increasing incidence worldwide, significant contagiousness, and high oncogenic potential of this pathogen. HPV is caused by the human papillomavirus (HPV) and occurs in 30.3% of the population of Uzbekistan and in 44.3% of patients visiting a gynecological clinic (1, 3, 5). HPV infection is associated with the risk of developing cervical intraepithelial neoplasia and invasive tumors. According to the World Health Organization (WHO), cervical cancer (CC) is the second most common malignant neoplasm of the reproductive system in women worldwide. The incidence of cervical cancer in Russia remains among the highest and has increased from 15.1 to 17.3 per 100,000 population over the past 10 years (2, 4, 6). Cervical cancer ranks first among all oncological diseases in women under 30 years of age (1, 7, 8). Epidemiological and clinical studies have established that high-risk HPV is a key factor in cervical carcinogenesis. However, the mechanisms determining the nature and course of the pathological process caused by HPV and the risk of developing malignant

transformation of the cervical epithelium have not been fully studied (3, 9, 10). The key event in the malignant transformation of epithelial cells is considered to be the integration of viral DNA into the DNA of the host cell. Despite the fact that the phenomenon of viral DNA integration is actively studied, the available data do not allow an unambiguous assessment of its clinical significance. Of great interest is the relationship between the microbiocenosis of the urogenital tract and the state of the cervical mucosa (1, 11, 12). According to existing observations, the immune system, primarily local protection of the female reproductive tract, plays an important role in the genesis of the development of neoplastic changes in the cervix in HPV (4, 13, 15). HPV does not cause a systemic or strong local immune response, since it does not belong to the class of lytic viruses. Infection is not accompanied by an inflammatory reaction, and viremia is not characteristic of HPV-mediated epithelial processes (2, 14, 16). Neoplastic cells are able to evade immune control mechanisms, which is accompanied by the formation of tolerance and immunosuppression (17). Direct participants in these processes are regulatory T cells (Treg) and cytokines—interleukin (IL) 10 and transforming growth factor beta (TGF-β), which normally play a significant role in maintaining immune homeostasis (18). How and why Treg activity increases in neoplasms, and the relationship between tumors and Treg, remain unclear.

Therefore, studying the patterns of immune response formation in HPV, the balance of suppressive cytokines, and the mechanisms of their activation will not only provide an understanding of the role of the immune system in carcinogenesis, but may also form the basis for more effective diagnostic solutions. It is generally accepted that the target for oncogenic HPV types is the transformation zone of the cervix, where precancerous changes develop. Cytologic data have demonstrated that there is not always a clearly reproducible diagnostic distinction between low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) (1, 3, 5). The problem is compounded by the fact that high-grade squamous intraepithelial lesions (HSIL) often coexist with low-grade squamous intraepithelial lesions (LSIL), the cells of which may dominate and mask high-grade lesions (HSIL) (13, 15). Furthermore, cytologic smears classified according to the Terminology Bethesda System (TBS) do not always accurately correspond to the histologic diagnosis. Thus, upon subsequent histologic examination, a less severe lesion was detected in 35%, and a more severe lesion in 31% of patients (1, 3, 5). Therefore, there is a need to develop new diagnostic methods that are more effective and unbiased, taking into account the specific pathogenesis of the disease and the behavior of the human papillomavirus in neoplastic lesions of the cervix. In particular, to improve the quality of diagnosis of cervical lesions, it is important to introduce new, highly informative laboratory methods into clinical practice, including methods for detecting HPV p16 and E7 biomarkers and transforming growth factors.

Thus, the high prevalence of HPV-associated cervical diseases, the potential for severe complications, including malignancy, difficulties in assessing the nature of the underlying infectious inflammatory process, and the need to gain new insights into the etiopathogenesis of HPV infection determine the relevance of this study.

The objective of the present study was to characterize the morphogenesis of cervical neoplasia associated with high-risk human papillomavirus (HR-HPV) infection. The study further aimed to investigate the histopathological and cellular alterations involved in the progression of HPV-induced cervical epithelial lesions, thereby contributing to a better understanding of the pathogenesis and progression of cervical neoplasia.

Materials and Methods

The study was based on morphological and immunochemical studies of cervical epithelium from 158 women aged 19-74 years who were inpatients at the Khorezm State Budgetary Healthcare Institution "City Clinical Oncology Dispensary" from January 2023 to September 2025.

Cytological, histological, immunocytochemical, immunohistochemical, and ultrastructural methods were used for the morphological examination. In all 158 cases, biological material was collected during the initial visit for cytological examination via brush biopsy and for histological examination via incisional biopsy of the cervical epithelium. Based on these results, 26 patients underwent cone electrosurgical excision of the cervix in the gynecology department, 132 women underwent combined treatment (radiological, chemotherapeutic, and surgical) depending on the stage of the malignancy, and 134 women were included in the follow-up group. All patients were divided into several groups based on age and morphological examination results.

Histological examination results were reported in accordance with the current WHO classification, while cytological examination results were reported in accordance with the WHO classification and the 2014 Bethesda System for Reporting Cervical Cytological Diagnoses. Classification groups included criteria for CIN, signs of mild, moderate, and severe dysplasia, Ca in situ, the degree of differentiation, and the malignancy of invasive cancer.

Sample for cytological examination of the vaginal portion of the cervix and cervical canal was obtained using a disposable sterile urogenital probe "Cytobrush" (type D ME-95) manufactured in China.

Sample obtained by electrosurgical excision of the cervix from iodine-negative areas of the mucosa using a Söring electrosurgical excision apparatus (Germany) or tumor tissue obtained by the Wertheim-Meigs procedure were used for histological examination. Cervical epithelial and stromal tissue samples or tumor samples were fixed in 10% neutral formalin, dehydrated in graded alcohols, embedded in paraffin blocks, sectioned on a sliding microtome at 5-7 µm thickness, and stained with hematoxylin and eosin.

Immunomorphological studies were performed on 158 women using immunocytochemistry (n=158) or immunohistochemistry (n=158) methods, using imaging systems and primary antibodies. Primary antibodies were diluted with UltraAb Plus Ab Diluent (REF: TA-125-UDX, Lot#UDX90521), Thermo Scientific for Lab Vision Corporation (USA). To unmask antigens, deparaffinized histological sections were placed in Target Retrieval Solution 10X Concentrate (Dako) before using diluted primary antibodies, and in Epitope Retrieval Solution (x10 Concentrate) pH9 (Novocastra TM Leica Biosystems) before using ready-to-use primary antibodies, after which they were heated in a water bath for 20 minutes.

Microscopy of cytological and histological preparations was performed using an Axiostar plus microscope (Karl Zeiss, Germany). Using ProgRes Capture Pro_V 2.7.7 software with a Progres C3 video camera in Measure mode (×100), the nuclear and cytoplasmic perimeters of all cells of the stratified squamous epithelium, reserve cells, metaplastic reserve cells, atypical cells, and tumor cells were measured and counted. Average values for the nuclear and cytoplasmic perimeters were calculated by taking the arithmetic mean of the desired parameters using ProgRes Capture Pro_V 2.7.7 software. Using the VideoTesT-Morphology video analyzer (computer version 5.2), we counted the number of cells of varying shapes, chromatin structure and density, mitotic cells (including pathological mitoses), cyanophilic and eosinophilic cytoplasm, and dystrophic changes in cytological and histological preparations. In immunohistochemical and immunocytochemical preparations, we counted the number of cells expressing the studied markers.

Statistical analysis of the study results was performed using the Statistica 6.0 software program. Conclusions regarding statistical significance were made at a p-value of 0.05 or less.

To study the various outcomes of CIN, we developed an original method combining criteria for the production of HPV capsid protein L1 and the nuclear mitotic apparatus protein NuMA1. 1. Biopsy collection and preparation. Women with morphologically verified (by histological and/or cytological examination) forms of CIN underwent ectocervical and endocervical material collection by scraping and placing it in a preservative (transport medium). In the laboratory, four preparations were prepared from the sediment obtained by centrifugation. 13 The first (from ectocervical material) and second (from endocervical material) preparations were stained using the Papanicolaou method. The third and fourth preparations were prepared from the combined ecto- and endocervical sediments. In one of them, a reaction was performed to detect the L1 protein in atypical cells, and in the other, NuMA1. 2. Result evaluation. A positive reaction was considered the presence of expression of the studied protein in at least 5% of atypical cells. A positive reaction to antibodies to both proteins or to one of them was considered a criterion for a low risk of intraepithelial lesion progression. Women in this group were included in the observation group. They underwent follow-up examinations every three months, during which a gynecologist collected samples for cytological examination. Indication for exclusion from this group was morphological confirmation of regression or progression of the initially diagnosed form of CIN. If morphological criteria for CIN progression were detected, women in the observation group underwent cervical electrosurgical excision. A negative reaction was defined as the absence of expression of both proteins and was interpreted as a high risk of CIN progression, which served as the basis for cervical electrosurgical excision.

Results and Discussion

In cases of cervical ectopia, HPV genotype 16 was detected in 51.53% (n=100) of cases. Of these, it was detected as a monotype in 52% (n=52), in association with HPV FGG α9, α7, α6 – in 48% (n=48) of women. HPV FGG α9 (without HPV16) was detected in 17.53% (n=34), HPV FGG α7 – in 15.47% (n=30) of studies. The combination of HPV FGG α9 (without HPV 16) and FGG α7 was detected in 6.19% (n=12), the combination of HPV FGG α6 was observed in 6.19% (n=12) of ectopia cases. Of the 158 cases of ectopia, 47.94% (n=93) of women were found to have pseudo-erosion in the healing stage, and 52.06% (n=101) had its recurrent form.

Regardless of the genotype of the HPV infecting the cervix, no impairments in the differentiation of the stratified squamous epithelium of the cervix were observed, which is confirmed by the preservation of stratification of the squamous epithelium, the absence of statistically significant differences (p in the perimeter of the nucleus, cytoplasm, and nuclear-cytoplasmic ratio of the cells of the corresponding layers with membrane expression in all of them ($p<0.01$) of E-cadherin (1).

The predominance in all studies ($p<0.01$) of basal cells expressing cytokeratin 5 over the number of basal cells producing cytokeratin 10 indicates the duration of the metaplasia process (2). This property is most pronounced in HPV16-positive ectopias, confirmed by the heterogeneity of the protein composition of the cytoplasm, manifested by the two-component nature of its staining (3) 33.84±0.95% of metaplastic cells ($p<0.05$).

Absence in The expression of Ki-67, PCNA, and p53 proteins in the predominant number of reserve and basal cells characterized their exit from the cell cycle, rather than "weak proliferative activity of basal cells" during epidermization of pseudo-erosion (4). Moreover, the number of basal cells in the interphase with NuMA1 expression exceeded the number of cells with BCL-2 and EGFR expression ($p < 0.01$), which confirmed their retention of the ability to trigger the apoptotic mechanism.

The M phase detected in single basal and parabasal cells was the result of mitotic arrest (5) at the cell cycle checkpoint (2). The number of metaphases ($p < 0.01$), noted in 0.22 ± 0.04% of cells in % of HPV16-positive cases, in 0.22 ± 0.04% of cells in 8.82% of studies associated with HPV 33 genotype FGG α9 and in 0.11±0.03% of cells in 8.33% of cases associated with HPV 56 and 66 genotypes FGG α6, corresponded to the mitotic index of squamous epithelium of the cervix of typical structure (1), but was inferior to the mitotic activity of "immature" squamous cell metaplasia during epidermization of pseudo-erosions (2). The detected mitotic delay was apparently caused by some DNA defect that did not allow the M phase to continue, but preserved the structure of the nuclear mitotic apparatus, confirmed by the expression of the NuMA1 protein in the metaphase plate in 83.33% of HPV16-positive ectopias, in 66.67% of cases associated with HPV 33 genotype FGGα9 and in all cases associated with HPV 56 and 66 FGG α6 genotypes.

In conclusion, Cervical neoplasia is associated with high-risk human papillomavirus genotype 16 (HPV HCR16) in 77.73% of cervical intraepithelial neoplasia (CIN), 90.14% of invasive squamous cell carcinoma, and cervical ectopia in 51.53% of cases. A positive reaction is considered to be the presence of expression of the test protein in at least 5% of atypical cells. Detection of expression of both proteins or one of them is considered a criterion for a low risk of intraepithelial lesion progression. The absence of expression of both proteins is interpreted as a high risk of CIN progression and serves as an indication for cervical electrosurgical excision.

Author Contributions

M. T. Khamdamova: Investigation, formal analysis, writing—original draft. Z. Z. Askarova: Validation, methodology, writing—reviewing. M. T. Xalilova:—Formal analysis, writing—review and editing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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