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ORIGINAL PAPERS

Assessment of the Level of Expression Activity and Localization of Cd-Receptors in the Postmenopausal Period

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Abstract

The cervical mucosa (CM) is a critical site in the female reproductive system, but despite extensive histological studies in reproductive-age women, there is a notable gap in our understanding of the local immune homeostasis in postmenopausal women. This lack of knowledge is particularly concerning given the pivotal role of immune phenotypes in regulating neoangiogenesis during malignancy. Furthermore, the reasons underlying the inadequate immune response in carcinogenesis remain elusive. In this study, the authors aimed to address these knowledge gaps by investigating the local immune homeostasis (LIH) of CM in postmenopausal women. Their findings revealed age-related and localized features in the LIH of CM, shedding light on the complex interplay between the immune system and cervical tissues. Understanding these unique immune dynamics has far-reaching implications for the field of gynecology. The identification of age-related variations in LIH has significant implications for the development of conservative treatment strategies, prevention of complications, and early diagnosis of malignancy in postmenopausal women. By unraveling the intricate relationship between immune responses and cervical mucosal changes, this research provides a foundation for developing targeted interventions to enhance immune surveillance and bolster the body's natural defenses against malignancies in this vulnerable population. In conclusion, this study underscores the importance of investigating the immune microenvironment of CM in postmenopausal women. The newfound knowledge regarding age-related and localized features in LIH not only advances our understanding of cervical health but also paves the way for more effective prevention, treatment, and early detection strategies, ultimately improving the overall quality of care for postmenopausal women at risk of cervical malignancies.

Keywords: CD-receptors, postmenopausal period, cervical cancer, neoangiogenesis, malignization.

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INTRODUCTION

The escalating incidence of cancer among postmenopausal women poses a significant global health challenge, with a particularly alarming rise observed in various regions, including Primorsky Region, Russian Federation. In this specific region, the incidence of newly diagnosed cases is strikingly 2.5 times higher than the national average. This concerning trend has far-reaching implications, impacting not only the affected individuals but also the broader societal fabric. The burden of cancer in socially significant age groups not only diminishes the quality of life for these women but also hampers their active participation in the socio-economic sphere, further emphasizing the urgency of comprehensive research initiatives^{1,2,3,4,5}.

In response to this pressing need, this study aims to delve into the intricate mechanisms of malignization in postmenopausal women. Understanding the fundamental pathomorphological substrates and identifying specific cellular targets are imperative steps toward the development of effective prevention methods, precise diagnostic tools, and pathogenetically grounded treatment approaches^{2,6,7,8,9}. Of particular interest are immunocytes and phagocytes within the cervical mucosa (CM) structure, which hold promising potential as cellular targets for the development of conservative treatment strategies and postoperative prevention of tumor recurrence^{3,6,10,11,12,13}.

This research is propelled by the necessity to explore the expression activity and localization patterns of CD receptors in the postmenopausal period. By evaluating the level of CD receptor expression and understanding its specific localization within the cervical mucosa, this study aims to unravel crucial insights into the immunological landscape of postmenopausal cervical tissues. This knowledge will not only deepen our understanding of the underlying mechanisms but also pave the way for the development of targeted therapeutic interventions, thereby mitigating the impact of cancer on postmenopausal women and improving their overall quality of life.

MATERIALS AND METHODS

The study included 149 CM biopsy specimens of Primorsky Region patients with severe postmenopause, obtained for clinical indications during diagnostic hysterectomy around ecto-, endocervix and in the place of transition of ectocervix to endocervix in accordance

with the provisions of the Declaration of Helsinki (2000, 2013) and with the permission of the Ethical Committee of Far Eastern Federal university (FEFU) for clinical indications. CM biopsy specimens were distributed considering the age groups of the patients adopted by the International Symposium on Age Periodization in Moscow (1965), according to the protocol with the completion of the patients' medical records of form No. 043/u. As a control we used the material of CM and endometrial tissue slices from 15 women over 50 years old with a favorable menopausal history and in the postmenopausal period who had undergone diagnostic hysterectomy for benign and noninflammatory reasons. Routine techniques were used (hematoxylin and eosin, Van-Gizon, Victoria blue, Brasher and al-cian blue staining. To illustrate and further comparative analysis of the dynamics of the number of immunocytes/phagocytes in different periods of ontogenesis and their participation in the mechanisms of physiological and reparative regeneration of CM structures we used immunohistochemical phenotyping on the basis of clusters of differentiation (CD) - T-lymphocytes (CD4±/CD8±), CD34, Langerhans cells (CD68±), interstitial macrophages (CD163±), mast cells (CD203a±). For statistical processing of the results, we used various methods of parametric and nonparametric statistics - Student's and Wilcoxon criteria, etc. using special standard software packages, including LYSYS II package ("Becton Dickinson Immunocytometry system").

RESULTS

With increasing duration of postmenopause, there is a sharp alkalization of the vaginal environment and development of dysbiotic processes like bacterial vaginosis, the latter is more characteristic of women with duration of postmenopause up to 3 years. This is reflected in the state of local immune homeostasis of CM (Fig. 1).

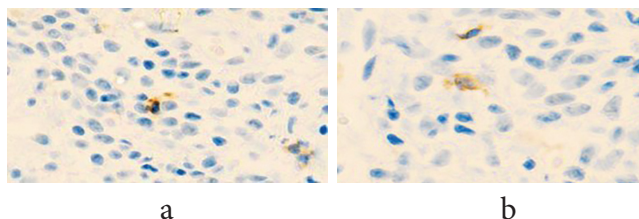


Figure 1. CM of a 51-year-old woman. A) ectocervix (CD8); b) transformation zone (CD4). Immunohistochemistry for detection of CD4 and CD8 localization with hematoxylin dyeing. Microphoto. Eq. x200.

The number of immunocompetent cells expressed by markers in the postmenopause is reduced in the zone of epithelial transformation and especially significantly in the endocervical area (Figure 2).

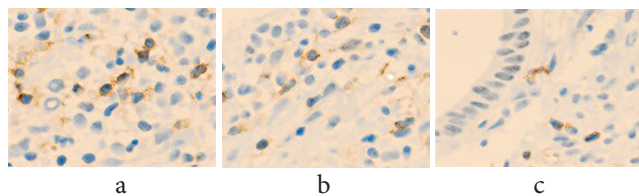


Figure 2. CM of a 54-year-old woman. a) ectocervix (CD8); b) transformation zone (CD4); c) endocervix (CD8). Immunohistochemistry for detection of CD4 and CD8 localization with hematoxylin dyeing. Microphotograph. Eq. x200

The number of CD68 effector cells decreases almost 2-fold in the transformation zone ($p < 0.01$) and is significantly reduced in the endocervix to 1-2 expressed cells in the field of view. Quantitative data on the content of immunocompetent cells in the CM structure against the background of the postmenopausal period are presented in Table 1.

Table 1. Age-specific indices of immunocompetent cells in CM during postmenopause (per 100 cells in the field of view).

Baseline indices of immunocompetent cells in CM during postmenopause (per 100 cells in the field of view) in normal course (* $P < 0.05$)			
Section of CM	Exocervix	Transformation zone	Endocervix
CD4	15,6±0,31	12,8±0,12	8,3±0,20
CD8	4,5±0,11	2,1±0,04	1,2±0,05
CD68	18,3±2,7	16,5±3,5	12,4±0,15
CD163	24,5±0,34	20,7±1,13	11,43±0,35
Total number	62,5	52,8	33,3

In pathologic course of the postmenopausal period the indices of immunocompetent cells in CM differ from the data obtained in the control group ($p < 0.05$). The significance of the differences is presented in Table 2.

Table 2. Baseline indices of immunocompetent cells in CM during postmenopause (per 100 cells per field of view) in pathologic course.

CM structures in the observation group	Average activity of Ki-67 gene in pathologic course of postmenopausal period (number of mitoses per 100 cells in %)				
	1 year PMP	2 year PMP	3 year PMP	4 year PMP	5 year PMP
Exocervix	4,2	2,9	2,5	2,6	1,7
Transformation zone	3,2	2,5	2,2	1,8	1,3
Endocervix	2,5	2,4	1,9	1,6	0,8
Total	9,9	7,8	6,6	6	3,8

CM thinning, decrease in the amount of mucus and IgA, providing local immune homeostasis, lead to the formation of polyps on the background of HPV, increased microbial contamination of the epithelium. To compensate for the barrier properties of epithelial layers there is an increase in proliferative activity in the structures of both multilayer squamous epithelium and cylindrical epithelium.

In case of prolonged HPV infection, apoptosis is noted on CM preparations. Monitoring during clinical follow-up of this patient showed malignization of CM tissue in the polyp area within 6 months, on the basis of which we concluded that apoptosis and absence of basal membrane in the epithelial lamina are unfavorable prognostic signs and may be a reflection of developing malignization of CM tissue.

Analysis of the proliferative activity of the cervical mucosa epithelium allowed us to establish that, despite the duration of postmenopause, weak proliferative phenomena in the multilayer squamous and cylindrical epithelium of the cervix can be observed during this period and, accordingly, in the first year of postmenopause proliferative types of smears make up 75%, which is consistent with our data. The longer the period of time the polyp was not removed, the greater morphologic abnormalities are noted in the study of biopsy material. The morphologic picture identifies areas of apoptosis, destruction of the basal membrane, immunohistochemically reveals increased activity of the Ki67 gene.

In the presence of polyps in the cervical mucosa, proliferative activity increases not only in the epithelial lamina, but is also registered in the intrinsic lamina.

DISCUSSION

The findings of this study provide valuable insights into the complex landscape of local immune homeostasis (LIH) within different segments of the cervical mucosa (CM), particularly in the context of postmenopausal women. The observed peculiarities in LIH across various CM regions highlight the importance of considering both age-related dynamics and specific localizations within the CM structure in understanding the immune responses associated with postmenopausal changes.

One significant revelation from this study is the decrease in the number of immunocompetent cells in CM structures during postmenopause, especially in pathological conditions. This decline in immunocompetent cells signifies a weakened immune defense, leaving postmenopausal women vulnerable to infections and potentially facilitating the progression of pathogenic processes. Furthermore, the study identifies a reduced immune response in cases of infectious contamination, affecting both cellular defense reactions and humoral responses. This impaired immune reactivity amplifies the challenges faced by postmenopausal women in combating infections, emphasizing the need for targeted interventions to bolster their immune defenses.

The study's findings also underscore the clinical relevance of understanding LIH in CM. By recognizing the age-related variations and localization-specific aspects of LIH, healthcare professionals can utilize this knowledge for diagnostic purposes. Monitoring changes in LIH can aid in the early detection of pathological alterations within CM, enabling timely interventions and tailored treatments. Additionally, the insights gained from this research have implications for postoperative care and the prevention of recurrences. Utilizing LIH data in screening observations of the postoperative period can enhance the effectiveness of follow-up protocols, ensuring a comprehensive evaluation of patients' immune status and facilitating the prevention of disease relapses.

CONCLUSION

Thus, it has been established that local immune homeostasis has peculiarities in different parts of CM, and is characterized by age-related dynamics. In pathological courses the number of immunocompetent cells in CM structures during postmenopause decreases, and in case of infectious contamination the immune response is re-

duced both in the system of cellular defense reactions and in the system of humoral response.

LIH of CM depends on the age period and localization in the CM structure. Decreased immune response is especially pronounced in the pathologic course of the postmenopausal period. LIH of CM data can be used to diagnose pathologic changes in CM, as well as in the dynamics of screening observations of the postoperative period and prevention of recurrences.

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