IMMUNOMODULATION IN GYNECOLOGY. OPINION OF AN IMMUNOLOGIST AND AN OBSTETRICIAN-GYNECOLOGIST

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Abstract: The currently available information on the epidemiological features and chronic clinical course of diseases caused by sexually transmitted pathogens is the reason for the search for drugs and methods that increase the effectiveness of their therapy [1]. A very serious problem for clinicians is the polyresistance of pathogens to antiviral, antimicrobial and antifungal drugs, the high frequency of infection of various population groups with herpes viruses, human papillomaviruses, their negative impact on the immune system and factors of colonization resistance of the reproductive tract [2].

Keywords: chronic, pathogen, immune system, reproductive, carcinoprevention

One of the main issues that worries practitioners - obstetrician-gynecologists, perinatologists, immunologists - is the lack of significant success in the treatment of diseases caused by human papillomaviruses (HPV) and Candida fungi, despite the variety of drugs used and methods of influencing the infectious agent [3]. For example, in 2008, cervical cancer was the third most common cancer in women worldwide, and in 2020 it ranked fourth in incidence and mortality among women [4].

Such negative dynamics, of course, causes concern among specialists. In this regard, the search for new formulas, drugs that can influence the state of factors that provide an adequate response to high concentrations of fungi of the genus Candida and viral agents on the surface of the mucous membranes is relevant. Complex, not fully understood mechanisms of regulation of the immune response under the action of agents of a viral, bacterial and fungal nature determine the versatility of the problem of immunomodulation, although it is the use of immunomodulating therapy that increases the physician's ability to provide medical care to patients with human papillomaviruses and those with chronic inflammatory diseases caused by fungi genus Candida.

Human papillomaviruses: structural features and pathogenetic role in the development of proliferative diseases in humans In the development of proliferative diseases, the role of human papillomaviruses of high carcinogenic risk (types 16, 18, 30, 31, 33, 39, 40, 42, 43, 51, 52) has been proven, 55, 57–59, 61, 62, 64, 67–70) [1]. Human papillomaviruses infect basal and immature metaplastic cells of stratified squamous epithelium. A high frequency of persistence of human papillomaviruses of the A9 phylogenetic group, in particular types 16, 33, 39, 52 and 58, was noted. Replication of viral DNA and synthesis of capsid proteins alter the cell cycle and lead to atypia of cellular elements and cells in general. By integrating into the cell genome, the virus transforms normal epithelial cells to CIN II–III/CIS. Embedding the nucleic acid of human papillomaviruses into the genome of epithelial cells is the main step towards their tumor transformation.

HPV detection in endometrial biopsy is three times higher in endometrial cancer (47.2%) than in healthy endometrium (13.8%). Human papillomavirus induces pathological changes in the expression of genes of Toll-like receptors (TLRs) on the surface of epithelial cells, primarily TLR9, TLR2. TLR4 agonists are involved in the activation of innate immune responses and the modulation of specific adaptive immunity to HPV, the production of interferon, which is crucial

for stopping an episode or relapse of the disease. TLRs are involved in the primary recognition of viral DNA and activate the production of pro-inflammatory cytokines. A consequence of a decrease in the expression of recognizing receptors is the establishment of an immunosuppressive status with inhibition of type I interferons [6].

Since virus-infected cells are a target target for human papillomavirus infection (PVI), strengthening the recognition abilities of immune cells will increase the effectiveness of therapy. Activation of the ability to recognize the viral agent TLR (innate immunity receptors) is an important step in therapeutic measures, to recognize the affected cells and promote their elimination [5]. Factors of viral aggression are also proteins E6 and E7, the activity of which contributes to:

• changes in genes that regulate the cell cycle (for example, pRb and p53), which leads to the proliferation of tumor cells;

• inactivation of genes suppressing carcinogenesis;

• inhibition of apoptosis of virus-modified cells;

• accumulation of genetic changes in epitheliocytes.

The persistence of highly oncogenic types of human papillomaviruses for two years or more is a dangerous factor in the progression of cervical precancer [6]. In most cases, human papillomaviruses are eliminated spontaneously, and the balanced work of the cellular and humoral components of innate and adaptive immunity can help eliminate HPV-infected cells. Persistence (long-term presence in the body) of HPV is due to the action of immunosuppressive mechanisms. HPV-infected cells cease to secrete the spectrum of pro-inflammatory Th1 cytokines characteristic of normal epitheliocytes. Moreover, in epitheliocytes, there is an upregulation of CTLA-4 and PD-1 inhibitor molecules with a decrease in the amount and activity of type I interferons [7].

Cervical intraepithelial neoplasia. LSIL (CIN I). Management tactics, relapse prevention

Cervical intraepithelial neoplasia (CIN) is characterized by the maturation and differentiation of the stratified squamous epithelium of the cervix [8]. The trigger factor for CIN is persistent HPV infection. 90% of cases of cervical intraepithelial neoplasia and more than 90% of cases of cervical cancer occur in patients with verified HPV infection [9]. With a morphologically confirmed diagnosis of LSIL (signs of HPV infection, koilocytosis, CIN I), expectant management is used with dynamic monitoring of the state of the cervix for 18–24 months in the form of cytological control once every 6 months and HPV testing once every 12 months. Observational tactics become ineffective as the woman may miss her doctor's appointment, leading to a high risk of missing a CIN.

Destructive treatment is recommended if there is no regression after 18–24 months. The recurrence rate of squamous intraepithelial lesions of the cervix after surgery is 20–30% [10]. In case of insufficient effectiveness of surgical treatment, activation of antiblastoma immune factors, the so-called cancer prevention technology, is effective.

Carcinoprevention is a set of measures aimed at systemically reducing the risk and incidence of malignant lesions. Carcinoprevention includes diagnostic (laboratory diagnostics) and drug (immunomodulatory drugs) mechanisms. Immunomodulatory therapy of the productive component of HPV infection is pathogenetically justified in addition to surgical methods [1], since activation of HPV infection and carcinogenesis are markers of immunosuppression. According to V.N. Serova et al., the appointment of treatment aimed at the immune system should proceed from the general principles of immunotherapy. The main requirements for immunomodulatory drugs

are that the drug has immunomodulatory or immunostimulatory properties, clinically proven high efficiency, preferably natural origin, safety, non-addictive, no side and carcinogenic effects [11].

The choice of an immunomodulator should be responsible and scientifically justified, since immune cells can exhibit dual activity against a tumor: type M1 macrophages, type 1 dendritic cells, N1 neutrophils have an antitumor effect, and M2 macrophages, type 2 dendritic cells, N2 neutrophils support carcinogenesis [12], and activation of immune cells without correction of their phenotype in HPV infection is not yet a guarantee of success in the use of immunomodulators in the treatment of PVI. Moreover, if the pro-oncogenic profile of cells of the immune system, the connective tissue stroma is not corrected, then immune activation does not achieve the main goal - cancer prevention.

Correction of immune disorders - a direction for increasing the effectiveness of therapy for HPV-associated diseases

An integrated approach to the treatment of patients with HPV-associated diseases of the cervix, including destructive treatment of lesions and the use of drugs with antiviral and immunomodulatory effects, can be considered as the most effective. A promising class of drugs for the treatment of PVI are drugs that activate Toll-like receptors of innate immunity cells.

The drug of choice that activates nonspecific immunity factors, which is fundamentally important for the correction of immune disorders in PVI, is Immunomax®. By chemical nature, it is peptidoglycan, which is recognized by Toll-like receptors of cells of the immune system, which enhances the activity of antiviral and antitumor immunity [12]. Immunomax® promotes the activation of immune cells with an anti-oncogenic activity profile. It has been shown that the cytolytic activity of NK cells increases three times two to three hours after in vitro application of the drug. In vitro studies have shown the ability

Immunomax to influence the transfer of the dendritic cell ("sentinel on guard" of homeostatic reactions) from the -M2 state, which promotes tumor progression, to the -M1 state with a suppressive effect in the 4T1 model of breast cancer. Immunomax® contributed to a decrease in the expression of the myeloid antigen CD38+, characteristic of monocytic leukemia cells. Positive regulation of transcription of TLR/RLR genes of pattern recognition receptors under the influence of the drug in tumor cell lines THP-1 and HCT-116 was revealed, which demonstrates the possibility of correcting the signaling mechanisms of the immune response in tumor cells THP-1 and HCT-116 [13, 14]. Immunomax® inhibits the immunosuppressive potential of pE6 and pE7 HPV, which allows you to realize your own capabilities of the immune system. Immunomax® 200 IU is administered intramuscularly, dissolved in 1 ml of water for injection before administration. The course of treatment is six injections on the 1st, 2nd, 3rd, 8th, 9th, 10th days of treatment.

The combined persistence of HPV with herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus, chlamydia and mycoplasmas, opportunistic fungi of the genus C. albicans is extremely unfavorable. The presence of vulvovaginal candidiasis prevents HPV self-elimination [15].

The state of factors of colonization resistance of the mucous membranes of the genitourinary system in urogenital candidiasis. Methods of correction using immunomodulatory therapy

In a large-scale study of 1927 strains of Candida fungi isolated from patients with vulvovaginal candidiasis, a progressive decrease in the etiological significance of C. albicans and an increase in the significance of C. non-albicans isolates were established. An increase in the resistance of Candida fungi to antimycotics is observed [16]. The etiological significance of taking

dapagliflozin, a selective reversible inhibitor of sodium glucose cotransporter type 2 (SGLT2), has been proven [17]. One of the methods of complex therapy of vulvovaginal candidiasis is to increase the colonization resistance of the mucous membranes of the organs of the genitourinary system. This approach to local immunotherapy is based on the available data on the key role of local mechanisms of immune defense of mucosal candidiasis [18]. Gepon® as part of a combination therapy for candidiasis is effective in the treatment of infections of the mucous membranes and skin caused by Candida fungi, reduces the intensity of inflammation (redness, swelling, itching, burning, pain) of the mucous membranes and skin, dryness of the mucous membranes, is used to prevent candidiasis of the mucous membranes and skin during antibiotic therapy. More than 80 published clinical studies involving more than 4,700 people testify to the effectiveness of Gepon®. Gepon® is an immunomodulator with local anti-inflammatory, immunoregulatory and antimycotic activity. Produced in the form of a sterile lyophilized powder, which contains, respectively, 1, 2 or 10 mg of the active substance of tetradecapeptide. The presence of anti-inflammatory effects of the drug is especially important in the treatment of lesions of smooth skin in complex therapy. In this case, topical application of the drug by applying a gauze napkin soaked in Gepon solution to the affected areas is relevant.

The immunomodulatory and anti-inflammatory effect of Gepon® is due to the fact that it changes the cytokine response of cells to a viral infection (the activity of IL-2, IL-6, IL-10, IL-12, IL-18 and TNF-α mRNA increases); causes the production of type I interferons, stimulating interferonogenesis, while regulating the production of pro-inflammatory cytokines - IL-1, IL-6, IL-8, mobilizes and activates the functional and metabolic status of macrophages; stimulates the production of antibodies to antigens of an infectious nature; increases the content of the subpopulation of CD4+ T-lymphocytes (Th) and NK cells, increases the functional activity of neutrophils, natural killer cells and CD8+ T-cytotoxic cells (Tc), which are key links in the body's defense against bacteria, viruses and fungi [18 -20].

The use of Gepon® ensures the normalization of the microflora on the surface of the mucous membranes and the homing effect of lymphocytes. The mucous membranes of the genitourinary system are an arena for the interaction of microorganisms with the most important depot of the body's immunocompetent cells - lymphoid tissue. The homing effect is explained by the affinity of lymphocytes for receptors (addressins) of the endothelial venules that drain the mucous membranes of the "home region" of the urogenital tract. Stages of the homing effect of lymphocytes:

- antigen presentation and antigenic stimulation of T-lymphocytes in lymph nodes;
- differentiation (specialization) of lymphocytes;
- lymphocytes enter the lymphatic vessels and bloodstream;
- lymphocytes return to the focus of infection, where they were stimulated by the antigen.

Chronic inflammation accompanying adhesion, colonization by fungi of the genus Candida leads to activation and hyperactivation of immune system cells, which reduces the effectiveness of the therapy. According to the results of studies, Gepon® contributed to an increase in the level of T-regs, which further reduced the severity of the inflammatory process [21]. Evaluation of the effectiveness of therapy with Gepon® in women with recurrent vulvovaginal candidiasis resistant to standard therapy is presented in the work of A.L. Tishchenko. Patients treated with Gepon® showed a prolongation of the period without exacerbations up to one and a half years. A month after treatment with Gepon®, clinical signs of candidiasis were absent in 90% of cases, microscopic examination revealed the absence of pseudomycelium in 84% of patients, the

qualitative and quantitative composition of the resident microflora of the mucous membranes of the vagina normalized, there were no discharges of a purulent and cheesy nature, dyspareunia (Fig. 3) [22, 23].

Conclusion

The treatment of diseases caused by pathogenic and opportunistic microorganisms, such as HPV and fungi of the genus C. albicans or non-albicans, is one of the leading directions in modern gynecology, dermatovenereology, and clinical immunology. The complexity of their therapy is associated with immunopathogenetic disorders, which result in a long-term persistence of the pathogen, leading to impaired immune surveillance and proliferation [22]. In HPV-mediated infection, the activity of CD8+ cytotoxic T-lymphocytes is affected by a decrease in antigen presentation (MHC-I / HLA-A) and a violation of the expression of TLR and CCR7 recognition protein on the surface of the membrane of infected cells, therefore, modulation of TLR-like receptors by Immunomax® is TLR agonist - restores the balance of immune mechanisms, which contributes to the activation of antitumor immunity against HPV-infected cells. Virus-mycotic associations are recorded much more often than monoinfection, so the normalization of local antimicrobial protection factors is a necessary step in the treatment of recurrent vulvovaginal candidiasis. The use of Gepon® has a pronounced anti-inflammatory effect - the symptoms of inflammation, itching, burning, dyspareunia decrease or disappear within one or two days, which makes it possible to reasonably recommend immunomodulatory therapy in the complex treatment of vulvovaginal candidiasis.

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