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ASPECTS OF IMPAIRMENT OF SOME HEMOSTASIS COMPONENTS IN RHEUMATOID ARTHRITIS

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Abstract. The review contains information about the physiology of the hemostasis system and its components, and discusses the relationship between the hemostasis system and inflammation. The physiology of normal hemostasis, the interaction of platelets with endothelial cells and leukocytes, as well as with von Willebrand factor and the complement system, and their role in rheumatoid arthritis are described. Thus, platelets can be considered not only as hemostatic, but also as inflammatory cells.

Keywords: blood coagulation system, rheumatoid arthritis, inflammation, blood coagulation factors, thrombosis, venous thromboembolism, complement, cytokines.

Interaction of platelets with endothelial cells and leukocytes

Endothelial integrity and selective permeability of the vascular wall are maintained by platelets. They are able to "block gaps" in the vascular wall, also contributing to the growth of the endothelium. In the absence of endothelial injury, various molecules, including nitric oxide and prostacyclin, maintain the antiadhesive nature of the endothelium. Damage to the endothelium (as part of inflammation) leads to the activation of endothelial cells, platelets and leukocytes with the formation of microparticles that trigger the blood coagulation system by activating TF. Microparticles are small (0.1–1.0 μm) membrane vesicles, the release of which is associated with important physiological effects [1]. In the blood there are microparticles of different types of cells: mainly platelets, erythrocytes, granulocytes, monocytes, lymphocytes. Platelet-derived microparticles are the most abundant in the blood stream. They constitute from 70 to 90% of circulating microparticles [1].

E.A. Knijff-Dutmer et al. [3] studied platelet microparticles in autoimmune diseases and demonstrated their increased level in elderly patients with RA. According to I.C. van Eijk et al. [4], patients with RA, even in the early stages, have elevated levels of microparticles compared with the control group. In patients with high RA activity, there was a tendency to a higher content of platelet microparticles compared to patients with remission. Thus, high levels of microparticles in patients with RA indicate an increased risk of thrombosis compared with that in healthy controls (control groups).

Moreover, the interaction of platelets with the endothelium promotes the release of inflammatory mediators, in particular IL1, a powerful pro-inflammatory mediator that increases the activity of other cytokines and cells in the focus of inflammation, as well as the surface expression of adhesion molecules. In addition, platelet CD40 ligand is a powerful endothelial stimulator and increases its adhesive properties for leukocytes. Soluble CD40 ligand can be used as an inflammatory

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marker. Finally, primary platelet adhesion receptors such as GPIb-IX-V or GPVI also regulate platelet and leukocyte adhesion: platelet GPIba receptors bind to leukocyte aMh2 receptors, and leukocyte PSGL-1 receptors bind to P-selectin on adherent activated platelets.

As you know, leukocytes are the main participants in the inflammatory process. Platelets, in addition to producing chemokines that promote the migration of neutrophils and monocytes to the area of injury, can cause the formation of platelet-neutrophil complexes and platelet monocyte aggregates (lamellar monocyte aggregates are considered useful markers of platelet activation). Violation of the interaction between platelets and monocytes/neutrophils led to a decrease in the severity of the inflammatory response [5]. The use of certain antiplatelet agents reduces the activation of platelets, which reduces their binding to leukocytes.

Interaction of platelets with von Willebrand factor and the complement system

The interaction of von Willebrand factor and platelets can lead to thrombocytopenia and microvascular thrombosis, which is often observed in inflammatory diseases. In acute and chronic inflammation, the level of the enzyme ADAMTS-13 (a metalloproteinase that breaks down the von Willebrand factor molecule) decreases. A.K. Chauhan et al. [6] demonstrated a deficiency of ADAMTS-13 in the presence of an excess of von Willebrand factor, which increased leukocyte adhesion in inflamed veins. Thus, von Willebrand factor and ADAMTS-13 can be used as inflammatory markers. Interrupting the interaction of von Willebrand factor with platelets and leukocytes through the ADAMTS-13 enzyme can suppress inflammation. The complement system is a major component of the immune system and plays a central role in many protective immune processes, including immune complex circulation, clearance, recognition of foreign antigens, modulation of humoral and cellular immunity, removal of apoptotic and dead cells, and involvement of injury resolution and tissue regeneration processes. However, inadequately controlled complement activation underlies the pathogenesis of human inflammatory and autoimmune diseases, including RA, in which cartilage, bone, and synovium are targeted. Autoimmune reactions in this disease develop in the preclinical stage, are asymptomatic, and cause synovial involvement in the inflammatory process [7]. The results of clinical and experimental studies suggest the involvement of the complement system in the development and progression of RA. In the blood of RA patients, levels of complement activation fragments increase and levels of circulating complement proteins decrease due to consumption. The content of complement activation fragments also increases in the synovial fluid and synovial tissue of patients with RA. One of the complement activation triggers can be immune complexes containing RA-associated antibodies [8]. In addition, some studies have shown that the active components of the coagulation cascade can cleave and/or activate proteins of the complement system and vice versa [9]. The number of potential complement activators at sites of thrombosis is enormous, with thrombin, plasmin, damaged endothelium, DNA, and elastase among the leading candidates

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[10]. It is known that cleavage of the C5 component of complement releases cleavage products C5a and C5b, which jointly activate platelets [9], induce TF expression [11], and activate endothelial cells, thereby causing the secretion of von Willebrand factor [10].

Interaction of platelets with inflammatory mediators

Chronic inflammation mediated by numerous cytokines (IL1, TNFα, IL6, IL8), growth factors and autoantibodies stimulate platelet turnover in the bone marrow. Stimulation of the bone marrow and an increase in platelet turnover contribute to an increase in the number of reticulated platelets (stress platelets, or activated platelets). These platelets are spherical, enlarged, and have pseudopodia [12]. They produce proteins that cause blood clots [13]. During a relatively short period of life (8–10 days), along with thrombus-promoting proteins, platelets produce P-selectin, CD40L (ligands), and platelet growth factor [13]. The level of reticulated platelets can be judged by the average volume of platelets (mean platelet volume, MPV). The association between inflammation, platelet activation, and prothrombotic state is also indicated by the revealed high MPV value in familial Mediterranean fever [12].

In addition, it is worth noting that platelet granules store various substances, including growth factors, cytokines, chemokines, biogenic amines, and adhesion molecules. In a review by A. Saghazadeh et al. [14] described the interaction of the components of the immune system, in particular, cytokines, chemokines, leukocytes, with the formation of venous thromboembolism. In addition, the direct effect of inflammatory mediators on some coagulation factors and thus the activation of the external pathway of blood coagulation has been proven [15]. So, when platelets are activated, polyphosphate, which is in dense granules, is released and enhances the activation of V and XII coagulation factors. It is also known that histones and nucleosomes have a direct damaging effect on the endothelium, triggering the external pathway of activation of the blood coagulation system [16]. In addition, they are responsible for the five signs of inflammation described by the famous Greek physician and philosopher Galen. Histamine causes redness, histamine and serotonin cause local fever, histamine and growth factor cause swelling/swelling, and together they contribute to loss of function and pain.

The role of platelets in some inflammatory diseases

RA, SLE, and systemic scleroderma are classic autoimmune diseases associated with chronic inflammation. In these nosological forms, the level of platelets correlates with the activity of the disease. Thrombocytosis in RA is considered as a manifestation of high activity, thrombocytopenia in SLE - as a marker of poor prognosis and the formation of microvascular thrombi, kidney damage. In all nosological forms, platelet hyperreactivity is noted with stimulation of platelet turnover in the bone marrow, which contributes to an increase in the number of reticulated platelets. An association between platelet activation and inflammation has been demonstrated in RA. Joint damage was associated with the presence of platelet and leukocyte microparticles. Similar changes were also detected in the systemic

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circulation [14]. The interaction of platelets and leukocytes in the joints can contribute to the destruction of cartilage, and platelet chemokines - angiogenesis and synovial hypertrophy. Treatment aimed at suppressing inflammation can reduce the number of activated platelets. However, it is not always clear what comes first - platelet activation or inflammation?

A series of studies reviewed in R.J. Bisoendial et al. [16], demonstrates increased activation of the coagulation/fibrinolysis cascade in RA patients and an inflammation-induced hypercoagulable state. Compared with the control group, patients with RA showed an increase in the levels of fibrinogen, von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator, D-dimer, and prothrombin fragment F1 + 2 (a marker of thrombin). Autoimmune diseases, including RA, are a risk factor for the development of venous thromboembolic complications (VTEC). The inflammatory process can be both a consequence of venous thromboembolism and its cause. However, modern anticoagulants are not designed to stop inflammation. Many risk factors for VTEC, such as obesity, surgery, sepsis, cancer, inflammatory bowel disease, and SLE, trigger thrombus formation by releasing inflammatory mediators. Subsequent activation of platelets by these compounds enhances the prothrombotic state. According to A.K. Bakani et al. [17], in 813 patients with RA, the risk of VTEC was more than twice as high as in the control group of the corresponding age and gender. In studies conducted in hospitals in England and the USA, an increased risk of VTEC was noted in patients with RA [17]. J.H. Kang et al. [18] found a significant relationship between RA and VTEC. The results of this work are consistent with the findings of a study conducted at Oxford University by S.V. Ramagopalan et al. [12], who showed that the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) was significantly higher in patients with immune disorders. They also found that the relative risk of DVT and PE was 1.75 times higher in patients with RA than in controls.

Acute lung injury can occur in various pathological conditions, including RA. High activity of SLE is accompanied by thrombocytopenia, high activity of RA - thrombocytosis. The activation of platelets, their interaction with leukocytes with the sequestration of these blood cells in the pulmonary vessels can be the cause of a decrease in the number of platelets. Violation of endothelial integrity in acute lung injury, as well as platelet function (support of endothelial integrity) can lead to an increase in endothelial permeability and the formation of edema.

When studying the role of platelets in bronchial asthma and allergic inflammatory diseases of the respiratory tract, it turned out that in lung tissue samples obtained during autopsy of patients who died from status asthmaticus, high levels of platelets were determined as a marker of activation, as well as platelet factor 4 in peripheral blood, which indicates on the participation of platelets in eosinophilic inflammation [55]. Another newer concept is that platelets, migrating into the lung tissue of patients with bronchial asthma, have a direct damaging effect on it.

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Inflammatory bowel disease. Thrombocytosis in IBD patients was noted as early as the 1960s. This phenomenon is associated with an increase in the level of IL6, which stimulates the production of thrombopoietin (platelet hormone) in the liver - as part of the acute phase response to iron deficiency anemia. The increase in platelet formation is due to the need for primary hemostasis, and is also a consequence of iron deficiency anemia. Treatment with iron preparations helps to normalize the number of platelets.

Alzheimer's disease - persistent platelet activation in this disease may be associated with increased lipid peroxidation due to inadequate levels of vitamin E.

The effect of certain drugs on the inflammatory process and hemostasis

According to a number of authors [19], methotrexate, the most commonly used in the treatment of RA, leads to a marked decrease in the number of cases of myocardial infarction (MI) and the total number of cardiovascular diseases. Treatment with TNFα inhibitors reduces CRP levels, as well as two recognized predictors of cardiovascular risk, PAI-1 and PAI-1/t-PA [20]. It also allows for a significant improvement in endothelial function. According to V. Zoller et al. [21], the risk of PE and DVT may be higher at an early stage of RA, for example, in the first year after the start of treatment with disease-modifying anti-inflammatory drugs (DMARDs) or the diagnosis of RA, which may be associated with uncontrolled inflammatory activity before a positive effect of antirheumatic therapy is achieved. However, the use of non-steroidal anti-inflammatory drugs and glucocorticoids (GCs) to control the inflammatory process is known to increase the risk of VTEC. It is also known that GCs increase the levels of blood clotting factors, which increases the risk of VTEC. S.C. Kim et al. [22] found that patients receiving TNFα inhibitors have a higher risk of VTEC compared with patients treated with DMARDs, in particular methotrexate.

Conclusion. Thus, platelets can be considered not only as hemostatic, but also as inflammatory cells. By modulating platelet function, the inflammatory process can be limited. These data indicate a close relationship between the inflammatory process in RA and disorders in the hemostasis system. In our recent study, the relationship between the development of VTEC in RA and disease activity was shown [22].

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