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## TRIPLE-NEGATIVE TRANSFORMATION OF THE ENDOMETRIUM, CERVIX AND MAMMARY GLAND ON THE BACKGROUND OF IMMUNODEFICIENCY

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**Abstract.** Triple-negative transformation of the endometrium, cervix and mammary gland on the background of immunodeficiency. Lytvynenko M.V., Gargin V.V. Precancerous processes of the female reproductive system continue to be an issue that is being actively studied, despite the successes of recent years. One of the key prognostic factors is the characterization of the receptor set, primarily the mammary gland and endometrium, namely estrogen (ER), progesterone (PR), epidermal growth factor-2 (HER2) receptors. Purpose – to identify the features of the distribution of estrogen, progesterone and epidermal growth factor receptors in the tissues of the endometrium, cervix and mammary gland with a combination of HIV infection and alcohol abuse. Fifty women of reproductive age from 20 to 40 years were studied. After routine conduction and immunohistochemical staining, ER and PR expression were determined by a modified D.Allred scale. HER2 expression was determined by a semi-quantitative method. The obtained digital data were statistically processed. A morphometric study indicates that the combination of HIV infection and alcohol abuse significantly affects the distribution of receptors in the female reproductive system. To a greater extent, the overall score is reduced by reducing the number of cellular elements with the expression of ER and PR. HER2 receptor expression is significantly reduced in the endometrium and mammary gland. These changes may be facilitated by atrophic changes in these organs, which occurs in immunodeficiency. According to the D.Allred scale, the mean score decreases from  $5.45 \pm 0.63$  to  $3.10 \pm 0.88$  in the endometrium, from  $4.68 \pm 0.65$  to  $2.47 \pm 0.58$  in the cervix, from  $6.57 \pm 0.67$  to  $3.57 \pm 0.77$  in the mammary gland ( $p < 0.05$ ). HER2 expression decreased from  $3.24 \pm 0.47$  to  $2.21 \pm 0.23$  in the endometrium, from  $3.43 \pm 0.66$  to  $2.36 \pm 0.32$  in the mammary gland ( $p < 0.05$ ). The development of immunodeficiency is characterized by the restructuring of female reproductive organs with a change in the receptor set of the endometrium, cervix and mammary gland and a decrease in both the qualitative and quantitative composition of the receptors, which may serve as a prerequisite for the development of a triple-negative phenomenon in tumors of these organs.

**Реферат.** Трипл-негативна трансформація ендометрія, шийки матки та молочної залози на тлі імунодефіциту. Литвиненко М.В., Гаргін В.В. Передракові процеси жіночої статеві системи продовжують залишатися питанням, що активно вивчається, незважаючи на успіхи останніх років. Одним з ключових факторів прогнозу є характеристика рецепторного набору, насамперед молочної залози та ендометрія, а саме рецепторів до естрогену (ЕГ), прогестерону (ПГ), гормону епідермального фактора росту-2 (ГЕФР2). Мета роботи – виявлення особливостей розподілу рецепторів естрогену, прогестерону та епідермального фактора росту в ендометрії, шийці матки та молочної залозі при поєднанні ВІЛ-інфекції та зловживання алкоголем. Досліджено 50 жінок репродуктивного віку від 20 до 40 років. Після рутинного проведення та імуногістохімічного зафарбовування визначали експресію ЕГ та ПГ за модифікованою шкалою D. Allred. Експресію ГЕФР2

визначали напівкількісним методом. Отримані цифрові дані статистично обробляли. Проведене морфометричне дослідження показало, що поєднання ВІЛ-інфекції та зловживання алкоголем суттєво впливає на розподіл рецепторів в органах жіночої статеві системи. Більшою мірою загальний бал знижується за рахунок зменшення кількості клітинних елементів з експресією ЕГ та ПГ. Експресія рецепторів ГЕФР2 достовірно зменшена в ендометрії та молочній залозі. Вказаним змінам можуть сприяти атрофічні зміни вказаних органів, що відбуваються при імунodefіциті. Відповідно до шкали D. Allred, середній бал зменшується з  $5,45 \pm 0,63$  до  $3,10 \pm 0,88$  в ендометрії, з  $4,68 \pm 0,65$  до  $2,47 \pm 0,58$  у шийці матки, з  $6,57 \pm 0,67$  до  $3,57 \pm 0,77$  у молочній залозі ( $p < 0.05$ ). Експресія ГЕФР2 зменшується з  $3,24 \pm 0,47$  до  $2,21 \pm 0,23$  в ендометрії, з  $3,43 \pm 0,66$  до  $2,36 \pm 0,32$  у молочній залозі ( $p < 0.05$ ). Розвиток імунodefіциту характеризується перебудовою органів жіночої статеві системи зі зміною рецепторного набору в ендометрії, шийці матки та молочній залозі зі зниженням як якісного, так і кількісного складу рецепторів, що може бути передумовою для розвитку трипл-негативного феномену пухлин у цих органах.

Precancerous states of the female reproductive system continue to be an actively studied issue despite the successes of recent years, primarily in relation to the prevention of cervical cancer and management of patients with mammary gland neoplasia [1, 2]. At the same time, one of the key predictive factors is the characteristics of the receptor set, primarily of the mammary gland and endometrium, namely, receptors for estrogen (ER), progesterone (PR), and epidermal growth factor hormone-2 (HER2) [3]. It is the determination of the receptor status of the tumor tissue that is decisive in the management of cancer patients of a given localization.

The very phenomenon of the combination of ER, PR and HER2 receptors remains completely unclear from the point of view of the reasons for the variability of the number of cellular elements and the degree of expression [4, 5]. Often this is explained by the fact that it is possible to assess only retrospective data of cancer patients.

Considering that the immune status is one of the determining factors in the development of malignant transformation, in particular, there is information on significantly higher rates of malignancy in the development of AIDS [6, 7], we considered it expedient to continue the study of changes in the morpho-functional state of the female reproductive system in the conditions of the development of immunodeficiency of viral etiology and alcohol abuse, as an additional factor affecting immune system [8]. The prevalence of alcohol abuse and HIV infection is still high [9, 10]. Based on the foregoing, the purpose of our study was to identify the features of the distribution of estrogen, progesterone and epidermal growth factor receptors in the tissues of the female reproductive system, particularly in the endometrium, cervix and mammary gland with a combination of HIV infection and alcohol abuse.

#### MATERIALS AND METHODS OF RESEARCH

The study was carried out on sectional material of 50 women of reproductive age from 20 to 40 years. All subjects were divided into 2 groups of 25 women in each. The study group consisted of women diagnosed

with HIV infection confirmed by laboratory data and a picture of chronic alcoholism detected both by autopsy findings (the main sign was the presence of alcoholic cirrhosis of the liver) and by history data (interviews with relatives). The comparison group consisted of women who died from diseases not related to alcohol abuse, disorders of the reproductive system without concomitant HIV infection (deaths as a result of accidents, injuries). HIV infection was verified by serum enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation. A CD4 lymphocyte count  $< 100$  cells/ $\mu$ L was considered "low". Tobacco smoking, use of contraceptives (oral contraceptive pills), age at first intercourse, somatic disorders and the number of pregnancies were not taken into account as subjects were recruited to groups according to the principle of randomness.

After routine processing and sectioning, samples were stained with hematoxylin and eosin, and immunohistochemistry (IHC) was performed. IHC was conducted by an indirect immunoperoxidase reaction with monoclonal antibodies (mAb) to estrogen (*Estrogen Receptor alpha Monoclonal Antibody*), progesterone (*Progesterone Receptor Monoclonal Antibody*), epidermal growth factor hormone 2 (HER2) (Thermo Scientific, USA). The reaction was visualized using the UltraVision LP Detection System HRP Polymer & DAB Plus Chromogen kit (Thermo Scientific, USA).

Microscopic examination was performed on an Olympus BX41 microscope with further morphometric assessment using Olympus DP-soft 3.12 software [16, 17]. The staining was evaluated independently by two observers, and a high level of consistency was achieved (90%). All samples were independently analyzed two times and the discrepancy between observers ( $< 10\%$ ) was reviewed a third time, after which the final judgment was made [11, 12].

The expression of ER and PR markers was assessed using the modified D. Allred scale [3]. Score from 0 to 6 was used to describe the proportion of cells showing positive nuclear staining – A (0= none;  $1 \leq 1\%$ ;  $2=2-9\%$ ;  $3=10-33\%$ ;  $4=34-66\%$ ;  $5 > 66\%$ ), and a score from 0 to 4 represented the intensity of the

staining – B (0= none; 1=weak; 2=moderate; 3=high). The result is described as the sum of A+B=TS (total score).

The expression of HER2 marker was evaluated taking into account the presence of membrane staining. Tissue was considered HER2-positive if it contained more than 10% of cells with an intense membrane reaction in the form of a thick line with the formation of a complete rim around the cells. All cases were assessed by a semi-quantitative method with 1 – negative reaction, 2 – weak incomplete staining of the membrane, 3 – average intensity of membrane staining of more than 10% of cells, 4 – intensive staining of the membrane of more than 10% of cells.

Statistical processing was performed using the methods of variation statistics. Correspondence to normal distribution was determined by the Shapiro-Wilk's test, which showed that the samples were close to normal distribution. Statistical indicators are presented in the  $M \pm \sigma$  format, where M is the arithmetic mean,  $\sigma$  is the standard deviation, Student's

t-test. Correlation analysis was carried out using Spearman's rank correlation coefficient. Statistical difference between the studied parameters was considered significant at  $p < 0.05$ .

All studies were carried out in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – “Ethical principles for medical research involving human subjects” and “Universal Declaration on Bioethics and Human Rights” (UNESCO) and approved by the Ethics Commission of Odesa National Medical University (Protocol No. 3 of 17 October 2011).

## RESULTS AND DISCUSSION

Morphometric study showed that the combination of HIV infection and alcohol abuse significantly affected the distribution of receptors in the organs of the female reproductive system. Transformation of expression is presented in Table 1 for estrogen and progesterone and in Table 2 for epidermal growth factor hormone receptors.

Table 1

**Distribution of ER and PR receptors in endometrium, cervix and mammary gland ( $M \pm m$ )**

Organ	Indicator	Comparison group, n=25	HIV-infected group with chronic alcoholism, n=25
Endometrium	Average score A (proportion of cells showing positive nuclear staining), 0-5	2.57±0.41	1.01±0.53*
	Average score B (staining intensity), 0-3	2.88±0.54	2.09±0.41*
	A+B=TS (total score), 0-8	5.45±0.63	3.10±0.88*
Cervix	Average score A (proportion of cells showing positive nuclear staining), 0-5	2.33±0.22	1.03±0.21*
	Average score B (staining intensity), 0-3	2.35±0.43	1.44±0.52*
	A+B=TS (total score), 0-8	4.68±0.65	2.47±0.58*
Mammary gland	Average score A (proportion of cells showing positive nuclear staining), 0-5	3.65±0.38	1.21±0.50*
	Average score B (staining intensity), 0-3	2.92±0.49	2.36±0.44
	A+B=TS (total score), 0-8	6.57±0.67	3.57±0.77*

All organs were found to have a decrease in the expression of ER and PR in the presence of a combination of HIV infection and alcohol abuse. At the same time, a decrease in expression is reflected in lowering of the total score, characterizing both the number of expressing cells and their quantity. To a greater extent, the total score decreased due to the lowered number of cellular elements with ER and PR expression. Thus, for each organ, indicator A

decreased significantly ( $p < 0.05$ ), while indicator B (the degree of staining intensity) was significantly reduced only in the cervix and endometrium.

Assessment of the correlations between changes in organs showed a strong relationship between changes in the endometrium and the mammary gland ( $r=0.792$ ), moderate – between the cervix and the mammary gland ( $r=0.634$ ) and strong – between the endometrium and the cervix ( $r=0.738$ ).

Table 2

## Expression of epidermal growth factor hormone receptors, standard units (M±m)

Organ	Comparison group, n=25	HIV-infected group with chronic alcoholism, n=25
Endometrium	3.24±0.47	2.21±0.23*
Uterine cervix	2.27±0.51	2.11±0.24
Mammary gland	3.43±0.66	2.36±0.32*

Note. In all tables \* is the presence of a significant difference relative to the comparison group ( $p < 0.05$ ).

Triple-negative mammary gland cancer, characterized by the lack of expression of the estrogen receptor / progesterone receptor (ER/PR) and human epidermal growth factor receptor 2 (HER2), has a worse prognosis compared to mammary gland tumors without this condition [3]. Until recently, systemic treatment for triple-negative cancers was limited to chemotherapy due to the lack of effective targets [13]. In this case, molecules of immune checkpoints are expressed on malignant cells or immune cells, infiltrating the tumor and are able to suppress anti-cancer immune responses. However, the exact moment of the impairment of control by immune checkpoints remains unclear. At the same time, the phenomenon of the development of triple-negative tumors remains unclear from the point of view of the mechanism of occurrence [14].

It is necessary to mention that successful management of patients with immunodeficiency states has resulted in an increase in life expectancy [15, 16] and, considering the growing category of such patients, requires research on the reproductive health of this category of patients [17, 18]. Women with immunosuppression are more likely to suffer from malignant transformations of the reproductive system, which can be explained by defects in antitumor protection, arising in this case [11]. On the other hand, additional exposure to ethanol, which is a category 1 carcinogen, serves as an additional factor, leading to tumor transformation [21, 22].

At the same time, characteristics of the receptor apparatus, in particular receptors for the ER, PR and HER2 are important in terms of the choice of tactics in the management of these patients, especially in mammary gland cancer, since cases with a negative receptor set have a poor prognosis [5].

The system for assessing the receptor status of tissues of the female reproductive system proposed by D. Allred and used by us, helps to assess the qualitative and quantitative set of cells expressing ER and PR [3]. Based on the interpretation of the D. Allred scale, it is possible to quantitatively identify cases

related to the triple-negative phenomenon. Thus, if the number of points is equal to or less than 4, it is possible to suggest absence of ER and PR expression and points above 4 can mean a positive result [5].

At the same time, changes in the receptor apparatus of the female reproductive system are important not only in tumor processes [23]. Hormone therapy can induce tissue transformation [24]. In particular, oral contraceptives are associated with inactive, atrophic or pseudosecretory glands and edematous stroma. Highly active progesterone can cause severe stromal and vascular hyperplasia and stromal myomatous nodules [25]. Ovulation induction therapy accelerates stromal maturation and is often associated with a mismatch between glands showing early secretory changes and edematous decidualized stroma. Hormone replacement therapy can stimulate endometrial proliferation when estrogens are used alone and cause endometrial hyperplasia and neoplasia [11]. Progesterone therapy for endometrial hyperplasia and neoplasia is accompanied by secretory changes in the endometrium, mainly subnuclear vacuoles, decidual reaction and sometimes scaly "morula". Endometrial secretory changes after progesterone therapy do not exclude residual carcinoma.

The decrease in the activity of the receptor apparatus of the female reproductive system in immunodeficiency revealed in our study is interesting in combination with previously published data on atrophic processes of this localization during suppression of the immune system [26].

It is necessary to mention a biological peculiarity of the fact that hormone-sensitive tissue has the ability not only to cyclically renew the cellular composition, but also to respond in a certain way to all changes in the hormonal and immune status at the level of the whole body [27], violations of which can trigger adverse consequences [28].

The results of treatment in patients with abnormal processes of the same localization with the same distribution, histological structure and degree of cell

differentiation can differ significantly [29]. That is why it is essential to identify tissue and molecular markers in the tissues of the studied organs, which determine the specific phenotype of the disorder and provide important diagnostic and prognostic information about the status of the disease and its biological properties [30, 31].

It can be stated that the loss of ER and PR receptors is an unfavorable sign of tissue transformation of the female reproductive system in immunodeficiency states, which can be observed in an inadequate response to hormonal therapy, creating the preconditions for the development of aggressive forms of malignant neoplasms.

Our results can be used to elaborate clinical and morphological criteria for predicting the development of pathological processes in the female reproductive system in immunodeficiency and identification of such cases can be an important stage of preventive measures in the management of such patients.

#### CONCLUSIONS

The development of immunodeficiency is characterized by the restructuring of female reproductive organs with a change in the receptor set of the

endometrium, cervix and mammary gland and a decrease in both the qualitative and quantitative composition of the receptors, which may serve as a prerequisite for the development of a triple-negative phenomenon of tumors in these organs.

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#### Contributors:

Lytvynenko M.V. – resources, research methodology, data collection, morphological research, formal analysis, research visualization;

Gargin V.V. – conceptualization, morphological research, methodology, writing – reviewing and editing.

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