Rheumatoid Arthritis: Disorders Of Hemostasis Components

Musaeva N. B Tashkent Medical Academy

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

The Interaction Of Plates With Endothelial Cells And Leucocytes

Endothelial integrity and selective permeability of the vascular wall are maintained by platelets. They are able to "block the gaps" in the vascular wall, and also contribute to the growth of the endothelium. In the absence of endothelial damage, various molecules, including nitric oxide and prostacyclin, maintain the antiadhesive properties 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 stimulate the blood coagulation system. Microparticles are small (0.1-1.0 μm) membrane vesicles, the release of which is associated with important physiological effects [1]. Blood contains microparticles of various types of cells: mainly platelets, erythrocytes, granulocytes, monocytes, lymphocytes. Microparticles derived from platelets are the most abundant in the bloodstream. They make up 70 to 90% of circulating microparticles [2].

E.A. Knijff-Dutmer et al [3] studied platelet subsets in autoimmune diseases and showed their levels in elderly patients with rheumatoid arthritis (RA). I.C. According to van Eijk et al. [4], patients with RA, even in the early stages, have higher levels of small parts compared to the control group. Patients with high RA activity tended to have higher amounts of platelet subsets than patients in remission. Thus, a higher level of small fractions in patients with RA indicates an increased risk of thrombosis compared to healthy (control groups).

In addition, the interaction of platelets with the endothelium promotes the release of inflammatory mediators, in particular, IL1, a powerful anti-inflammatory mediator that increases the activity of other cytokines and cells in the inflammatory site, and also increases the surface expression of adhesion molecules. In addition, platelet CD40 ligand is a potent endothelial stimulator, increasing its adhesive properties for leukocytes. Soluble CD40 ligand can be used as an inflammatory marker. Finally, primary platelet adhesion receptors such as GPIb-IX-V or GPVI also regulate platelet and leukocyte adhesion: platelet GPIbα receptors bind to leukocyte αMh2 receptors, and leukocyte PSGL-1 receptors bind to R-selectin, which is activated on adherent plaques.

It is known that leukocytes are the main participants in the inflammatory process. In addition to the production of chemokines that stimulate the migration of platelets, neutrophils, and monocytes to the injured area, platelet-

neutrophil complexes and platelets can lead to the formation of monocyte aggregates (platelet monocyte aggregates are useful markers of platelet activation). Disruption of the interaction between platelets and monocytes/neutrophils led to a decrease in the severity of the inflammatory response [5]. The use of some antiaggregant agents reduces the activation of platelets, which reduces their binding to leukocytes.

The 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 ADAMTS-13 enzyme (a metalloproteinase that breaks down the von Willebrand factor molecule) decreases. A.K. Chauhan et al. [6] demonstrated ADAMTS-13 deficiency in the presence of von Willebrand factor, which enhances leukocyte adhesion in inflamed vessels. Thus, von Willebrand factor and ADAMTS-13 can be used as markers of inflammation. Blocking the interaction of von Willebrand factor with platelets and leukocytes through the ADAMTS-13 enzyme can suppress inflammation. The complement system is a key 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 wound healing and tissue repair. participation in processes. However, inadequately controlled complement activation underlies the pathogenesis of human inflammatory and autoimmune diseases, including RA, which target cartilage, bone, and synovium. 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 indicate the involvement of the complement system in the development and exacerbation of RA. In patients with RA, levels of complement-activating fragments increase and circulating complement proteins decrease due to consumption. The content of complement-activating fragments is also increased in the synovial fluid and synovial tissue of patients with RA. One of the triggers of complement activation may be immune complexes containing antibodies associated with RA [8]. In addition, some studies have shown that active components of the coagulation cascade degrade and/or activate proteins of the complement system and vice versa [9]. Thrombin, plasmin, damaged endothelium, DNA, and elastase are the number of potential complement activators at sites of thrombosis [10]. Cleavage of the C5 component of complement is known to release cleavage products C5a and C5b that co-activate platelets [11], induce TF expression [12], and activate endothelial cells, thereby inducing the secretion of von Willebrand factor [13].

Platelet Interactions 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 increased platelet turnover contribute to an increase in the number of reticular platelets (stress platelets or activated platelets). These platelets are spherical, enlarged and have pseudopodia [14]. They produce proteins that cause blood clots [15]. In a relatively short period of life (8-10 days), platelets produce P-selectin, CD40L (ligands) and platelet-derived growth factor in addition to thrombus-promoting proteins [16]. The level of reticular platelets can be estimated by mean platelet volume (MPV). The relationship between inflammation, platelet activation and a prothrombotic state is also indicated by the high MPV value found in familial Mediterranean fever [17].

In addition, it should be noted that platelet granules contain various substances, including growth factors, cytokines, chemokines, biogenic amines and adhesion molecules. A. In a review by Saghazadeh et al. [18] 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 extrinsic pathway of blood coagulation has been proven [19]. Thus, when platelets are activated, polyphosphate contained in dense granules is released and enhances the activation of coagulation factors V and XII. In addition, it is known that histones and nucleosomes have a direct damaging effect on the endothelium, triggering the extrinsic pathway to activate the coagulation system [20]. In addition, they are responsible for the five signs of inflammation described by the famous Greek physician and philosopher Galen. Histamine causes flushing, histamine and serotonin cause localized fever, histamine and growth factor cause edema/swelling, and together they cause loss of function and pain.

The Role Of Platelets In Certain Inflammatory Diseases

RA, systemic lupus erythematosus (SLE), and systemic scleroderma are classic autoimmune diseases associated with chronic inflammation. In these nosological forms, the level of platelets is related to the activity of the disease. Thrombocytosis in RA is a manifestation of high activity, thrombocytopenia in SQ is a bad prognosis and formation of microvascular thrombi, as a sign of kidney damage. Hyperreactivity of platelets in all nosological forms is noted with the stimulation of platelet exchange in the bone marrow, which contributes to an increase in the number of reticular platelets. A correlation between platelet activation and inflammation has been shown in RA. Adnexal damage was associated with the presence of small fractions of platelets and leukocytes. Similar changes were also detected in the systemic circulation [21]. The interaction of platelets and leukocytes in the joints contributes to the destruction of the uncle 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?

R.J. A number of studies reviewed in Bisoendial et al [22] show increased activation of the coagulation/fibrinolysis cascade in patients with RA and a hypercoagulable state associated with inflammation. Compared to the control group, RA patients had increased levels of fibrinogen, von Willebrand factor, plasminogen activator inhibitor-1 (PAI1), tissue plasminogen activator, D-dimer, and prothrombin fragment F1+2 (marker). thrombin). Autoimmune diseases, including RA, are risk factors for the development of venous thromboembolic complications (VTEA). The inflammatory process can be a consequence of venous thromboembolism and its cause. However, modern anticoagulants are not designed to stop inflammation. Many risk factors for VTEA, such as obesity, surgery, sepsis, cancer, inflammatory bowel disease, and SQYu, induce thrombus formation by releasing inflammatory mediators. Subsequent activation of platelets by these compounds enhances the prothrombotic state. A.K. According to Bacani et al [12], 813 patients with RA had twice the risk of VTEA compared to age- and sex-matched controls. Studies in UK and US hospitals have reported an increased risk of VTEK in patients with RA [22]. J.H. Kang et al [14] found a significant association between RA and VTEA. The results of this work were presented at Oxford University by S.V. Ramagopalan et al. [12], which showed a significantly higher risk of deep vein thrombosis (DVT) and pulmonary artery thromboembolism (PATE) in immunocompromised patients. They also found that the relative risk of ChTT and OATE was 1.75 times higher in patients with RA than in controls.

Acute lung injury can occur in a variety of pathological conditions, including RA. High activity of SQYu leads to thrombocytopenia, high activity of RA leads to thrombocytosis. The activation of platelets, their interaction with leukocytes and the sequestration of these blood cells in the pulmonary vessels can cause a decrease in the number of platelets. In acute lung injury, disruption of endothelial integrity as well as platelet function (supporting endothelial integrity) can lead to increased endothelial permeability and edema.

In the study of the role of platelets in bronchial asthma and allergic inflammatory diseases of the airways, it was found that high levels of platelets were detected as a marker of activation in lung tissue samples taken during autopsy of patients who died of asthma, as well as platelet factor 4 in peripheral blood, which indicates the participation of platelets in eosinophilic inflammation [15] . Another new concept is that platelets that enter the lung tissue of patients with bronchial asthma have a direct damaging effect on it.

Inflammatory bowel disease (IBD). Thrombocytosis in CKD 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. Increased platelet production is associated with the need for primary hemostasis and is a consequence of iron deficiency anemia. Treatment with iron preparations helps to normalize the number of platelets.

In Alzheimer's disease, persistent activation of platelets in this disease may be associated with increased lipid peroxidation due to insufficient vitamin E deficiency.

Effect Of Some Drugs On Inflammatory Processes And Hemostasis

According to a number of authors [16-18], methotrexate, the most widely used in the treatment of RA, leads to a significant reduction in the total number of myocardial infarction (MI) and cardiovascular diseases. Treatment with TNFα inhibitors reduces CRO levels, as well as PAI-1 and PAI-1/t-PA, two recognized predictors of cardiovascular risk [19 , 20]. In addition, it allows to significantly improve the endothelial function. V. According to Zoller et al. [21], the risk of OATE and CTT may be higher in the early stage of RA, for example, in the first year after starting treatment with disease-modifying anti-inflammatory drugs (DMARDs) or when RA is diagnosed. may be associated with uncontrolled inflammatory activity until the positive effect of antirheumatic therapy is achieved. However, the use of nonsteroidal anti-inflammatory drugs and glucocorticoids (GCs) to control the inflammatory process is known to increase the risk of VTEA. In addition, GCs are known to increase levels of clotting factors, which increases the risk of VTEA. S.C. Kim et al [22] found that patients receiving TNFα inhibitors had a higher risk of VTEA than patients treated with BYaQDV, particularly methotrexate.

Conclusion

Thus, platelets can be considered not only hemostatic, but also inflammatory cells. It is possible to limit the inflammatory process by modulating the function of platelets. These data show 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 VTEA and disease activity in RA was shown [22].

References

1. Cunningham M, Marks N, Barnado A, et al. Are Microparticles the Missing Link between Thrombosis and Autoimmune Diseases? Involvement in Selected Rheumatologic Diseases. Semin Thromb Hemost 2014 Sep;40(6):675-681. doi: 10.1055/s-00341387924. Epub 2014 Aug 31.
2. Holers VM, Banda NK. Complement in the Initiation and Evolution of Rheumatoid Arthritis. Front Immunol. 2018 May 28. 9. P.1057. doi: 10.3389/ fimmu.2018.01057.eCollection 2018.
3. Trouw LA, Pickering MC. Blom AM. The complement system as a potential therapeutic target in rheumatic disease. Nat Rev Rheumatol. 2017 Sep;13(9). P. 538-547. doi:10.1038/nrrheum.2017.125. Epub 2017 Aug 10.
4. Wiegner R, Chakraborty S, Huber-Lang M. Complement-coagulation crosstalk on cellular and artificial surfaces. Immunobiology. 2016 Oct;221;(10). P.1073-1079. doi: 10.1016/j.imbio.2016.06.005. Epub 2016 Jun 19.

5. Foley JH. Examining coagulation-complement crosstalk: complement activation and thrombosis. Thromb Res. 2016 May;141 Suppl 2. P. 50-54. doi: 10.1016/S0049-3848 (16)30365-6.
6. Langer F, Spath B, Fischer C, et al. Rapid activation of monocyte tissue factor by antithymocyte globulin is dependent on complement and protein disulfide isomerase. Blood. 2013 Mar 21;121(12). P. 23242335. doi: 10.1182/blood-2012-10-460493. Epub 2013 Jan 11.
7. Egge KH, Thorgersen EB, Pischke SE, et al. Organ inflammation in porcine Escherichia coli sepsis is markedly attenuated by combined inhibition of C5 and CD14. Immunobiology. 2015 August;220(8). P. 999-1005. doi: 10.1016/j.imbio.2015.04.002. Epub 2015 Apr 27.
8. Landsem A, Fure H, Christiansen D, et al. The key roles of complement and tissue factor in Escherichia coli-induced coagulation in human whole blood. Clin Exp Immunol. 2015 Oct;182(1). P. 81-89. doi: 10.1111/cei.12663. Epub 2015 Aug 2.
9. Ovstebo R, Hellum M, Aass HC, et al.
10. Microparticle-associated tissue factor activity is reduced by inhibition of the complement protein 5 in Neisseria meningitidis-exposed whole blood. Innate Immun. 2014 Jul;20(5). P. 552-560. doi: 10.1177/1753425913502099. Epub 2013 Sep 19.
11. Gasparyan AY, Stavropoulos-Kalinoglou A,
12. Mikhailidis DP, et al. Platelet function in rheumatoid arthritis: arthritic and cardiovascular implications. Rheumatology International. 2011 Feb;31(2). P. 153-164. doi: 10.1007/s00296-010-1446-x.