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THE ROLE OF MODERN BIOMARKERS AND RESEARCH METHODS IN THE DIAGNOSIS OF PRECANCEROUS PATHOLOGIES OF THE CERVIX AFFECTED BY VIRAL INFECTIONS

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ABSTRACT.

Introduction. In the modern world, cervical cancer is one of the most common cancers of the female genital area and occupies one of the leading places in the structure of mortality.

The purpose of this study was to determine the significance and value of biochemical and immunocytochemical (IC) diagnostic markers for HPV in women with background and precancerous diseases in the cervix.

Materials and Methods: Examined 152 women with precancerous and background diseases of the cervix (erosions and endocervicitis), whose age ranged from 23 to 59 years, with an average of 33 ±1,9 years. All 152 patients with underlying conditions of cervical cancer underwent Pap smears, liquid cytology, PCR test to identify the HPV virus, and verification of specific proteins p16/ki67.

Research results. All patients underwent a cytological examination of the cervix using the Pap test and liquid cytology with interpretation of the results according to the Betesta system (2014). This means that in comparing two methods for identifying intraepithelial lesions of the cervix in two groups, false-positive results were in 11 and 10, and false (+) results were in 9 and 3 in the two corresponding groups. And 6 in 2-group. According to WHO recommendations, for verification, NSIL requires intensive treatment; using a surgical method, samples with ASCUS and LSIL should be subject to strict monitoring, since in the future they may develop into severe dysplasia.

Conclusion. In patients with CIN associated with HPV, persistent PVI was present in 83.3% of cases. CIN II-III showed significant overexpression of biomarkers p16ink4α and Ki-67, unlike CIN I. New diagnostic technologies promise advancements in cervical screening and treatment.

KEYWORDS: cervical cancer, HPV, PAP test, Betesta system, liquid cytology, immunocytochemical research method, markers proteins p16 and ki 67.

INTRODUCTION

In the modern world, cervical cancer is one of the most common cancers of the female genital area and occupies one of the leading places in the structure of mortality [3, 5].

The frequency of cervical cancer according to different sources varies within 14-29% (1,4).

Therefore, due to the annual increase in cases of cervical cancer, this problem requires improvement of early diagnosis of background and precancerous diseases [1, 5].

According to the literature, the leading role in the development of cervical cancer is played by viral lesions of the female genital area, in particular the human papillomavirus (HPV), as well as the clinic of HPV in association with cytomegalovirus infection(CMVI) and herpes simplex virus type 2(HSV 2-type) and other sexually transmitted infections(STI) are more complex and are subject to a special type of diagnosis [2, 3, 6].

In HPV infection, a special place is occupied by oncogenic strains of the pathogen - 16,18,31,33, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, but among them the most common ones were 16,18, 31.33 strains.

The purpose of this study was to determine the significance and value of biochemical and immunocytochemical (IC) diagnostic markers for HPV in women with background and precancerous diseases in the cervix.

To diagnose cervical pathologies, we used such research methods as verification of HPV and its types using PCR, methods of traditional and liquid cytology PAP test (with Papanicolaou staining) and interpretation according to the Betesta system from 2014, immunocytochemical research method with detection of double staining of markers proteins p16 and ki 67.

MATERIAL AND METHODS

We examined 152 women with precancerous and background diseases of the cervix (erosions and endocervicitis), whose age ranged from 23 to 59 years, with an average of 33 ±1,9 years.

At the beginning of the study, all 152 patients were tested for the presence of the HPV virus in their blood, of which 104 had a negative result, and the remaining 48 had a positive result.

The colposcopy data of 152 women were as follows: satisfactory colposcopic picture in 67 women, unsatisfactory in 85 women, which was due to varying degrees of inflammation. All 152 colposcopy results were divided according to the classification (2014), 1-degree - with mild lesions (thin acetate epithelium), with uneven, not clear edges, delicate mosaic and punctuation - in 95, 2nd degree with densely expressed epithelium with clear contours, with rapid whitening, acetate epithelium with a dense rim around open glands, with rough mosaic and punctuation in 76 women, atypical vessels were identified in 11 samples.

All patients underwent a cytological examination of the cervix using the Pap test and liquid cytology with interpretation of the results according to the Betesta system (2014).

In the group without HPV, the Pap test showed the following results: NILM-67, where no intraepithelial malignant changes were detected, ASC-US (atypical squamous epithelial cells of undetermined significance) -10, LSIL (CIN-I or mild intraepithelial lesions of squamous epithelium) -7 , the remaining samples were within normal limits.

RESULTS

In the group with the identification of the HPV virus in 48 patients, cytology results: NILM-1, where no intraepithelial malignant changes were detected, ASC-US-10 - atypical squamous epithelial cells of undetermined significance, ASC-H-10, where atypical squamous epithelial cells were detected, not excluding severe intraepithelial lesions, LSIL (CIN-I), mild intraepithelial lesions of squamous epithelium) - 17, HSIL or high-grade intraepithelial lesions of squamous epithelium, including: (CIN-II) - in 4 women, CIN-III - in 6.

Comparing the results of Pap smear and liquid cytology, there were the following differences: in group 1 without HPV: NILM-74 (7 more), ASC-US-14 (4 more) LSIL(CIN-I, intraepithelial lesions of the squamous epithelium of the lung degrees) -16 (9 more).

In the 2nd group with HPV carriers were the following: Of 48 – NILM-4 (3 more, instead of 1), ASC-US-12 (2 more), ASC-H-16 (6 more), LSIL(CIN-I, mild intraepithelial lesions of squamous epithelium) -15 (2 less), HSIL or high-grade intraepithelial lesions of squamous epithelium, including: (CIN-II) - in 7 women (3 more), CIN-III - three (3 less).

This means that in comparing two methods for identifying intraepithelial lesions of the cervix in two groups, false-positive results were in 11 and 10, and false (+) results were in 9 and 3 in the two corresponding groups. And 6 in 2-group.

According to WHO recommendations, for verification, NSIL requires intensive treatment; using a surgical method, samples with ASCUS and LSIL should be subject to strict monitoring, since in the future they may develop into severe dysplasia.

The purpose of the immunocytochemical study was to identify two oncoproteins P16 and Ki 67 in 57 patients with ASC-US, ASC-H and LSIL, which is a novelty in our region, since these protein markers will be used to determine the degree of neoplasia in CIN-2 and CIN- 3.

In group 1 where ASC-US-14 and LSIL(CIN-I) - 16 immunocytochemical , cytoplasmic staining for the presence of the antiproliferation protein P16 is stained bright brown, and the nucleus is red, the cytoplasm of the cell and red nuclear staining for the proliferation protein Ki 67) did not give any staining.

In the 2nd group where ASC-US-12 immunocytochemical (ICC) staining for the detection of protein P16/Ki 67 (brown cytoplasmic staining for the presence of the antiproliferation protein P16 and red nuclear staining for the proliferation protein Ki 67) gave positive staining in 7, and in the group with LSIL(CIN-I) out of 15 – in 8 women. The positive result of double staining p16/Ki-67 prevailed mainly among patients in the group with HPV-infected patients, with ASC-US-12 and LSIL(CIN-I) in 15 sick women, and had a direct correlation with changes confirmed by liquid cytology, and colposcopy examinations were all unsatisfactory.

In the groups without identification of the HPV virus, ASC-US-14 and LSIL(CIN-I) were all normal, but double staining of p16/Ki-67 did not reveal the characteristic signs inherent in proliferation, i.e. there were no signs of pathological proliferation.

DISCUSSION

According to the results of a number of researchers, if changes characteristic only of p16 are detected, a wait-and-see approach should be recommended (1,2,3), with mandatory treatment in the presence of mixed viruses such as HSV-2 type and CMVI (10), but we performed double staining in all samples.

Since the clinical interpretation of ICC results, the study with positive double staining of p16/ki67 is based on assessing the level of proliferative activity of the cervical epithelium and we used it to develop subsequent management tactics for patients with severe degrees of dysplasia

after liquid-based cytology. Considering the risk of transformation of ASC-US, LSIL (CIN-I) into a more severe one such as HSIL, it is subject to constant monitoring, especially with a complicated history and recurrent inflammatory processes in the female genital area(8,9).

According to a number of authors, Dimitriad et al., Klinyshkova T.V. and colleagues (2), the use of ICC studies with Ki 67 and p16/INK4a makes it possible to objectify the primary diagnosis of the degree of CIN, as well as to identify patients with a high and low risk of developing severe damage. This is especially true for a group with a moderate degree of dysplasia such as CIN-2 CIN-3 and the use of IHC in primary diagnosis will contribute to: improving the information content of the state of intraepithelial lesions, which is important when choosing management tactics, with subsequent treatment.

According to Russian scientists Bebnev and co-authors (1), with an increase in the severity of cervical lesions, the proportion of patients with tumor markers increased (with 20% in NILM to 100% in HSIL), and the intensity of Ki-67/p16 expression is moderate in patients with LSIL and high in HSIL. A higher statistically significant viral load was detected for the DNA group HPV A9 (16, 31, 33, 35, 52, 58 types) in the detection of tumor markers compared with their absence, and these data coincide with the opinions of a number of scientists (3,4,7).

The results of our studies differ in that we examined samples ASC-US, LSIL (CIN-I) to identify the degree of proliferation, to accurately verify the degree of pathological intraepithelial lesions, i.e. transition to severe degrees of dysplasia - CIN-2, CIN_3 (HSIL) in order to make an accurate diagnosis in a timely manner, followed by the development of management tactics.

When checking for the presence of proteins in samples with ASC-US, LSIL (CIN-I) responses in women with HPV infection, all patients had a positive result of double staining of the cervical epithelium, therefore such patients should be advised to expand surgical methods - removal of the pathological area of the cervix - conization or excision .

And in the absence of differences in the coexpression of p16/Ki-67 in epithelial cells, which corresponds to the absence of proliferation and there is no need for palliative treatment methods, we recommended monitoring for 3 or more years.

CONCLUSION

1. In patients with CIN associated with HPV, the following features have been established: more frequent presence persistent form of PVI (83.3%), correlationassociation between CIN grade and overexpression of biomarkers p16ink4α and Ki-67 in CIN II-III compared with these indicators in CIN I, where changes in Ki-67 were not detected at all.

2. In patients with cervical precancer against the background of persistent PVI, a statistically significant increased coexpression of p16ink4α and Ki-67 in CIN II-III, in contrast to that with CIN I and with the latent form infections.

3. The introduction of new diagnostic technologies opens up prospects for improving cervical screening and treatment approaches for this pathology.

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