ВЗАИМОСВЯЗЬ СИСТЕМНОЙ ВОСПАЛИТЕЛЬНОЙ РЕАКЦИИ И ГИПЕРКОАГУЛЯЦИИ У ПАЦИЕНТОВ С ИММУНОВОСПАЛИТЕЛЬНЫМИ РЕВМАТИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ

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Резюме. Взаимосвязь процессов коагуляции и воспаления обеспечивает защиту организма от потенциально опасных биологических агентов. Однако гипервоспаление влечет за собой повышение прокоагуляционного потенциала, а активация факторов гемостаза поддерживает воспалительный процесс. Этот процесс получил название «иммунотромбоз» или «тромбовоспаление». Гиперцитокинемию можно трактовать как проявление системной воспалительной реакции (СВР), которая является атрибутным феноменом типового патологического процесса – системного воспаления. Иммуновоспалительные ревматические заболевания (ИВРЗ) являются идеальной моделью для изучения взаимосвязи процессов коагуляции и воспаления на системном уровне. Изучение тромбовоспалительных механизмов является актуальной проблемой современной медицины, поскольку в перспективе поможет улучшить терапию заболеваний, в патогенезе которых тромбовоспаление играет существенную роль.

Цель работы – провести сравнительный анализ выраженности системной воспалительной реакции у пациентов с иммуновоспалительными ревматическими заболеваниями (ИВРЗ) с наличием и отсутствием проявлений гиперкоагуляции.

Для достижения поставленной цели был проведен сравнительный анализ провоспалительных маркеров (IL-6, IL-8, IL-10, TNFα, sIL-2R, CRP, ECP, β2-микроглобулин) в крови пациентов с ИВРЗ (системной красной волчанкой, ревматоидным артритом, реактивным артритом, анкилозирующим спондилитом, псориатическим артритом, ревматической болезнью сердца). На основании определяемых биомаркеров воспаления по оригинальной авторской методике оценивали также интегральный показатель выраженности СВР – уровень реактивности (RL). По наличию повышенного уровня D-димера (> 500 нг/мл) выборка была разделена на 2 группы: с наличием признаков гиперкоагуляции (n = 56) и без признаков гиперкоагуляции (n = 119). Группу контроля составили доноры крови (n = 50).

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Результаты исследования показали, что у пациентов с ИВРЗ, независимо от гемостатического потенциала крови, развивается выраженная СВР. Пациенты с признаками гиперкоагуляции характеризовались более высокими значениями большинства провоспалительных молекулярных маркеров (наибольшие отклонения выявлены в отношении уровня IL-6), а также повышенным интегральным уровнем СВР, что свидетельствует о тесной взаимосвязи процессов коагуляции и воспаления на системном уровне. И, напротив, с возрастанием выраженности СВР (оцененной с помощью интегрального показателя – УР) увеличивается вероятность развития гиперкоагуляции. Таким образом, наблюдается переход количественно более выраженных факторов на иной качественный уровень развития патологического процесса.

Патогенез иммуновоспалительных ревматических заболеваний характеризуется развитием системной воспалительной реакции (гиперцитокинемией, острофазным ответом, внутрисосудистой активацией лейкоцитов), выраженность которой тесно связана с внутрисосудистым микротромбообразованием.

Ключевые слова: системная воспалительная реакция, гиперкоагуляция, тромбовоспаление, иммунотромбоз, ревматические заболевания, цитокины

RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATORY RESPONSE AND HYPERCOAGULATION IN PATIENTS WITH IMMUNO-INFLAMMATORY RHEUMATIC DISEASES

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Abstract. The relationship between the processes of coagulation and inflammation protects the organism from potentially dangerous biological agents. However, hyperinflammation leads to an increase in the procoagulation potential, and activation of hemostasis factors maintains the inflammatory process. This phenomenon is called “immunothrombosis” or “ thromboinflammation”. The study of thromboinflammatory mechanisms is an actual problem of modern medicine, because in the future it will help to improve the therapy of diseases, in the pathogenesis of which thromboinflammation plays a significant role. The aim: to carry out a comparative analysis of the severity of the systemic inflammatory response in patients with immuno-inflammatory rheumatic diseases depending on the manifestations of hypercoagulation.

To achieve the aim, a comparative analysis of proinflammatory markers (IL-6, IL-8, IL-10, TNFα, sIL-2R, CRP, ECP, β2-microglobulin) in the blood of patients with immune-inflammatory rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, rheumatic heart disease) was performed. Based on these inflammatory markers according to the authors’ original methodology, the integral index of systemic inflammatory response (SIR) – Reactivity Level (RL) – was calculated. The cohort was divided into 2 groups: with the presence of signs of hypercoagulation and without signs of hypercoagulation according to the presence of elevated D-dimer level (> 500 ng/mL). Control group – healthy blood donors.

The results of the study showed that SIR develops in patients with immuno-inflammatory rheumatic diseases regardless of the blood hemostatic potential. Patients with signs of hypercoagulation were characterized by higher values of most proinflammatory molecular markers, as well as increased integral level of SIR, which indicates a strong relationship between coagulation processes and inflammation at the systemic level. In addition, the probability of hypercoagulation increases with increasing severity of SIR (assessed by means of the integral index – RL). Thus, there is a transition of quantitatively more pronounced signs to a new qualitative level of pathological process development.

The pathogenesis of immuno-inflammatory rheumatic diseases is characterized by the development of SIR (hypercytokinemia, acute phase response, intravascular leukocyte activation), the severity of which is closely related to intravascular microthrombosis.

Keywords: systemic inflammatory response, hypercoagulation, thromboinflammation, immuno-thrombosis, rheumatic diseases, cytokines

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Introduction

The relationship between the processes of coagulation and inflammation protects the organism from potentially dangerous biological agents. However, uncontrolled mutual activation of the hemostasis and inflammation mechanisms causes the development of pathological process, recently named "immunothrombosis", or "thromboinflammation" [4, 9]. Molecular studies have allowed to explain the complex relationship between certain factors of the platelet-vascular and coagulation hemostasis, inflammation and immunity [3, 5, 11]. Cytokines play an important role in intercellular interactions, including those in thromboinflammation. Hypercytokinemia and especially "cytokine storm" can be interpreted as a manifestation of systemic inflammatory response (SIR), which is an attributive phenomenon of a general pathological process – systemic inflammation [14]. Immuno-inflammatory rheumatic diseases (RD) is an optimal model to study the relationship between coagulation and inflammation processes at the systemic level.

The aim of the present work was to carry out a comparative analysis of the severity of the systemic inflammatory response in patients with immuno-inflammatory rheumatic diseases depending on the manifestations of hypercoagulation.

Materials and methods

A retrospective study included 175 patients with rheumatic diseases, including systemic lupus erythematosus (n = 49), rheumatoid arthritis (n = 42), reactive arthritis (n = 30), ankylosing spondylitis (n = 27), psoriatic arthritis (n = 12), chronic rheumatic valvular heart disease (n = 15). The levels of a key molecular marker of hypercoagulation, D-dimer, as well as levels of inflammatory mediators such as C-reactive protein (CRP) and cytokines (IL-6, IL-8, TNFα, IL-10) were measured in blood plasma in all patients. On the basis of these inflammatory markers according to the authors' original methodology, the integral index of SIR – Reactivity Level – RL (min 0 – max 5) was calculated [14]. Additional markers of SIR, indicating intravascular activation of various leukocyte subpopulations, were also measured in some patients: levels of eosinophilic cationic protein (n = 96), soluble receptor to IL-2 – sIL-2R (n = 91), and β2-microglobulin (n = 108). The study was performed using a closed system for immunochemiluminometric assay, Immulite (Siemens Medical Solutions Diagnostics, USA).

The cohort was divided into 2 groups: with the presence of signs of hypercoagulation (n = 56) and without signs of hypercoagulation (n = 119) according to the presence of elevated D-dimer level (> 500 ng/mL). The control group was healthy blood donors aged 18-55 years (n = 50).

Statistical analyses were performed using Statistica 12.0 program (Stat Soft, Inc., USA). The descriptive statistics are presented by their main characteristics: m (mean value) ± SD (standard deviation). Comparisons between the groups were performed using the Mann–Whitney test. All the results were considered statistically significant if the p-value was < 0.05.

Results and discussion

In both study groups, the levels of all proinflammatory mediators (IL-6, IL-8, TNFα, CRP, ECP, β2-microglobulin, sIL-2R) and RL values were statistically significantly higher than those in the control group, which indicates the development of significant SIR in patients with rheumatic diseases, regardless of the blood hemostatic potential (Table 1). The IL-10 concentration did not exceed the analyzer detection level (5 pg/mL) in 88.6% of the total patient sample and in 100% of the control subjects, so no basic statistical characteristics were calculated for this index. Thus, SIR, manifested as intravascular leukocyte activation, hypercytokinemia and acute phase response, plays a significant role in the pathogenesis of immuno-inflammatory rheumatic diseases.

A comparative analysis demonstrated that patients with elevated D-dimer levels were characterized by significantly higher proinflammatory markers (except for ECP levels) compared to patients without signs of hypercoagulation (Table 1). The greatest differences (more than 6-fold) were found for IL-6. The results obtained are in agreement with the data of some authors indicating a significant correlation of proinflammatory cytokines with hypercoagulability indices in rheumatic diseases [2, 12].

Since SIR is a multi-factorial process, it was important to assess its severity in the studied subgroups not only by individual markers, but also using integral indices. Our suggested integral RL was also significantly ($p < 0.05$) higher in patients with hypercoagulation (Table 1). An analysis of the distribution of patients by RL from 0 (no SIR) to 5 (hyperergic variant of SIR) showed the following. Increased hemostatic potential in rheumatic diseases is most often associated with R = 1-2 (SIR, which is most typical for Low-grade systemic inflammation and classical inflammation); RL = 0, which indicates the absence of significant SIR, was found in this group only in single cases. In contrast, patients without signs of hypercoagulation are most characterized by RL = 0-1. It is noteworthy that unusual for a chronic process RL = 5 (increase of proinflammatory cytokines in the blood by thousands

TABLE 1. VALUES OF PROINFLAMMATORY MARKERS IN THE STUDIED GROUPS

Marker		Patients with hypercoagulation	Patients without hypercoagulation	Control group
CRP, mg/dL		2.32±2.66	0.97±1.25*	0.26±0.24
IL-6, pg/mL		373.50±1762.95	59.75±347.82*	2.02±0.45
IL-8, pg/mL		1326.72±4895.19	266.96±926.30*	5.58±1.56
TNFα, pg/mL		53.12±116.97	53.31±179.69*	4.33±1.03
ECP, ng/mL		11.37±12.74	6.76±10.69	3.87±1.61
sIL-2R, U/mL		1598.5±1900.1	696.0±738.7*	315.6±101.2
β2-microglobulin, ng/mL		2707.7±1319.1	2198.5±835.3*	1508.4±232.1
RL, point		2.07±1.20	1.08±1.27*	0
RL, %	RL = 0	5.4	43.7	100
	RL = 1	32.1	28.6	0
	RL = 2	30.4	12.6	0
	RL = 3	16.1	6.7	0
	RL = 4	14.3	7.6	0
	RL = 5	1.7	0.8	0

Note. The control group was statistically significant different from both studied groups for all indicators ($p < 0.05$); *, $p < 0.05$ between the groups of patients with and without signs of hypercoagulation.

and tens of thousands of times) were observed in two patients with systemic lupus erythematosus.

The ranking of the total sample by RL showed that, in general, the increase in the severity of SIR was associated with an increase in the rate of D-dimer detection (Figure 1).

Also of interest was a comparative assessment of commonly used clinical criteria of diseases activity depending on the manifestation of signs of hypercoagulation. This analysis was performed in the groups of patients with rheumatoid arthritis (DAS28 scale) and systemic lupus erythematosus (SLEDAI scale). In this case, statistically relevant differences were found only in the rheumatoid arthritis group (DAS28: 5.92±1.11 points in the group with D-dimer and 4.65±1.45 points in patients without D-dimer). In patients with SLE with and without signs of hypercoagulation, the SLEDAI index did not differ significantly and was 23.2±12.1 and 19.8±10.5, respectively. This phenomenon can be explained by the fact that the clinical scales mainly focus on

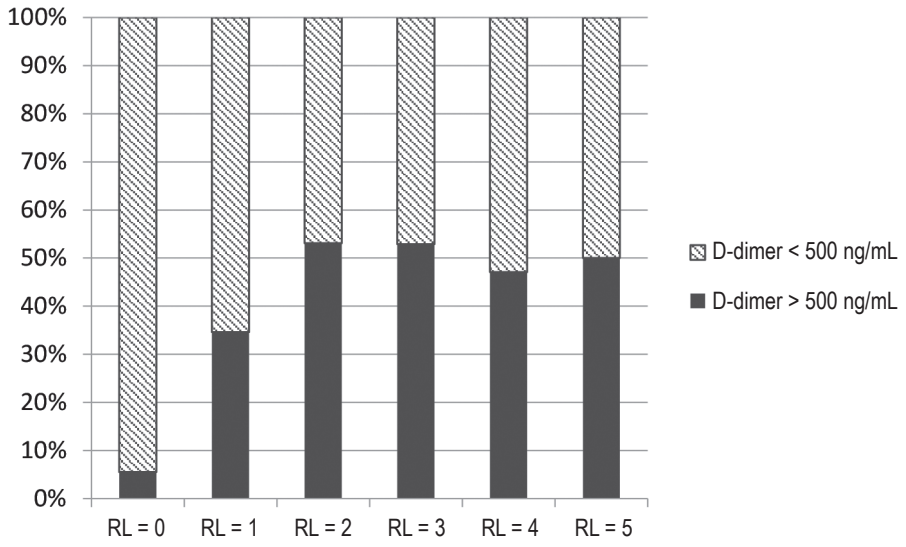

Figure 1. Rates of D-dimer detection at different severities of SIR

specific clinical manifestations of diseases, but not on the systemic pathogenetic pattern of these disorders.

Thus, the detected increase in separate molecular and integral markers of SIR in patients with increased procoagulation potential indicates a strong relationship between these processes in patients with rheumatic diseases. The impact of damage factors (in particular, immune complexes, cytotoxic antibodies, molecules from own damaged cells, etc.) as well as proinflammatory triggers (primarily cytokines) leads to microcirculatory disorders. These are based on such processes as endothelial glycocalyx degradation and endothelium activation with increased vascular permeability, interstitial edema, exposure of endotheliocyte cell membranes expressing receptors to proinflammatory and platelet-derived factors, and increased procoagulant potential. Increased hemostatic potential is associated with the production of tissue factor, as well as with the inhibition of anticoagulant pathway and suppression of fibrinolysis (in particular, by increasing the production of Plasminogen activator inhibitor-1 – PAI-1).

It is known that some proinflammatory cytokines (IL-6, TNFα, TGF-β) significantly increase PAI-1 synthesis [7]. Thus, hyperinflammation leads to a shift of hemostatic balance towards its increase, and activation of vascular and platelet hemostasis, production of soluble coagulation factors promote maintenance of the inflammatory process. Thus, there is formed a self-sustaining vicious pathogenetic circle of pathological process, which becomes independent of the damage factors at a certain stage of development. This process, called "thromboinflammation" or "immunothrombosis" is considered today as a universal pathogenetic mechanism of many acute and chronic diseases [1, 5, 8, 10, 11]. The results of the present study showed that the risk of hypercoagulation increases with increasing severity of SIR. Thus, there is a transition of quantitatively more pronounced signs to a new qualitative level of pathological process development.

It is also noteworthy that unlike acute conditions in which pro-inflammatory remodeling of the microcirculation leads to the development of critical complications, including acute disseminated intravascular coagulation and multiple organ dysfunction, microcirculatory changes in chronic diseases are latent. Probably, in the latter case an adequate long-term anti-inflammatory therapy plays a role, as well as "inclusion" of the feedback mechanisms, including inhibition of the system of transcription factors (for example, increase in the expression of mRNA of suppressor of cytokine signaling 1 (SOCS1), suppressing the activity of JAK) [6], negative control of the expression of receptors to proinflammatory mediators on the target cells, and increased levels of soluble forms of receptors in the blood circulation [13].

Conclusion

The pathogenesis of immuno-inflammatory rheumatic diseases is characterized by the development of SIR (hypercytokinemia, acute phase response, intravascular leukocyte activation), the severity of which is closely related to intravascular microthrombosis. At the same time, the levels of individual proinflammatory mediators and the severity of systemic inflammatory response in general are higher in patients with hypercytokinemia, and, on the other hand, the more intensive the impact of proinflammatory mediators, the higher the procoagulation potential of blood.

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