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THE ROLE OF CYTOKINES IN PATHOGENESIS, DIAGNOSTICS, AND PROGNOSIS CERVICAL NEOPLASIA

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ABSTRACT

Background: It is generally recognized that the problem of cervical tumors is associated not only with a persistently high incidence of cancer, but also with the difficulties in diagnosing cervical intraepithelial neoplasia, which is one of the stages of malignancy of cervical epithelium. **Objective:** A prospective study was conducted of 177 patients with cervical intraepithelial neoplasia of the cervix uteri who were examined. **Methods:** Determination of the concentration of cytokines IL-1β, TNF-α, TGF-β in cervical mucus was carried out using standard commercial ELISA kits. **Result:** The obtained data convincingly indicate a pronounced imbalance of the cytokine regulation of the mechanisms of immune control of cell homeostasis against the background of viral infection, which determines the formation and progression of neoplastic lesions of the cervix. **Conclusion:** Clinical and morphological factors for the prognosis of cervical intraepithelial neoplasia and cervical cancer have a direct correlation with infection of the cervix, production of cytokines.

KEYWORDS: Cervical intraepithelial neoplasia, immunity, cytokines.

INTRODUCTION

It is generally recognized that the problem of cervical tumors is not only related with a persistently high incidence of cancer, but also with the difficulties in diagnosis cervical intraepithelial neoplasia, representing one of the stages of malignancy of cervical epithelium. According to WHO experts,[1] cervical cancer is a completely preventable disease if it is detected at the stage of precancer.

As in known, the development of cervical intraepithelial neoplasia and cervical cancer is associated with infection with oncogenic types of HPV. Long-term persistence of viruses in the cervical epithelium is accompanied by their integration into the cell genome and the appearance of mutations, and neoplastic transformation is more likely to occur when HPV interaction of with other STIs that are quite common in the population.[2]

The results of research testify that strengthened transcription of viral oncogenes and the functioning of viral oncoproteins associated with impaired cytokines related expressions, not only with anti-infectious, but also with anti-tumor immunity. Some cytokines, in particular, TNFα, IL-1β, TGFβ, have been shown to be active participate in the regulation of stability factors of the cell genome.[3] Considered to be, that the process of neoplastic transformation is associated with a change in balance of apoptosis and cell proliferation.[4] Recently, great importance has been attached to the study of proliferative activity as an indicator of the biological aggressiveness of tumors.

The study of various molecular biological factors in cervical intraepithelial neoplasia during its transition to cancer and the progression of the initial stages of cancer is of great clinical interest. This is due to the desire to detect cervical cancer at the preclinical stage of development, when the timely most sparing treatment of cervical intraepithelial neoplasia has an optimal radical effect, which allows achieving a complete cure.[5] Improving the treatment of already existing tumors is achieved by individually predicting the clinical course of cervical cancer. Using molecular biological criteria characterizing the malignant potential of the tumor, along with traditional prognosis factors, it is possible to determine the likelihood of progression of the initial stages of cervical cancer and to raise effectiveness of the high-risk patient management program.

SUBJECTS AND METHODS OF RESEARCH

A prospective study was conducted of 177 patients with cervical intraepithelial neoplasia of the cervix uteri who were examined, treated and followed up at the Republican Oncology Center of the Republic of Karakalpakstan in 2017-2019. The age of the examined varied from 27 to 60 years, and averaged 37.9 ± 8.1 years. Diagnosis of cervical intraepithelial neoplasia was based on a comprehensive clinical examination, the results of extended colposcopy, cytological and

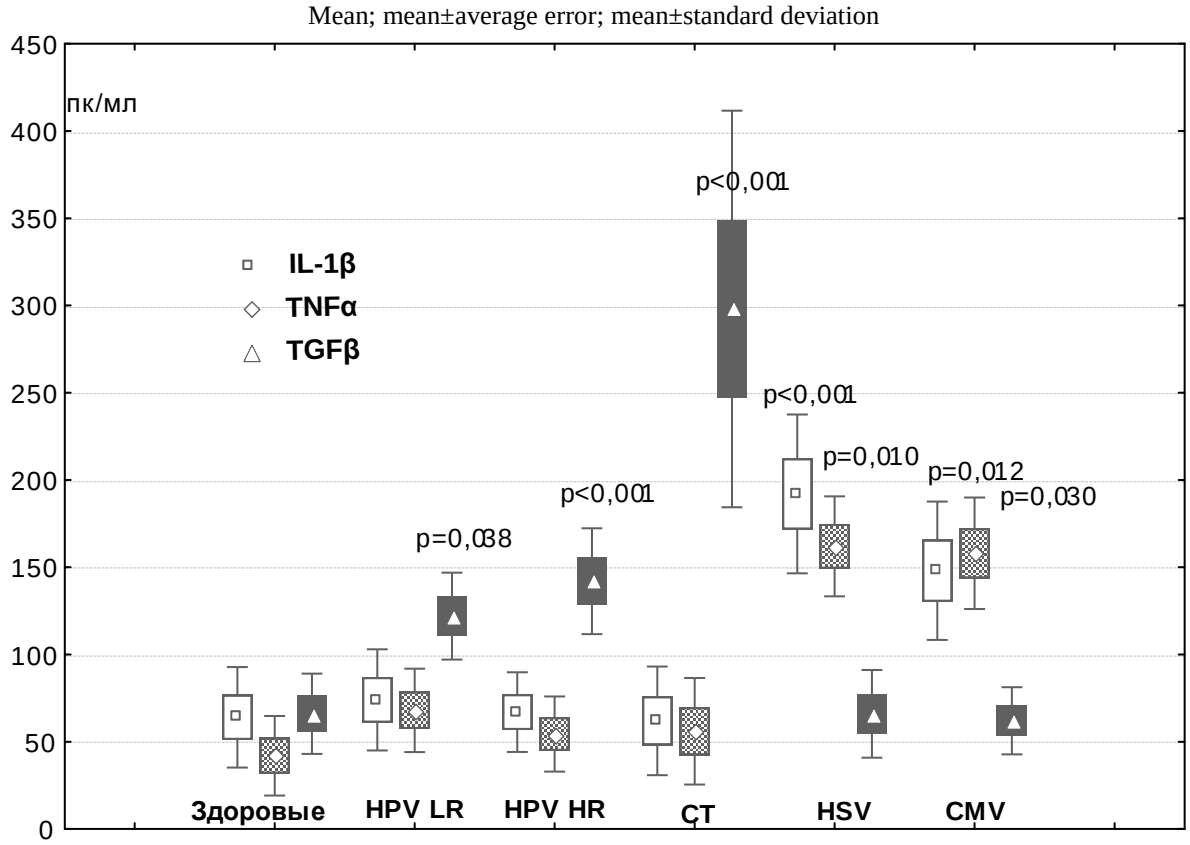
histological studies. The criterion for the selection of patients was a morphologically confirmed diagnosis of cervical intraepithelial neoplasia (CIN). Depending on the severity of the cervical lesion, the groups of patients were distributed as follows: 53 women were diagnosed with CIN I; 50 - CIN II; 74 – CIN III. Treatment of cervical intraepithelial neoplasia in 62 (35.0%) patients was performed in the amount of cervical electrocoagulation (CIN I-II), in 29 (16.3%) cryodestruction (CIN I-II), in 68 (38.4%) - electroconization (CIN III, CIN I-II when combined with cicatricial cervical deformity), 15 (8.4%) - knife amputations of the cervix (CIN III against cicatricial deformity, cervical hypertrophy), 3 (1,6%) - hysterectomy (CIN II-III in combination with uterine myoma, adenomyosis).

Determination of the concentration of cytokines IL-1β, TNF-α, TGF-β in cervical mucus was carried out using standard commercial ELISA kits. As a control group for the study of genital infections, cytokines and estrogen metabolites, a representative sample of 20 healthy women formed by random selection from the general population was used. Statistical data processing was carried out in accordance with the rules of variation statistics.

RESULTS AND DISCUSSION

On the background of genital infections, develop most lesions of the cervix with a violation processes cell of the proliferation, differentiation and death, and infections acquire a chronic relapsing course. Among sexually transmitted infections, viruses and chlamydia, the infection of which is associated with the potential risk of malignancy of the cervical epithelium, have the greatest modulating effect on the course of cervical pathological processes. The results of the study showed that among healthy women without pathological changes in the cervical epithelium, HPV was detected in 10.0 ± 2.6% and HSV and CMV in 3,0 ± 2.8%, which indicates a fairly high prevalence of HPV in healthy women. In cervical intraepithelial neoplasia, 67,3 ± 2.1% of patients were infected (p <0.001). The most common cases were HPV, which in 53,2 ± 4,8% of cases was combined with other STIs: in 16,6 ± 4,0% - with ST, in 10,6 ± 3,2% - CMV and in 5,1 ± 1,3% - HSV. Most infected women had chronic inflammatory diseases of the genitals – 37,2 ± 7,8 (p = 0,033).

In the genesis of neoplastic changes in the cervix, local immune reactions, the regulation mechanism of which is associated with the production of cytokines, are of crucial importance. A comparative assessment of the local production of the cytokines TNFα, IL-1β, and TGFβ depending on the cervical infection variant revealed the following features (Fig. 1). When monoinfected with HPV HR and HPV LR, an increase in TGFβ production was observed against the background of IL-1β and TNFα values stable relative to the control.



p- statistical significance of differences compared to control

Fig. 1: The content of IL-1β, TNFα, TGFβ depending from infection of the cervix.

The lack of an adequate response of defense systems with HPV is associated with the immunosuppressive properties of a persistent virus.[6] However, the prolonged presence of viruses leads to a change in the antigenic structure of epithelial cells, causing activation of immunocompetent cells and an increase in TGFβ production.[7] High levels of TGFβ in associated chlamydial papillomavirus infection are associated with the production of heat shock CT proteins. An increase in the production of TGF-β, which inactivates the cytotoxic activity of macrophages, is accompanied by a decrease in the expression of TNFα and IL-1β.[8] It is known that TNFα and IL-1β, the production of which increased upon infection of the cervix HPV HR in combination with HSV and CMV, are associated with local protective reactions against intracellular viruses. Despite the activation of anti-infection protection mechanisms, the elimination of herpes viruses and cytomegaly does not occur, their persistence continues with damage to the cervical epithelium cells. The failure of protection systems for HPV infection in combination with HSV and CMV is associated with the expression of viruses of genes homologous to cytokines and their receptors, which allows viruses to interfere with their presentation to immunocompetent cells, affect viral replication and block the antiviral activity of IF and TNFα.[9,10,11]

The normal microflora of the cervical mucous membrane of the cervix uteri provides a sufficiently high level of cytokine production in the cervical secretion of healthy women. With a decrease in the production of pro-inflammatory cytokines, which are noted in the group of virus carriers without pathological changes, the cervix, viruses can persist in epithelial cells, for a long time and when exposed to certain factors, they can cause neoplastic transformation of cells. The progression of cervical neoplasia is associated with the development of local immunodeficiency. Infected epithelial cells, macrophages, Langerhans cells of the cervical mucosa are not capable of processing the corresponding cytokine levels.[12,13] TGFβ has a deactivating effect on macrophages with a decrease in the expression of pro-inflammatory cytokines. The increasing level of TGFβ detected in our study correlated with the severity of cervical neoplasia: an increase in TGFβ from 150 pkg / ml to 240 pg / ml corresponded to CIN I-II, from 240 pg / ml to 500 pg / ml r CIN III. An increase in TGFβ expression at the stages of the precancerous lesion of CIN I-II leads to inhibition of growth and the transfer of proliferation to cell differentiation. The obtained data convincingly indicate a pronounced imbalance of the cytokine regulation of the mechanisms of immune control of cell homeostasis against the background of viral infection, which determines the formation and progression of neoplastic lesions of the cervix.

CONCLUSIONS

1. With cervical intraepithelial neoplasia and cervical cancer with different frequencies detected 16, 18, 31, 33, 35, 45 types of HPV. The most common type of cervical intraepithelial neoplasia is type 16 HPV.
2. Latent papillomavirus infection of the cervix uteri is characterized by a decrease in the concentration of proinflammatory cytokines IL-1β and TNF in cervical mucus, determining the occurrence of local immunosuppression and the possibility of transition to the clinical stage, which requires correction of immune disorders and biocenosis.
3. An analytical criterion for the severity of lesions in cervical intraepithelial neoplasia is an increase in local production of TGFβ: the concentration of TGFβ in cervical mucus is 150-240 pcg / ml corresponds to CIN I-II, TGFβ 240-500 pcg / ml corresponds to CIN III.
4. Clinical and morphological factors for the prognosis of cervical intraepithelial neoplasia and cervical cancer have a direct correlation with infection of the cervix, production of cytokines.

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