ДИАГНОСТИЧЕСКИ ЗНАЧИМЫЕ ИЗМЕНЕНИЯ СУБПОПУЛЯЦИЙ $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ НЕЙТРОФИЛЬНЫХ ГРАНУЛОЦИТОВ ИММУНОКОМПРОМЕТИРОВАННЫХ ЖЕНЩИН С ХРОНИЧЕСКИМИ ИНФЕКЦИОННО-ВОСПАЛИТЕЛЬНЫМИ ЗАБОЛЕВАНИЯМИ ГЕНИТАЛЬНОГО ТРАКТА РАЗЛИЧНОЙ ЭТИОЛОГИИ

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Резюме. Хронические воспалительные заболевания органов малого таза (ХВЗОМТ) у женщин остаются основной проблемой в структуре гинекологических заболеваний ввиду значимости медицинских и социально-экономических последствий. Течение и исход ХВЗОМТ зависят от состояния иммунной системы. Актуальным представляется изучение рецепторного аппарата нейтрофильных гранулоцитов (НГ), участвующих в противоинфекционной защите при заболеваниях различной этиологии. Цель: уточнить особенности вариантов количественных и фенотипических изменений субпопуляций НГ $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ иммунокомпрометированных женщин в период обострения ХВЗОМТ различной этиологии. Тестировали НГ периферической крови 70 женщин 20-40 лет: группа исследования 1 (ГИ1) – 20 иммунокомпрометированных женщин в период обострения ХВЗОМТ с моно- или микст-латентными или рецидивирующими различными вирусными инфекциями (хронические герпес-вирусные инфекции, папилломавирусная инфекция, рекуррентные ОРВИ); группа исследования 2 (ГИ2) – 30 иммунокомпрометированных женщин с

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ХВЗОМТ бактериальной этиологии; группа сравнения – 20 условно-здоровых женщин. Методом проточной цитометрии (CYTOMICS FC500, США) определяли количество НГ и уровень экспрессии рецепторов субпопуляций $CD11b^+CD64^-CD32^+CD16^+$НГ (мажорной) и $CD11b^+CD64^+CD32^+CD16^+$НГ (минорной). Установлено, что у иммунокомпрометированных женщин с ХВЗОМТ в период обострения выявлены диагностически значимые различия в субпопуляционном составе НГ. При ХВЗОМТ бактериальной этиологии (ГИ2) снижение субпопуляции $CD11b^+CD64^-CD32^+CD16^+$НГ и увеличение в 7,6 раз субпопуляции $CD11b^+CD64^+CD32^+CD16^+$НГ в отличие от ХВЗОМТ, протекающих в сочетании с рецидивирующей или персистирующей вирусной инфекцией (ГИ1). Негативная трансформация субпопуляций НГ связана с преимущественным снижением уровня экспрессии активационного CD16. Выявлено отсутствие адекватного ответа на воспаление – отсутствие повышения экспрессии активационного CD11b в мажорной субпопуляции в ГИ1, а также в минорной субпопуляции в ГИ1 и ГИ2. В мажорной субпопуляции ГИ2 выявлено нарушение – снижение экспрессии активационного маркера CD11b в период обострения ХВЗОМТ. Также при наличии различной вирусной инфекции и ХВЗОМТ (ГИ1) в негативно измененной минорной субпопуляции выявлено снижение уровня экспрессии CD16, повышение уровня экспрессии CD64 и CD32. Определение субпопуляционного состава $CD11b^+CD64^-CD32^+CD16^+$ и $CD11b^+CD64^+CD32^+CD16^+$ НГ и их фенотипа можно использовать как в качестве диагностических маркеров для дифференциальной диагностики ХВЗОМТ вирусной и бактериальной этиологии, так и для последующей разработки новых методов таргетной иммуномодулирующей терапии.

Ключевые слова: нейтрофильные гранулоциты, субпопуляции, фенотип, диагностический маркер, хронические воспалительные заболевания органов малого таза, иммунокомпрометированность

DIAGNOSTICALLY SIGNIFICANT CHANGES IN SUBSETS $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ NEUTROPHILIC GRANULOCYTES OF IMMUNOCOMPROMISED WOMEN WITH CHRONIC INFECTIOUS AND INFLAMMATORY DISEASES OF THE GENITAL TRACT OF VARIOUS ETIOLOGIES

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Abstract. Chronic pelvic inflammatory disease (PID) in women remains a problem due to the importance of medical consequences. The study of the receptor apparatus of neutrophilic granulocytes (NG) involved in anti-infective protection in diseases of various etiologies seems to be relevant. Aim: to clarify the features of variants of quantitative and phenotypic changes in subsets of NG $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ of immunocompromised women during exacerbation of chronic PID of various etiologies. We were tested women 20-40 years: Study Group 1 (SG1, n = 20) – chronic PID during the exacerbation with mono- or mixed latent/recurrent various viral infections (chronic herpes-virus infections, papillomavirus infection, recurrent ARVI); Study Group 2 (SG2, n = 30) – chronic PID of bacterial etiologies; Comparison Group (CG) – 20 healthy women. The number of subsets $CD11b^+CD64^-CD32^+CD16^+$NG (major) and $CD11b^+CD64^+CD32^+CD16^+$NG (minor), receptor expression density (MFI) was determined (FC500, USA). It was found that in PID during the period of exacerbation, diagnostically significant differences in the

subset composition of NG were revealed. We got a decrease in the $CD11b^+CD64^-CD32^+CD16^+$NG subset and in 7,6 times increase in the $CD11b^+CD64^+CD32^+CD16^+$NG subset in SG2 with chronic PID of bacterial etiology, in contrast to chronic PID occurring in combination with recurrent/persistent viral infection SG1. Negative transformation of NG subsets is associated with a predominant decrease in the level of expression of the activation CD16. The absence of an adequate response to the infectious and inflammatory process was revealed – the absence of an increase in the expression of the activation CD11b in the major subset in SG1, as well as in the minor subset in groups SG1 and SG2. In the major subset of NG in groups SG2 a decrease in the expression of the activation marker CD11b. In the various viral infections and PID (SG1), in the negatively altered minor subset of NG we got a decrease of expression of CD16, an increase of expression of CD64 and CD32. Determination of subsets of $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$NG and their phenotype can be used as diagnostic markers for the differential diagnosis of PID of viral and bacterial etiology, and for the development of new methods of targeted immunomodulatory therapy.

Keywords: neutrophilic granulocytes, subsets, phenotype, diagnostic marker, chronic pelvic inflammatory disease, immunocompromised

Introduction

Chronic inflammatory diseases of the pelvic organs (pelvic inflammatory disease, PID) are one of the main problems among gynecological diseases due to their wide distribution, and they can be represented both as separate nosological forms and in various combinations. Despite the improvement of methods of diagnosis and treatment according to the World Health Organization (WHO), 448 million new cases of chronic inflammatory diseases of the pelvic organs are registered annually in the world (up to 60% of the total number of gynecological diseases) [10, 12]. According to modern scientific data, the etiology of chronic PID is polymicrobial, associated not only with obligate pathogens (Neisseria gonorrhoeae, Chlamydia trachomatis, etc.), but also with opportunistic microflora that is part of the normal vaginal microbiota. The main features are the variety of the clinical picture, with a short interrecurrent period or a sluggish protracted course [2, 3, 9]. Cases with a severe and complicated course have become more frequent; persistent recurrence of the inflammatory process, the absence of a positive effect on the ongoing etiotropic and pathogenetic therapy, as a result of which the formation of an adhesive process and impaired reproductive functions is possible.

The immune system plays a significant role in the pathogenesis of chronic PID, and it is from its adequate or defective functioning that the characteristics of the course and outcome of the disease depend [8]. Thus, impaired functioning of local or systemic immunity contributes to the emergence of atypically occurring acute or chronic infectious and inflammatory diseases of the reproductive tract causes the onset and chronicity of infectious and inflammatory processes of extragenital localization of various etiologies, which are resistant to therapy – antiviral, antibacterial, antifungal and anti-inflammatory [7], which also indicates clinical signs of immunocompromised being. The particular interest is the study of the functioning of neutrophilic granulocytes (NG), one of the most important cells of innate immunity, which perform a number of effector and regulatory functions during the infectious process. They are the first cells and ready to respond to the invasion of pathogens and the increase in the growth of opportunistic microorganisms in the microbiome. At the same time, the symbiotic microflora (lacto- and bifidobacteria), being in close relationship with NG, stimulates the formation of NET, thereby exerting a regulatory effect on the state of the microbiocenosis of the genital tract [11].

According to modern scientific data, the antimicrobial activity of NG is associated with certain surface membrane receptors. Thus, the surface membrane molecules of NG receptors CD64, CD32, CD16, CD11b form different subsets of NG with different phenotypes, performing both effector and regulatory functions: immunomodulating, immunostimulating, immunosuppressive [1]. Overexpression or defects in the expression of one or more receptors cause disturbances in the effector and/or regulatory functions of various NG subsets. Thus, in case of dysfunctions of the NG receptor apparatus caused by impaired expression of CD16, CD11b molecules, which are activation markers of the NG effector functions, dysregulatory disorders of the anti-infective immune defense are observed. Because of this there are acute severe infectious and inflammatory diseases, prolonged sluggish or recurrent chronic infectious and inflammatory processes that do not respond to etiotropic therapy. At the same time, studies devoted to the study of the quantitative characteristics and phenotypic features of the

$CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+NG$ subsets of immunocompromised women with chronic PID have not been conducted.

Taking into account the above, it seems promising to study the quantitative characteristics and phenotypic features of subsets of $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ neutrophilic granulocytes of women with chronic PID. Clarification of variants of the defective phenotype of NG subsets and their quantitative imbalance can contribute to the development the methods for diagnosing the defective functioning of NG subsets. The obtained new data can be the basis for the creation of new targeted methods of immunomodulatory therapy, organically included in the complex treatment of chronic PID.

Aim: to clarify the features of variants of quantitative and phenotypic changes in subsets of $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+$ neutrophilic granulocytes of immunocompromised women during the exacerbation of chronic PID of various etiologies.

Materials and methods

Under our supervision were 50 women from 20 to 40 years old in the period of exacerbation of chronic PID (chronic metritis, chronic salpingo-oophoritis), with clinical signs of immunocompromised. Groups were formed depending on the clinical and anamnestic data: Study Group 1 (SG1) and Study Group 2 (SG2). Women of both groups were characterized by a long history of chronic PID (more than 5 years), frequent exacerbations (3 or more times a year) or a sluggish protracted course of exacerbations, the absence of a stable clinical effect when using systemic and local anti-inflammatory therapy. SG1 included 20 immunocompromised women with chronic PID (40% of all cases). When studying the history data according to the "immunological history" program (Nesterova I.V., 1992), criterial signs of immunocompromise were revealed, indicating that SG1 patients suffered from mono- or mixed latent or recurrent various viral infections in 100% of cases. They had chronic herpes virus infections caused by herpes simplex viruses types I and II, genital and orofacial localization with a frequency of exacerbations up to 5-6 times a year, human papillomavirus infection (anogenital warts), recurrent acute respiratory viral infections with a frequency of episodes up to 7-8 times a year. SG2 included 30 immunocompromised women (60%) with chronic PID of various bacterial etiologies. The comparison group (CG) consisted of 20 conditionally healthy women of reproductive age from 20 to 40 years old who applied to the clinic to choose a contraceptive method. An immunological study of the "major" and "minor" subsets, $CD11b^+CD64^-CD32^+CD16^+$, $CD11b^+CD64^+CD32^+CD16^+NG$, was carried out with the determination of the percentage of each NG subset (%NG) and assessment of their phenotype, taking into account the density of expression of each receptor by the value of the mean of fluorescence index (MFI) by flow cytometry (CYTOMICS FC500, USA). Appropriate monoclonal antibodies to CD11b, CD64, CD32, CD16 molecules were used. For statistical processing of the obtained data, Microsoft Excel 2016, StatPlus 2010 software packages and non-parametric tests – the Wilcoxon and Mann–Whitney criteria were used. The results were expressed as a median (upper and lower quartile) – Me ($Q_{0.25}$-$Q_{0.75}$). Differences were considered statistically significant at $p < 0.05$.

Results and discussion

It was revealed that in the peripheral blood samples of the comparison group (CG) (conditionally healthy women), the major subset of NG $CD11b^+CD64^-CD32^+CD16^+$ occurs in 94.90 (93.98-97.40) %, and the minor subset of NG $CD11b^+CD64^+CD32^+CD16^+$ – in 1.24 (0.29-5.41) %.

In women with SG1 during the exacerbation of chronic PID, the quantitative composition of the major and minor subsets did not statistically significantly differ from the indicators of the comparison group ($p > 0.05$). At the same time, a negative transformation of the phenotype of both subsets was revealed. Thus, in the major subset $CD11b^+CD64^-CD32^+CD16^+NG$, the CD16 expression level was in 1,3 times lower, and the CD32 expression level was in 1.2 times higher relative to the CG ($p_{1,2} < 0.05$). At the same time, in the minor subset of $CD11b^+CD64^+CD32^+CD16^+NG$, there was a statistically significant increase in the expression density of the CD64 molecule according to MFI – in 3 times, and the CD32 molecule – in 1.9 times relative to CG ($p_{1,2} < 0.05$). A significant decrease in the level of expression of the CD16 molecule was found by 1.6 times relative to CG ($p < 0.05$). The revealed fact attracted attention that the expression of the CD11b molecule in the major and minor subsets did not change and remained at the CG level ($p > 0.05$) (Table 1).

In SG2 during the exacerbation of chronic PID, a statistically significant decrease in the proportion of the major subset $CD11b^+CD64^-CD32^+CD16^+NG$ – up to 87.35 (84.69-88.38) and a significant increase by 7.6 times in the content of the minor subsets of $CD11b^+CD64^+CD32^+CD16^+NG$ relative to CG

TABLE 1. CHANGES IN SUBSETS OF $CD11b^+CD64^-CD32^+CD16^+$ AND $CD11b^+CD64^+CD32^+CD16^+$ NEUTROPHIL GRANULOCYTES OF IMMUNOCOMPROMISED WOMEN DURING EXACERBATION CHRONIC PELVIC INFLAMMATORY DISEASES, Me ($Q_{0.25}$-$Q_{0.75}$)

Indicator	Comparison Group (CG)	Study Group 1 (SG1)	Study Group 2 (SG2)
$CD11b^+CD64^-CD32^+CD16^+$			
%NG (%NG)	94.90 (93.98-97.40)	93.98 (89.84-95.71)	87.35 (84.69-88.38)* ^
MFI CD16	118.5 (108.00-146.25)	90.5 (79.37-106.50)*	93.90 (81.80-107.00)*
MFI CD32	3.79 (3.50-4.13)	4.73 (4.36-6.42)*	4.04 (3.00-4.85)
MFI CD11b	25.10 (21.60-27.15)	22.10 (19.05-26.77)	15.50 (11.06-20.70)*
$CD11b^+CD64^+CD32^+CD16^+$			
%NG (%NG)	1.24 (0.29-5.41)	2.32 (1.42-6.97)	9.42 (7.53-11.40)* ^
MFI CD64	2.40 (2.07-5.06)	7.34 (6.88-15.35)*	1.69 (1.51-1.97)* ^
MFI CD16	149.00 (128.00-157.00)	94.80 (55.20-126.00)*	109.00 (89.90-121.00)*
MFI CD32	5.84 (4.24-6.50)	11.10 (7.27-18.55)*	5.21 (3.68-5.84)^
MFI CD11b	33.70 (24.10-37.40)	30.75 (23.80-46.75)	23.20 (16.92-29.35)

Note. *, the reliability of differences in indicators from the values of the comparison group, $p < 0.05$; ^, the reliability of differences in indicators in relation study group 1 (SG1), $p < 0.05$.

($p_{1,2} < 0.05$). The expression density level of the CD11b molecule in SG2 was statistically significantly reduced by 1,6 times in the minor subset of $CD11b^+CD64^+CD32^+CD16^+$NG ($p < 0.05$), while in the major subset of $CD11b^+CD64^-CD32^+CD16^+$NG it remained at the level of CG indicators ($p > 0.05$). The expression density level of the CD32 molecule in SG2 did not change statistically, both in the major and minor NG subsets relative to the CG ($p_{1,2} > 0.05$) (Table 1).

Comparing the results of NG phenotyping in women during the exacerbation of chronic PID in SG1 and SG2, statistically significant changes were revealed. In SG2 the relative content of the major subset $CD11b^+CD64^-CD32^+CD16^+$NG was reduced by 1.1 times ($p < 0.05$), and the subset of the minor $CD11b^+CD64^+CD32^+CD16^+$NG was increased by 4 times compared to SG1 ($p < 0.05$). Changes in the phenotype were found only in the minor subset. Thus, in SG1, compared with SG2, the expression level of the CD64 receptor increased by 4.3 times, and the expression level of CD32 increased by 2.1 times ($p_{1,2} < 0.05$) (Table 1).

Taking into account the data obtained, it is evident that in immunocompromised women during the exacerbation of chronic PID in the 2 groups of SG1 and SG2, there are quantitative changes and various options for negative restructuring of the phenotype of the NG subsets as a "watchdog" of the predominant major subset $CD11b^+CD64^-CD32^+CD16^+$NG and a minor subset $CD11b^+CD64^+CD32^+CD16^+$NG.

In SG1 a transformation of the phenotypic profile in the subsets $CD11b^+CD64^-CD32^+CD16^+$NG and $CD11b^+CD64^+CD32^+CD16^+$NG was revealed due to a decrease in the density of CD16 expression and an increase in the density of CD32 expression. However, the level of CD64 expression density in the minor subset increased statistically significantly, which may indirectly indicate the stimulation of its expression by the cytokine environment associated with the presence of recurrent or persistent viral infection.

In SG2, in the subset $CD11b^+CD64^-CD32^+CD16^+$NG, the phenotypic profile is characterized by a quantitative decrease in CD16 expression relative to the Comparison Group. An increase in the number of the $CD11b^+CD64^+CD32^+CD16^+$NG subset, which is diagnostically significant in the presence of a bacterial infection was revealed. We have previously shown that the content of the $CD11b^+CD64^+CD32^+CD16^+$NG subset increases many times with the progression of

the severity of the inflammatory process [4, 6]. Also in the SG2 there was a decrease in the expression density of CD16 in the NG subsets and CD64 in the minor NG subset.

It is shown lack of receptor expression CD11b in subsets of NG women in both SG during an exacerbation of chronic PID. It is known that the CD11b receptor is a signaling partner for other receptors, in particular Fcγ receptors, which regulate chemotaxis of NG to the inflammation, adhesion, phagocytosis, respiratory burst, and degranulation [5]. A defect in the activation of the CD11b receptor and Fcγ receptors indirectly indicates a violation of the effector functions of NG.

Changes in the subset composition of NG and their phenotype do not contribute to the full implementation of the effector functions of NG in immunocompromised women with chronic PID and may be the reason for the maintenance of a chronic inflammatory process and the absence of a stable positive effect from etiopathogenetic therapy.

Conclusion

As a result of this study, it was found that in immunocompromised women suffering from chronic PID for more than 5 years, diagnostically significant differences in the subset composition of NG were revealed during the exacerbation period. There is a decrease in the $CD11b^+CD64^-CD32^+CD16^+$NG subset and in 7,6 times increase in the $CD11b^+CD64^+CD32^+CD16^+$NG subset in chronic PID of bacterial etiology (SG2), in contrast to chronic PID occurring in combination with recurrent or persistent viral infection (SG1). Negative transformation of NG subsets is associated with a predominant decrease in the level of expression of the activation molecule CD16. The absence of an adequate response to the infectious and inflammatory process was revealed: the absence of an increase in the expression of the activation molecule CD11b in the major subset in SG1, as well as in the minor subset in groups SG1 and SG2. At the same time, in the major subset of SG2, a significant impairment: a defect characterized by a decrease in the expression of the activation marker CD11b in the major subset during the exacerbation of chronic PID. In SG1 there is a negative change in the minor subset of $CD11b^+CD64^+CD32^+CD16^+$NG, a decrease in CD16 expression, an increase in the expression level of CD64 and CD32.

Taking into account the data obtained it can be assumed that the determination of the subset composition of $CD11b^+CD64^-CD32^+CD16^+$ and $CD11b^+CD64^+CD32^+CD16^+$NG and the clarification of their phenotypic characteristics can be used as diagnostic markers for the differential diagnosis of chronic PID of viral and bacterial etiology, however this issue requires further research.

The obtained data on the negative quantitative and phenotypic transformation of NG subsets – major $CD11b^+CD64^-CD32^+CD16^+$ and minor $CD11b^+CD64^+CD32^+CD16^+$ in women suffering from chronic PID of various etiologies, can serve as the basis for creating new integrated approaches to the immunodiagnosis of multivariate changes in major and minor subsets of NG. In addition, prospects are opening up for the development of new methods of targeted immunomodulatory therapy aimed at reprogramming negatively transformed subsets of NG in chronic PID, which should help to restore the full effector functions of NG, improve the implementation of both antiviral and antibacterial protection, and, as a result, achieve positive results, including clinical and immunological effects.

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