FEATURES OF PATHOGENETIC MECHANISMS OF THE INTERACTION OF VIRUSES AND PLATELETS IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA (REVIEW OF LITERATURE)

Dudnyk V. M., Furman V. H., Izuymets O. I., Fedchishen A. P., Sinchyck N. I., Kutsak O. V.
National Pirogov Memorial Medical University, Vinnytsya (Pyrogov street 56, Vinnytsya, Ukraine, 21018)

Annotation. One of the urgent interdisciplinary problems of modern medicine is to study the mechanisms of development of virus-induced thrombocytopenia in patients. The aim is to sum up current knowledge of viruses and platelets interaction, how viruses affect platelet and modulate adaptive immune response. A systematic review of the articles in the Pub Med database was conducted between 2007 and 2020, using search terms: platelets, thrombocytopenia, viral infection. Current data on the study of the mechanisms of platelet interaction with different types of viruses in immune thrombocytopenia in children were analyzed. We studied activation of platelets by a viral infection and how the immune response works. We know that the immune response is a cyclic multistage process involving T-lymphocytes, B-lymphocytes, macrophages, cytokines, NK-cells. Antiplatelet antibodies are increase platelet clearance from the blood. The combination of antibodies with platelets leads to phagocytosis. In patients with immune thrombocytopenia IgG antibodies are produced against GP/II b/III or GP/II b/IX glycoproteins located on the platelet surface. In this situation it is possible to produce antibodies of other subclasses of IgG, also a complement of fixing Ig G, rarely Ig A to other glycoprotein, or to other complexes Ib IX, Ia/IIa. Since megakaryocytes express glycoprotein Ib/IIa, le as well as other platelet antigens, they become a target for autoantibodies. Viruses can interact directly with platelets and megakaryocytes. In addition, platelets can be activated by viral antigen-antibody complexes and B-lymphocytes can produce antiplatelet antibodies. All of these processes are activate platelets and lead to increased consumption and remove of platelets, this causes hemorrhagic manifestation in patients.

Keywords: platelets, thrombocytopenia, virus infection, patients.

Introduction

Thrombocytopenia accompanies the course of many diseases that differ in pathogenesis and clinical features. Establishing causal factor is important, as it determines the treatment tactics and the possibility of early prevention of its irreversible consequences [2]. According to an expert group of the American Society of Hematologists (2008), in 95% of cases, thrombocytopenia has no direct explanation or connection with any causes or conditions that can cause them. In such cases, immune thrombocytopenic purpura (ITP) is diagnosed. The acute form of ITP is more common in children and ends in complete recovery in 75% of cases. Among adults, the chronic form of ITP is more common. Unfortunately, statistics show that 5% of adults who develop ITP die from hemorrhage, mainly in the brain. Due to the fact that there are currently no specific criteria for the diagnosis of ITP, the basis for the diagnosis is the exclusion of any cause of secondary thrombocytopenia [1, 2, 17].

It is known, that the incidence of thrombocytopenic purpura (TP) in the world is 1.6-3.9 cases per 100 thousand populations per year, the prevalence ranges from 4.5 to 20 cases per 100 thousand populations. Thrombocytopenia has no geographical features. Men get sick 5-6 times less often than women. TP is more common in people aged 20 to 40 years - 54% of patients, from 40 to 60 years - 30% and very rarely younger than 20 and older than 70 years (5% and 11%, respectively) [18].

The structure of triggers of TP: infectious processes (often viral) - 59%, pregnancy - 19%, stress - 15%, surgical manipulations - in 4%, exercise - in 2%, vaccines - in 1% of patients [13]. The largest proportion in this group are immune thrombocytopenias. Thrombocytopenia in infection occurs by direct suppression of bone marrow function or increased peripheral platelet intake. Approximately 30% of patients with sepsis have thrombocytopenia due to inhibition of megakaryocyte growth in infections caused by gram-positive and gram-negative bacteria or fungi [5, 19].

TP is often found in the presence of hepatitis B and C viruses, chickenpox, rubella, mumps, Epstein-Barr virus, HIV, cytomegalovirus, parovirus B19 [20].

The mechanism of development of TP of immune character includes emergence of antibodies of different direction - autoantibodies to megakaryocytes and thrombocytes; autoantibodies to platelets; antibodies against auto- or xenoantigens that are adsorbed on the surface of platelets; antibodies against immune complexes that bind to platelets.

Autoimmunisation against platelets can occur due to a number of reasons: infection (viral, rarely bacterial), preventive immunization, hypothermia, mental and physical trauma, medication, allergic and shock conditions.

Viruses play a special role in the occurrence of the autoimmune process. It is known that viruses can infect bone marrow cells directly, destroying them. Viruses can...
cause the induction of an autoimmune response due to:
the production of antiidiotypic antibodies to antiviral
antibodies; enhancing the expression of MCH-HLA class I
and II molecules, which are very similar to certain areas
of viral genomes; molecular mimicry between viruses and
platelets; violation of the host's immune response; changes
in endogenous antigens.

In recent years, there has been growing evidence that
platelets can modulate the innate and adaptive immune
response. In addition, platelets can be activated by viral
antigen-antibody complexes, and in response to some
viruses, B-lymphocytes can generate antiplatelet
antibodies. All these processes that promote platelet
activation lead to increased consumption and removal of
platelets.

The aim the analyses the professional literature on the
generalization of current knowledge about the interaction
of platelets with different types of viruses, the viral effect on
platelet activation and platelet-mediated modulation of
adaptive immune responses.

Materials and methods

A systematic review of the articles in the Pub Med
database was conducted between 2007 and 2020, using
the search terms: platelets, thrombocytopenia, and viral
infection.

Results. Discussion

Thrombocytopenia is common after viral infections, and
viruses use different strategies to reduce circulating platelet
counts. Virus-mediated thrombocytopenia is often
multifactorial and has its own mechanisms of occurrence
[5, 6].

The immune response underlying the development
of thrombocytopenia is a cyclic multistage process involving
T-lymphocytes, B-lymphocytes, macrophages, cytokines,
NK cells. Antiplatelet antibodies accelerate the clearance
of platelets from the circulation. Binding of antibodies to
platelets results in Fcy receptor-mediated platelet
destruction by phagocytes. Patients with idiopathic
thrombocytopenic purpura produce mainly Ig G
autoantibodies against glycoproteins GP/II b/IIIa or GP/II b/\nIX platelet surface. In this situation, it is possible to produce
antibodies of other subclasses Ig M, and less often, Ig A to other glycoproteins, or to their
complexes, such as Ib IX, la/IIa. Because megakaryocytes express glycoprotein Iib/IIIa, Ib, and other platelet antigens, they also become a target for autoantibodies [1].

Today, modern methods for detecting antiplatelet
antibodies are: thromboagglutination, complement binding
reaction, direct and indirect antiglobulin consumption tests,
platelet immunofluorescence test (PFIT), enzyme
immunosorbent enzyme (ELISA), antimotrobinial
antimotarization method. Two different methods are usually
used to detect antibodies to platelets. The most accessible
and informative are PFIT in combination with ELISA [1].

It has been shown that reducing the number of platelets
to 85% of all circulating in the blood is sufficient to maintain
vascular integrity [11]. In a lymphocytic choriomeningitis
virus model, mice with severe thrombocytopenia were
shown to develop only local hemorrhage at the site of
inflammation, and that bleeding dependent on lymphocytic
choriomegnitis virus was the result of platelet / IF
dysfunction caused by IF. Mice lacking the functional IFNα/
β receptor have less pronounced anemia and hemorrhage
due to the restored ability of platelet aggregation during
infection with this virus [10]. This indicates that platelet
dysfunction has more stunning consequences than
thrombocytopenia in these pathologies.

Note that many hemorrhagic fever viruses inhibit platelet
function. Juninivirus, the causative agent of Argentine
hemorrhagic fever, induces a decrease in the signaling
dependence of IFNα/β in the production and function of
platelets. Ebola virus also induces an increase in IFNα,
which correlates with increased mortality. The Ebola virus
additionally induces the expression of TF associated with
Ebola hemorrhagic fever. Gantavirus and lasavirus also
cancel the platelet response due to plasma-mediated
inhibition of platelets and / or their direct interaction [8].

The disintegration of the pathological complex of
hypertension occurs by its destruction in the spleen and by
cytostatic and complement-dependent lysis. T-lymphocytes
play a significant role in the formation of the immune
response in thrombocytopenia. There is an increase in the
ratio of subpopulations Th1/Th4 (CD4 + helpers), Ts1/Ts2
(cytotoxic CD8 + cells), decreases the number of regulatory
CD4 +, CD25 + T lymphocytes) [2].

Although thrombocytopenia is common in patients with
Dengue virus, bleeding is rare. However, if bleeding occurs,
they are associated with a high risk of mortality. Note that in
those infected with the Dengue virus, the platelet count
does not predict the risk of bleeding. However, systemic
platelet activation may contribute to the procoagulant status
in these patients, who often develop DIC syndrome [12].
Influenza H1N1 infection enhances the activation of
circulating platelets and leads to increased thrombosis
events [10].

Platelet dysfunction increases the risk of hemorrhage
and, consequently, mortality. Animal experiments have
shown that pharmacological inhibition of either platelets
or the coagulation cascade increases the mortality of H1N1-
injected mice [7]. Aspirin treatment, which inhibits platelet
activation through cyclooxygenase inhibition and
subsequent TxA2 production, hypothesized that aspirin
reduce the incidence and severity of the influenza
pandemic in the 1910s.

The heteroimmune nature of thrombocytopenia is
observed in newborns. Antibodies are produced against
an antigen located on the surface of platelets [6].

Hemorrhagic syndrome caused by thrombocytopenia
is observed in 25% of all newborns. Infectious and
inflammatory diseases (64.8%) are the most common
cause of neonatal thrombocytopenia. Intrauterine, especially viral infections in 7.0% of newborns cause hemorrhagic syndrome. Immune thrombocytopenia in neonates with intrauterine infection occurs due to insufficient production of platelets by the bone marrow. It is proved that at the same time the lacing of platelets from the megakaryocyte sprout by pathogen toxins, the phenomenon of hypersplenism, DIC syndrome is inhibited. Manifestations of hemorrhagic syndrome caused by thrombocytopenia in newborns with intrauterine infection depend on the type of pathogen and the gestational age at which the infectious agent affected the fetus [1,6]. Detection of diagnostically significant increase in antibody titer to any pathogen Barr, rubella virus, herpes simplex, etc.) confirms the secondary nature of thrombocytopenia (heteroimmune forms of the disease) [3, 6].

Viruses can regulate the process of platelet formation. Viruses affect the cytokine profile of the host, which in turn leads to changes in the production of thrombopoietin (TP) in the liver in Simian immuno deficiency virus (SIV), human herpes virus 6, which can interfere with the proliferation of megakaryocytes, human herpes virus 7, which can disrupt the differential megakaryocytes [8, 9].

Hepatitis C virus (HCV) disrupts the production of TP by destroying liver tissue, resulting in reduced TP synthesis, which leads to delayed synthesis of megakaryocytes and platelets. Infection of bone marrow stromal cells and hematopoietic stem cells changes the production of cytokines and reduces the number of progenitor cells, thereby disrupting hematopoiesis. Virus-infected megakaryocytes have been shown to express less surface c-Mpl, which is a receptor for TP [8].

Studies show that seropositivity to CMV or HCV is an independent marker of cardiovascular risk. CMV and HCV are additionally associated with increased graft rejection, restenosis after coronary angioplasty, and vascular sclerosis during transplantation, suggesting that latent virus is reactivated during immunosuppression and contributes to adverse effects [9, 15]. animals CMV in the presence of platelets increased the influx of T-lymphocytes to atherosclerotic plaques and neutrophil extravasation [9].

Infection with the human influenza virus can lead to acute coronary syndrome and myocardial infarction [15]. Animal experiments have shown that influenza causes inflammatory and thrombotic reactions in atherosclerotic plaques and reduces the protective role of high-density lipoproteins [15, 16].

Platelets can bind CMV via TLR2, which triggers platelet activation and degranulation and enhances platelet-to-neutrophil interaction. It has recently been shown that encephalomyocarditis virus interacts with platelet TLR7, which also leads to platelet degranulation and direct interactions of platelets and neutrophils. Platelet fragments are subsequently phagocytosed by neutrophils, and this helps to reduce the number of platelets. Rotavirus uses the GP IIb/IIIa fibrinogen receptor. However, GPIIb/IIIa is not a unique receptor for platelet-to-adenovirus interaction, as inhibition of GPIIb/IIIa does not alter the internalization of platelets and adenoviruses [8, 13].

Epstein-Barr virus (EBV) interacts with platelets through the complement 2 receptor (CR2). HIV and Dengue virus activate platelets by binding to lectin receptors, such as the C-type lectin domain of family 2 (CLEC-2) and the cell-specific intercellular adhesion molecule 3-capturing non-intriggin (DC-SIGN). Platelets and/or megakaryocytes can additionally interact with HIV envelope proteins via the C-X-C chemokine receptor type 4 (CXCR4) or via the chemokine (C -C) ligand (CCL) 3 (MIP-1α) and 5 (RANTES). However, HIV-1 changes the use of co-receptors from CCR5 to CXCR4 only after many years of infection, and this change in the receptor is a transition to non-CD4-dependent platelet activation in the later stages of the disease [6, 8].

These direct interactions often lead to platelet activation and adhesion of activated platelets to leukocytes. Binding of platelets to neutrophils triggers platelet phagocytosis, and platelet activation itself promotes platelet clearance in the spleen and liver.

However, platelets are activated not only by direct interaction with viruses. Host defense mechanisms in response to viral infections can also lead to platelet activation. For example, many viral infections lead to systemic inflammation, which in turn triggers platelet activation and reduces platelet life expectancy. In addition, influenza virus, rhinovirus, and CMV infection lead to increased regulation of cytokines such as interleukin 6 (IL-6) [9].

Platelets can be activated by cytokines, which leads to platelet-leukocyte interaction. This promotes the activation of leukocytes and endothelium by enhancing platelet activation and clearance by splenic macrophages or Kupffer cells in the liver. Monocytes that come in contact with the Dengue virus, for example, begin to generate platelet activating factor (PAF), which is a lipid mediator, which triggers platelet activation. This leads to increased platelet apoptosis and accelerates platelet clearance in secondary dengue infection [9, 12].

Some viral infections activate the coagulation cascade by inducing the expression of tissue factor in target cells. Generation of thrombin by the activated coagulation cascade causes platelet activation and subsequent clearance by protease-activating receptor signaling. Proteases on platelets, endothelial cells and leukocytes are important modulators in viral infections that modulate the innate immune response [7, 15].

Platelets also recognize immunoglobulin-coated viral particles through their FcγRII receptor, leading to Fc receptor-mediated activation, aggregation and clearance of platelets. FcγRII-mediated platelet activation depends on the involvement of IgG and GP Ib/IIa and involves ADF and thromboxane A2 feedback mechanisms to induce platelet aggregation [7, 12].

In addition, platelet destruction in response to viral
Infections may occur due to impaired portal vein pressure and increased platelet sequestration by an enlarged spleen, as is the case with HCV infection [8, 15].

Immune thrombocytopenia has complex developmental mechanisms in chronic HCV infection. The development of HCV-associated thrombocytopenia is autoimmune in nature and is accompanied by the production of antiplatelet autoantibodies. The primary immune defect is based on the production of autoantibodies tropical to platelet surface glycoproteins. B-lymphocytes are produced by surface glycoproteins due to the reduced level of autotolerance of T-lymphocytes. The inhibitory effect of HCV, which replicates in hematopoietic progenitor cells, on platelet production in the bone marrow and the positive effect of antiviral treatment of HCV-associated thrombocytopenia, in particular in cases of thrombocytopenia resistant to corticosteroids, have been demonstrated.

HCV-induced liver dysfunction leads to decreased TP production, which in turn leads to impaired platelet production in the bone marrow. Restoration of TP levels and an increase in platelet counts after successful liver transplantation in people infected with HCV underscores the importance of this mechanism in HCV-induced thrombocytopenia. Moreover, portal hypertension leads to platelet activation and reduces platelet survival due to increased platelet sequestration in the spleen [4, 8].

Thrombocytopenia, which is caused by the human immunodeficiency virus, has different mechanisms of occurrence. HIV has been shown to reduce the number and activity of megakaryocytes. Surface glycoprotein gp120 leads to increased apoptosis of megakaryocytes in vitro by increasing the TGFβ receptor and reducing the regulation of platelet proliferation. In addition, gp120 interacts with CD4+, which is expressed by immature megakaryocytes, which also express CCR5, and leads to their infection. Megakaryocyte HIV infection can lead to decreased expression of TPO receptors (c-Mpl) [8].

Viruses also have enzymes that can modulate platelet function. For example, the influenza virus secretes neuraminidase (sialidase), which hydrolyzes the terminal residues of sialic acid from the receptors of host cells and thereby shortens the lifespan of platelets. In addition to affecting platelet life expectancy, neuraminidase further alters megakaryocyte ploidy, as well as platelet morphology and size [10, 14].

The interaction of platelets and leukocytes and the modulation of leukocyte functions can be further accelerated by the binding of CD40 ligand (CD40L/CD154) to CD40. Platelets express and secrete (soluble) CD154, thereby causing a host reaction and exacerbating inflammation.

Platelets interact directly with T-lymphocytes and B-lymphocytes and modulate their function through direct cell interactions as well as soluble mediators. Platelet-released CXCL4 and CCL5 enhance the production of pro-and anti-inflammatory cytokines by T lymphocytes. CXCL4 is an important mediator in T cell differentiation, leading to an increase in regulatory T lymphocytes and limiting Th17 differentiation [8, 14].

Binding of IgG-coated viruses causes the expression of platelets CD154 and CCL5, which, in turn, primers the protective T-cell mediated immunity [4, 14].

It remains unclear to what extent platelet interactions with the virus are beneficial to the host. Potentially adverse effects of platelet interaction with the virus can be observed in HIV infection. In response to the interaction with HIV, platelets become active and release CCL5, leading to the accumulation of highly sensitive target cells such as T lymphocytes and monocytes. HCV has also been shown to take advantage of platelets as a safe transport system to reach the liver, where platelet activation further enhances the interaction of platelets and liver cells. This interaction prolongs the time of possible infection of the liver tissue with the virus [4, 8, 10].

Taken together, viruses can either increase platelet activation, leading to prothrombotic events, or reduce platelet response, thereby leading to bleeding. Platelet counts are insufficient to predict adverse platelet effects, and parameters such as platelet activation and reactivity may be more accurate in predicting the risk of bleeding in patients.

Conclusions and prospects for further development

1. Thrombocytopenia is a common complication of viral infections and viruses use different strategies to trigger the mechanism of platelet breakdown, and also play a key role in maintaining adequate host responses.

2. Viruses can cause induction of autoimmune response due to: molecular mimicry between viruses and platelets, production of anti-idiotypic antibodies to antiviral antibodies, increased expression of MCN-HLA class I and II molecules, which are very similar to certain regions of viral genomes, host immune changes in endogenous antigens.

3. The immune response underlying the development of thrombocytopenia is a cyclic multistage process involving T-lymphocytes, B-lymphocytes, macrophages, cytokines, Nk - cells. Antiplatelet antibodies accelerate the clearance of platelets from the circulation. Binding of antibodies to platelets results in Fcy receptor-mediated disintegration of platelets by phagocytes.

Prospects for further research is to study the interaction of platelets with different types of viruses, the viral effect on platelet activation. Research aimed at further study of platelet-mediated modulation of adaptive immune responses is promising.
ному рецептором Fcy распаду тромбоцитов фагоцитами. У пациентов с иммунной тромбоцитопенией вырабатываются главным образом IgG-аутоантитела на гликопротеины GP/II в/III, или GP/I в IX поверхности тромбоцитов. Так как мегакариоциты экспрессируют гликопротеин Ille/Ila, Iв и другие антигены тромбоцитов, они также стают мишенью для аутоантигена. Вирусы могут непосредственно взаимодействовать с тромбоцитами и мегакариоцитами. Тромбоциты могут активироваться вирусными комплексами антиген-антитело, и в ответ на некоторые вирусы B-лимфоциты могут вырабатывать антитромбоцитарные антитела. Все эти процессы, которые способствуют активации тромбоцитов, приводят к увеличению потребления и удаления тромбоцитов, что служит причиной геморрагических проявлений у больных.

Ключевые слова: тромбоциты, тромбоцитопения, вирусная инфекция, больные.