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COVID-19 and systemic thrombotic syndromes

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Abstract

COVID-19 is one of the most dangerous diseases of the current decade that has significantly affected the overall morbidity, mortality, quality of health and life of global population. Among multiple early and late post-COVID complications observed in patients with a new coronavirus infection, perhaps the main place is held by thrombosis. The significant role of microthrombosis, disseminated intravascular coagulation, thrombotic angiopathies in COVID-19 pathogenesis is noted. The accumulated data from clinical studies and the presented expert opinions made it possible to establish the significance of the "immunothrombosis–NETosis–thromboinflammation" relationship in the pathological effects caused by SARS-CoV-2 virus, as well as to reveal the mechanisms underlying formation of thrombotic syndromes mediated by anticoagulant therapy and vaccination. The information obtained about hemostasis disorders allows to move deeper into understanding the long-term sequelae in COVID-19 convalescent patients.

Keywords: COVID-19, thrombosis, thrombotic syndromes, immunothrombosis, thrombotic storm, NETosis, disseminated intravascular coagulation, vaccine-induced immune thrombotic thrombocytopenia

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COVID-19 и системные тромботические синдромы

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Резюме

COVID-19 является одним из грозных заболеваний текущего десятилетия, значительно повлиявшее на общую заболеваемость, смертность, качество здоровья и жизни населения планеты. Среди множества осложнений, наблюдаемых у пациентов с новой коронавирусной инфекцией, пожалуй, главное место в структуре постковидных ранних и поздних осложнений занимают тромбозы. Отмечена значимая роль микротромбозов, диссеминированного внутрисосудистого свертывания, тромботических ангиопатий в патогенезе COVID-19. Накопленные данные клинических исследований и представленные экспертные мнения позволили установить значимость связи «иммунотромбоз–нетоз–тромбовоспаление» в патологических эффектах, вызванных вирусом SARS-CoV-2, а также раскрыть механизмы формирования тромботических синдромов, опосредованных антикоагулянтной терапией и вакцинацией. Полученные сведения об особенностях нарушений системы гемостаза позволяют продвинуться в понимании отдаленных последствий среди пациентов, перенесших COVID-19.

Ключевые слова: COVID-19, тромбоз, тромботические синдромы, иммунотромбоз, тромботический шторм, нетоз, диссеминированное внутрисосудистое свертывание, вакцин-индуцированная иммунная тромботическая тромбоцитопения

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2024 • Vol. 18 • № 6
Obstetrics, Gynecology and Reproduction

Importance of thrombotic complications in COVID-19 / Актуальность тромботических осложнений при COVID-19

According to the World Health Organization (WHO) 2024 data, more than 750 million COVID-19 cases have been recorded since the onset of the pandemic [1]. As one of the most severe diseases of the current decade, COVID-19 has had a profound impact on global morbidity, mortality, and population health. The disease is known for its severe and frequent complications, including significant immune system dysfunctions such as lymphopenia, inflammation, autoimmune responses, and respiratory disorders like pneumonia and tissue fibrosis in affected areas. However, thrombosis holds a leading position among both early and late post-COVID complications [2].

In COVID-19 patients, thrombosis typically presents as venous and arterial macrothrombosis, pulmonary embolism (PE) with or without deep vein thrombosis (DVT), microcirculatory thrombosis, or thrombosis associated with extracorporeal membrane oxygenation (ECMO). According to global studies, the incidence of thrombotic complications in COVID-19 patients ranges from 60 to 80 % [3]. Although mortality in COVID-19 is primarily associated with severe pulmonary failure and thrombosis, it is important to note that pulmonary failure is often directly linked to localized pulmonary vessel thrombosis caused by SARS-CoV-2-induced coagulopathy [4].

Microthrombosis in COVID-19 patients / Микротромбозы у пациентов с COVID-19

At the onset of the pandemic, the importance of distinguishing between primary pulmonary thrombosis and PE without DVT in patients with severe COVID-19 was raised [5]. In addition to the clinical manifestations of primary pulmonary thrombosis and signs of interstitial inflammation, histopathological evidence confirmed the presence of microthrombi in alveolar septa. In deceased patients, interstitial and perivascular lymphocytic pneumonia accompanied by multifocal endothelial inflammation was observed. These pathological changes were associated with microthrombi within the alveolar septa, as indicated by thickened alveolar walls containing numerous fibrin microthrombi in the alveolar capillaries (**Fig. 1**). The intra-alveolar spaces also exhibited extravasated erythrocytes and a loose fibrin network [6].

Most pathological changes in the lung tissue of deceased COVID-19 patients correspond to the typical course of acute respiratory distress syndrome (ARDS) observed in influenza A (H1N1) fatalities. However, several distinct vascular alterations have been identified in COVID-19 patients: severe endothelial damage, widespread thrombosis with microangiopathy, and *de novo* formation of blood vessels predominantly through intussusceptive angiogenesis [6].

Scanning electron microscopy allowed to compare vessels state in the alveolar plexus in healthy people (**Fig. 2A**) and in COVID-19 patients. Evaluation of ultrastructural changes in vessels of COVID-19 patients revealed disruption of microvascular architecture (**Fig. 2B**). A loss of the clear hierarchical organization of the alveolar vascular network was noted, resulting from the formation of new blood vessels through intussusceptive angiogenesis. Intravascular pillars were observed (**Fig. 2C**), along with ultrastructural destructive changes in endothelial cells and the presence of SARS-CoV-2 particles (**Fig. 2D**) [6].

The role of disseminated intravascular coagulation in severe COVID-19 / Роль диссеминированного внутрисосудистого свертывания при тяжелых формах COVID-19

The progression of hemostatic disorders in COVID-19 patients involves multiple pathogenic pathways, including platelet activation, the extrinsic and intrinsic coagulation pathways, suppression of fibrinolysis leading to disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA), and localized intravascular coagulation within the lungs. Clinically, this manifests as venous and arterial thrombosis, including atypical sites of thrombosis and multiple organ failure (MOF), resembling catastrophic antiphospholipid syndrome (CAPS) or heparin-induced thrombocytopenia (HIT) and thrombosis due to widespread systemic thrombosis. This condition

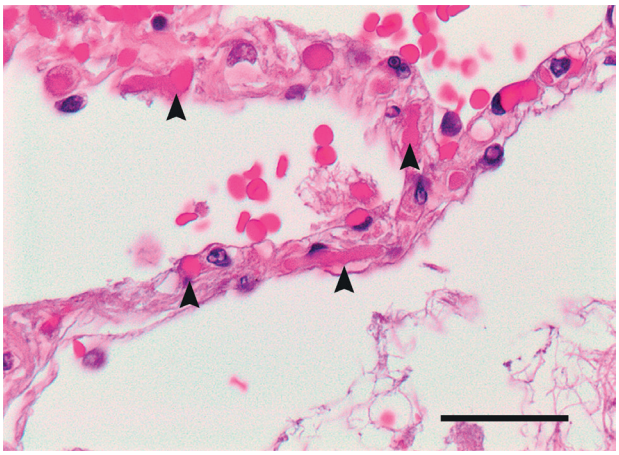

Figure 1. Microimage of the interalveolar septum in a deceased COVID-19 patient [6].

Note: *arrows indicate areas with fibrinous microthrombi; bottom right – black line depicts a scale bar corresponding to 50 μm.*

Рисунок 1. Микрофотография межальвеолярной перегородки погибшего пациента с COVID-19 [6].

Примечание: *стрелками обозначены участки с фибринозными микротромбами; черная линия внизу справа – масштабная линейка, соответствующая 50 мкм.*

2024 • Том 18 • № 6
Акушерство, Гинекология и Репродукция

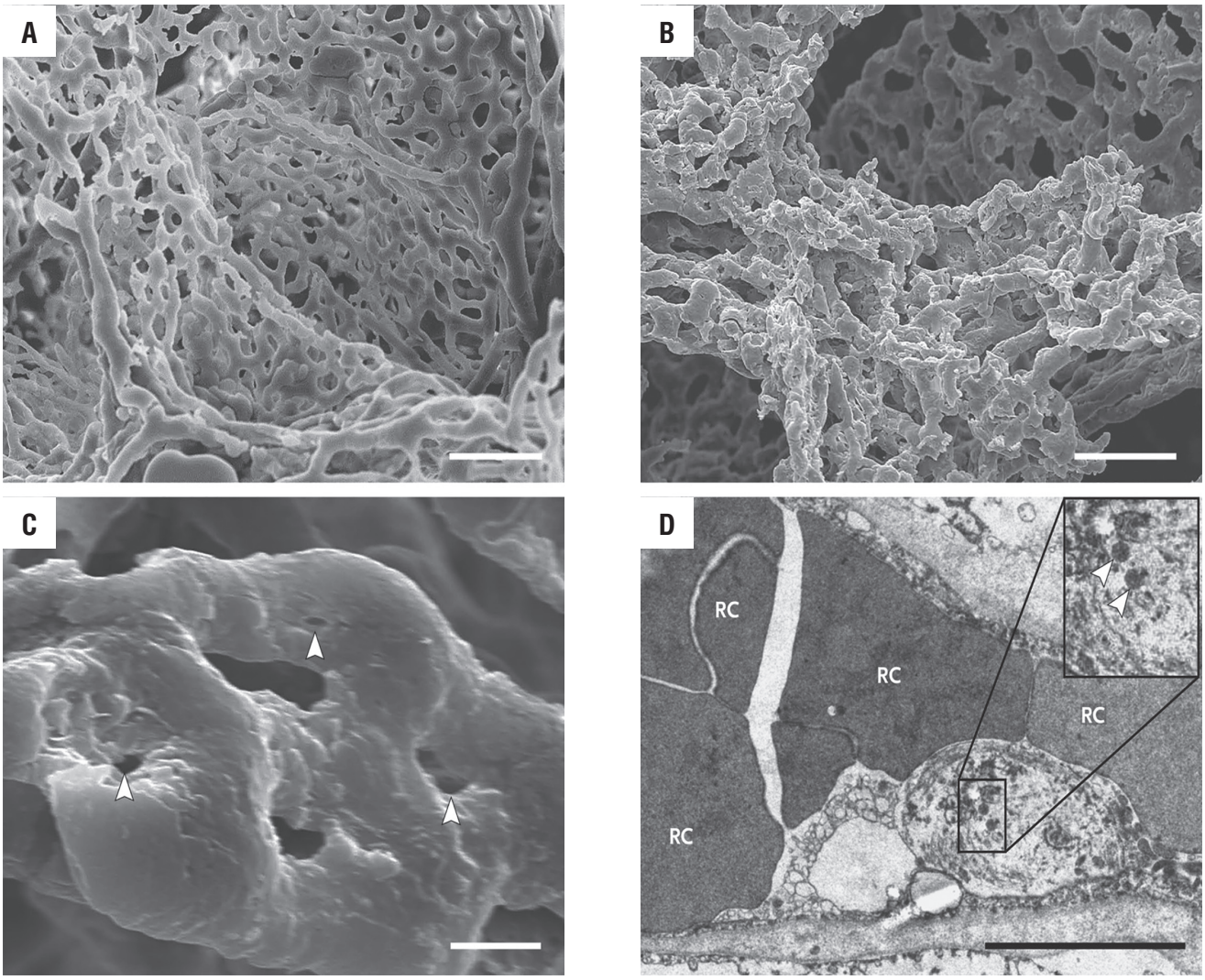

Figure 2. Microimages at the ultrastructural level of vessels in the alveolar plexus in healthy people (**A**) and vessel morphological changes in deceased COVID-19 patients (**B**, **C**, **D**) [6].

Note: *white arrows in figure C depict the localization of intussusceptive pillar; white arrows in figure D depict the localization of SARS-CoV-2 virions; RC – red blood cells; bottom right – black line depicts a scale bar corresponding to 50 μm.*

Рисунок 2. Микрофотографии на ультраструктурном уровне состояния сосудов в альвеолярном сплетении у здоровых людей (**A**) и морфологических изменений в сосудах у погибших пациентов с COVID-19 (**B**, **C**, **D**) [6].

Примечание: *белые стрелки на рисунке C – место локализации инвагинальных столбов; белые стрелки на рисунке D – место локализации вирионов SARS-CoV-2; RC – эритроциты; линия внизу справа – масштабная линейка, соответствующая 5 мкм.*

has been termed "thrombotic storm", analogous to the "cytokine storm" in severe infections [7].

Although SARS-CoV-2 is primarily a respiratory virus, COVID-19 is a systemic disease that affects multiple organs. COVID-19-associated thrombotic syndromes can be broadly categorized into those caused by the disease-related pathogenic processes and those triggered by therapeutic interventions. Conditions such as DIC, TMA, and, less frequently, antiphospholipid syndrome (APS) or CAPS are directly linked to the disease progression. In contrast, heparin-induced or vaccine-induced thrombocytopenia and thrombosis are adverse effects of the therapeutic interventions used to manage the disease.

Early in the pandemic, it was evident that, like other severe infections, COVID-19 triggers hematological disorders such as DIC or sepsis-induced coagulopathy due to systemic inflammation. Our first study on DIC in COVID-19 was published in 2020. Unfortunately, neglecting the role of hemostasis dysfunction in severe cases, the lack of anticoagulant therapy in the early stages of the pandemic, and an exclusive focus on mechanical lung ventilation (MLV) significantly contributed to the high mortality rates [8].

In severe COVID-19, there is near-simultaneous activation and interplay between cellular and molecular host defense constituents involved in DIC pathogenesis such as pathway activation with depletion of natural

2024 • Vol. 18 • № 6
Obstetrics, Gynecology and Reproduction

anticoagulants, severe endothelial dysfunction, complement and platelet activation, poorly controlled inflammation, neutrophil extracellular traps (NETosis), and impaired fibrinolysis due to dysfunctional microcirculation characterized by widespread endothelial damage [9].

Despite varying clinical presentations – ranging from thrombotic occlusions to hemorrhagic diathesis – the underlying DIC etiology typically involves excessive coagulation activation and dysregulation of anticoagulant and fibrinolytic functions. The initiation of coagulation is triggered by intravascular tissue factor (TF) expression or contact pathway activation in response to pathogen-associated molecular patterns (PAMPs) or host cell damage-associated molecular patterns (DAMPs). This process is further amplified through inflammatory and immunothrombotic mechanisms. The consumption of anticoagulants and disruption of endothelial homeostasis reduce regulatory control, leading to widespread microvascular thrombosis [9].

While the DIC clinical spectrum ranges from asymptomatic to thrombotic or hemorrhagic presentations, the core pathophysiology involves an imbalance between procoagulant factors and endogenous anticoagulant and fibrinolytic mechanisms, ultimately driving disseminated microvascular thrombosis (**Fig. 3**) [10].

Excessive thrombin activation leads to the proteolytic fibrinogen conversion and the intravascular fibrin formation. When the consumption rate of clotting factors surpasses their synthesis, a consumption coagulopathy develops. Combined with thrombocytopenia, this condition significantly increases the risk of bleeding. Intravascular fibrin formation is counterbalanced by plasmin-mediated fibrinolysis, which results in elevated levels of fibrin degradation products, such as D-dimers, in the bloodstream. However, when fibrinolysis cannot offset the excessive coagulopathy, obstructive microthrombosis may cause hypoperfusion and hypoxia of peripheral organs, ultimately leading to MOF [10].

Microvascular thrombosis and hemorrhage are primary contributors to MOF, with the lungs and kidneys being particularly vulnerable to coagulopathic dysfunction. The DIC clinical progression in patients is associated with worsened morbidity and increased mortality, regardless of the underlying pathology. This is especially true in severe COVID-19, making the early detection of DIC crucial for reducing disease burden. Given the wide range of triggers and pathogenic mechanisms leading to DIC, its diagnostics relies on algorithms that quantitatively assess hemostatic imbalances, thrombocytopenia, and fibrinogen conversion.

Since current diagnostic approaches primarily detect overt manifestations of consumption coagulopathy, there is an urgent need to improve the identification of subclinical DIC, pre-DIC states, or chronic DIC forms. Early recognition of such latent forms can significantly aid in preventing severe thrombotic and hemorrhagic complications in critically ill patients, including those with COVID-19.

Thrombotic microangiopathy in COVID-19 and ADAMTS-13 role in COVID-19 / Тромботическая микроангиопатия и роль ADAMTS-13 при COVID-19

Thrombotic microangiopathy often underpins the development of microcirculatory disturbances resulting from cytokine and thrombotic storms. TMA encompasses a group of heterogeneous clinical conditions characterized by arteriolar and capillary thrombosis, leading to hemolytic anemia, thrombocytopenia, and ischemic organ damage, which may culminate in MOF.

TMA presents significant diagnostic and clinical challenges, especially in emergency and life-threatening situations. Multiorgan dysfunction is the typical TMA clinical manifestation. However, in some cases, atypical symptoms such as malignant hypertension, neurological disorders, and HELLP syndrome during pregnancy may be observed.

Although TMA has various etiologies, one of the key factors contributing to its development is the metalloproteinase ADAMTS-13 deficiency that impairs the proteolysis of von Willebrand factor (vWF) multimers, which have a high capacity to activate platelets. During a SARS-CoV-2-induced cytokine storm and endothelial injury, there is an excessive consumption of ADAMTS-13 by elevated levels of high-molecular-weight vWF that leads to the accumulation of ultra-large vWF multimers that, in combination with adhered and aggregated

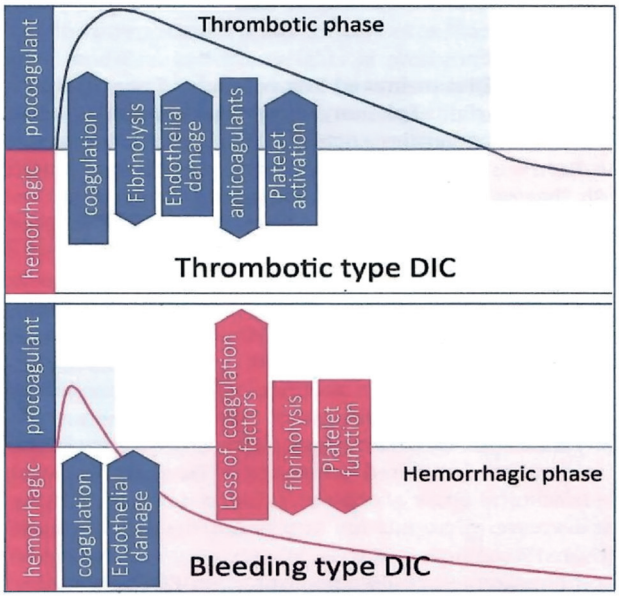

Figure 3. Thrombotic and hemorrhagic types of disseminated intravascular coagulation [10].

Рисунок 3. Тромботический и геморрагический типы диссеминированного внутрисосудистого свертывания [10].

platelets, cause microcirculatory thrombosis and subsequent organ failure (**Fig. 4**). The understanding of thrombotic thrombocytopenic purpura (TTP) – a condition primarily driven by ADAMTS-13 deficiency – has shed light on the critical role of ADAMTS-13 in other forms of TMA and thrombotic disorders associated with endothelial dysfunction, such as ischemic stroke and ischemic heart disease [11–13].

As a part of a grant from the Russian Academy of Sciences, we conducted a study titled "COVID-19, Thromboinflammation, and Thromboembolism," aimed at assessing the role of hemostasis parameters and inflammatory biomarkers in the pathogenesis of severe COVID-19 cases. Among other hemostatic indicators, the study analyzed ADAMTS-13 activity, vWF level, and a key NETosis marker – myeloperoxidase (MPO) activity. The data analysis revealed a strong threshold-dependent correlation between vWF and MPO activity levels and intensive care unit (ICU) patient outcomes. These findings underscore the critical role of inflammation, endothelial injury, and microangiopathy in severe COVID-19, reinforcing the predictive value of these biomarkers. Notably, MPO activity demonstrated even greater predictive significance than vWF [14].

Multivariate analysis confirmed that elevated MPO activity and vWF levels are independent predictors of poor survival in critically ill COVID-19 patients requiring MLV [15].

Thrombotic storm and immunothrombosis in COVID-19 / Тромботический шторм и иммунотромбоз при COVID-19

The primary pathogenic effects triggered by SARS-CoV-2 infection are linked to the activation of monocytes, macrophages, neutrophils, the complement system, and endothelial dysfunction, ultimately leading to both a cytokine storm and a thrombotic storm. The thrombotic storm is a phenomenon characterized by multiple thromboses developing over a short period of time, similar to CAPS, yet without the presence of elevated antiphospholipid antibodies (aPL) [16].

P. Libbi and D.I. Simon (2001) were among the first to highlight the link between localized thrombosis and inflammation [17]. Later, J.F. Tanguay et al. (2004) introduced the term "thromboinflammation" to describe the interaction between platelets and neutrophils in the context of in-stent arterial restenosis during a clinical study [18]. Subsequently, P. Blair et al. (2009)

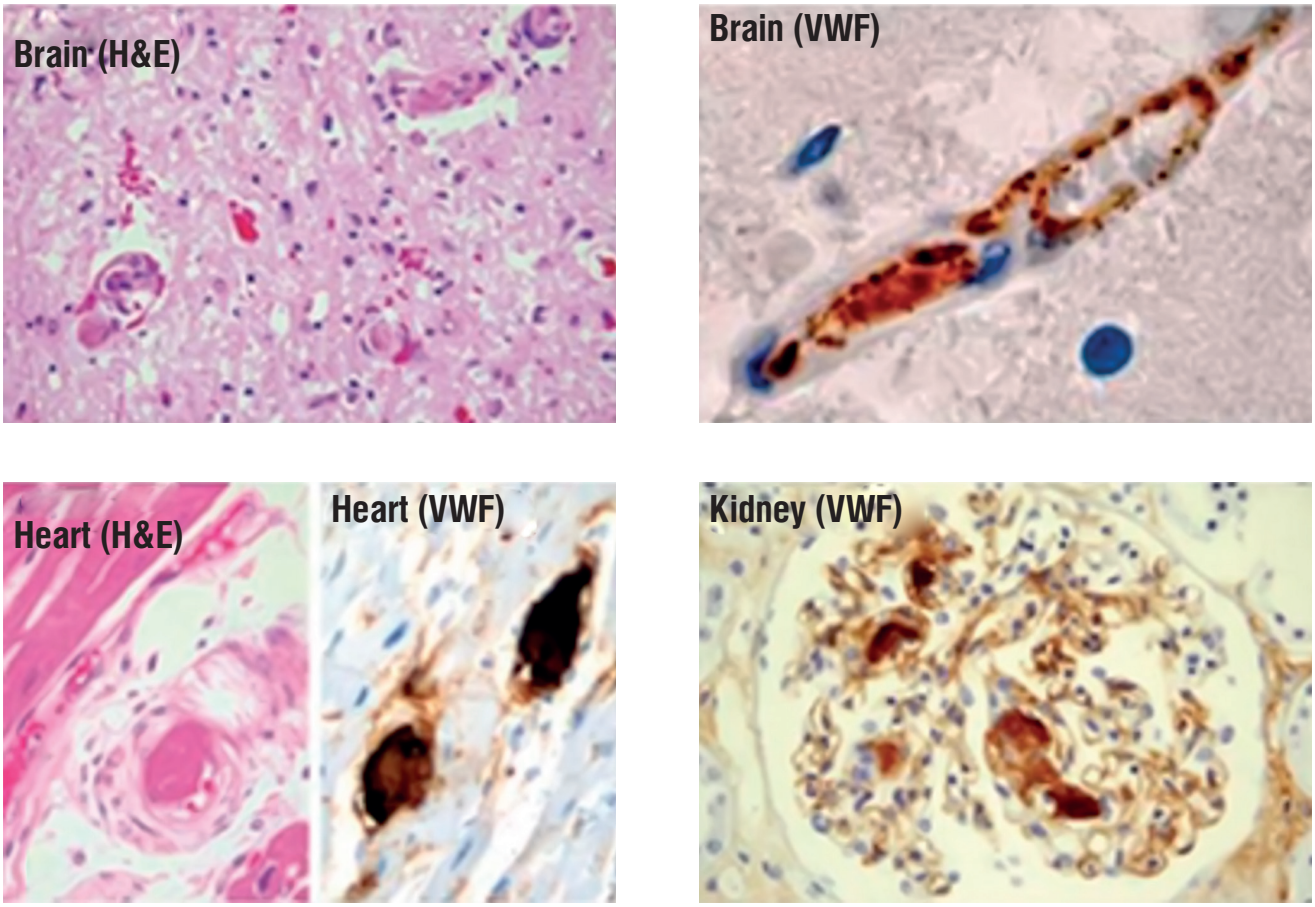

Figure 4. Von Willebrand factor-containing blood clots [13].

Рисунок 4. Тромбы, содержащие фактор фон Виллебранда [13].

2024 • Vol. 18 • № 6
Obstetrics, Gynecology and Reproduction

identified a mechanism of thromboinflammatory activation involving toll-like receptors (TLRs) [19]. Today, it is widely recognized that endothelial dysfunction, thromboinflammation, and immunothrombosis are key pathogenic mechanisms in COVID-19.

Physiological immunothrombosis represents a controlled microcoagulation process that does not result in adverse clinical outcomes. On the contrary, it aids in immobilizing invading pathogens or foreign "danger" structures, facilitating their neutralization or removal by immune cells. However, excessive inflammatory responses disrupt this balance, leading to coagulopathic disorders and thrombosis, emphasizing the finely tuned interplay between the immune system and hemostatic mechanisms (**Fig. 5**) [20].

Infections triggered by PAMPs, such as viral or bacterial infections, and sterile inflammatory diseases induced by DAMPs, such as hemolytic disease or ischemia/reperfusion injury, can result in thromboinflammatory states. The activation of the immune system by PAMPs or DAMPs leads to unregulated activation of coagulation factors, platelets, endothelial cells, and the complement system. These processes cause P-selectin surface expression on platelets and endothelial cells, facilitating leukocyte recruitment. The increased TF expression in monocytes and the release of leukocyte-derived TF-containing extracellular vesicles initiate the coagulation cascade [20].

Thrombin and other proteases involved in the coagulation cascade, including factor Xa and factor VIIa, not only mediate fibrin generation but also regulate cellular functions, which affect hemostatic and inflammatory responses. These proteases can activate protease-activated receptors (PARs) abundantly expressed on the surface of platelets, leukocytes, and endothelial cells. Once activated, PARs stimulate multistep intracellular signaling pathways, leading to platelet activation, endothelial expression of adhesion markers, and the release of proinflammatory cytokines. Additionally, PAR activation lowers nitric oxide production, thereby promoting endothelial dysfunction and triggering proinflammatory and proapoptotic responses [20].

NETosis in COVID-19 / Нетоз при COVID-19

The procoagulant potential in immunothrombosis is not limited to the expression of platelet factors by monocytes or endothelial cells. Extracellular DNA released within neutrophil extracellular traps (NETs) can also initiate the coagulation cascade via the contact pathway, representing a key mechanism of immunothrombosis. It is important to note that platelets are not merely activated by immunothrombotic processes – they can also initiate them. For instance, the interaction between platelets and neutrophils serves as a threshold switch for NETosis.

During infection, NETs formation serves a dual role. On one hand, NETs capture and kill bacteria, providing a platform for more efficient leukocyte activity. On the other hand, NETs also serve as a potent prothrombotic and procoagulant stimulus by providing a negatively charged surface that captures coagulation factors and platelets. Citrullinated histones and immobilized vWF on NETs surface activate platelets, whereas

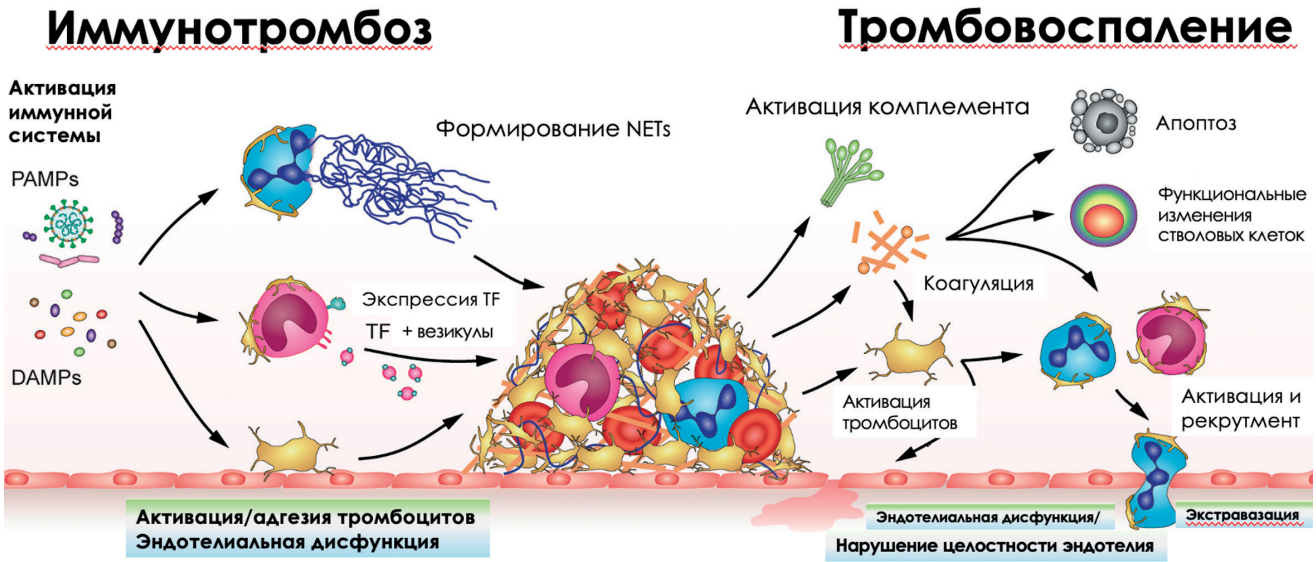

Figure 5. The relationship between immunothrombosis and thromboinflammation [20].

Note: *PAMPs – pathogen-associated molecular patterns; DAMPs – damage-associated molecular patterns; NETs – neutrophil extracellular traps; TF – tissue factor.*

Рисунок 5. Взаимосвязь между иммунотромбозом и тромбовоспалением [20].

Примечание: *PAMPs – патоген-ассоциированные молекулярные паттерны; DAMPs – молекулярные паттерны, ассоциированные с повреждениями; NETs – внеклеточные ловушки нейтрофилов; TF – тканевой фактор.*

negatively charged DNA can trigger the coagulation cascade via factor XIIa-induced thrombin generation. Moreover, neutrophil elastase within NETs inactivates anticoagulant mechanisms by cleaving thrombomodulin and tissue factor pathway inhibitor (TFPI). NETs-driven activation of factor XIIa contributes significantly to thromboinflammation in COVID-19. In sepsis models, inhibiting factor XIIa has been shown to reduce NETs level, interleukin-6 (IL-6) production, and complement activation.

Such processes affect not only the local microenvironment by promoting microthrombosis and vascular occlusion but also exert systemic, long-term effects beyond ischemic events, potentially leading to immune suppression.

In addition to their prothrombotic effects, NETs can contribute to TMA in systemic inflammatory conditions by directly inhibiting the natural anticoagulant function of ADAMTS-13.

A number of autoimmune diseases and syndromes, including APS, are accompanied by NETosis activation. Moreover, patients with aPL circulation demonstrate high resistance to the profibrinolytic activity of anticoagulants, further exacerbating the risk of thrombotic complications [21].

Thrombotic syndromes mediated by COVID-19 therapy / Тромботические синдромы, опосредованные терапией COVID-19

Pharmaceutical companies responded to the COVID-19 pandemic with unprecedented speed, developing adenovirus-based and mRNA-based vaccines. However, by March 2021, safety concerns emerged regarding adenovirus-vector vaccines. Previously healthy recipients developed severe thromboses, particularly in cerebral and splanchnic vessels, accompanied by thrombocytopenia, typically during the second week after initial vaccination. These cases were reported following various adenovirus-vector vaccines, confirming that the complication is unrelated to the country of origin. The incidence of vaccine-induced thrombosis ranges from 3.2 to 16.1 cases per million doses. There is concern that low- and middle-income countries may underreport cases, as only a few dozen instances have been documented in Asia, Africa, and Latin America. Early detection and treatment are crucial, potentially reducing mortality by up to 90%.

Drawing parallels with HIT, this condition was termed vaccine-induced immune thrombotic thrombocytopenia (VITT) and became a subject of extensive debate in 2021. Several national and international guidelines for its diagnostics and treatment were published, with updates provided by the WHO in 2023. The British Society for Haematology proposed diagnostic criteria for VITT [22]:

- symptom onset 5–30 days post-vaccination (up to 42 days for isolated DVT or PE);
- presence of thrombosis;
- thrombocytopenia (platelet count < 150 × 10^9/л);
- D-dimer level > 4000 μg/mL;
- positive anti-PF4 antibodies detected via ELISA.

Platelet factor 4 (PF4) plays a central role in both HIT and VITT pathogenesis. PF4, also known as chemokine (C-X-C motif) ligand 4 (CXCL4), is a small cytokine belonging to the CXC chemokine family. It is released from alpha-granules of activated platelets during aggregation and binds strongly to heparin and other glycosaminoglycans.

Platelet factor 4 primary physiological role is to neutralize heparin-like molecules on endothelial surfaces, thereby lowering antithrombin activity and promoting coagulation. As a highly cationic tetrameric protein, PF4 forms multimolecular PF4/heparin complexes. When negatively charged heparin binds to positively charged PF4, it neutralizes PF4 charge, allowing PF4 tetramers to cluster – a crucial step for antigenic complex formation.

This aggregation facilitates thrombus formation by promoting platelet aggregation. Direct platelet activation by PF4-containing immune complexes is a key pathogenic mechanism in HIT. The resulting ultralarge PF4/heparin complexes possess antigenic properties, triggering IgG antibody production against PF4/heparin complexes [23].

Interestingly, the antigenic sites on PF4 that support heparin-independent antibody reactivity differ from those involved in heparin-dependent responses. These sites may resemble those recognized by antibodies in VITT cases (**Fig. 6**) [24].

Anti-PF4 antibodies identified in VITT patients recognize distinct epitopes compared to those seen in HIT. VITT-associated anti-PF4 antibodies target amino acids also involved in PF4-heparin binding, which has significant therapeutic implications. Because heparin can inhibit the binding of VITT antibodies to cognate target, it may act as an antidote by blocking antigen-antibody interactions [23].

Immune complexes composed of PF4 and heparin-independent antibodies capable of activating platelets have been found in patients with spontaneous HIT and VITT. Furthermore, the close proximity of PF4 tetramers facilitated by heparin-independent antibodies can generate heparin-dependent antigens, even in the absence of heparin. HIT patients typically have both heparin-dependent and heparin-independent antibodies. Both types of ultralarge immune complexes bind to platelet surfaces via the FcγIIa receptor, triggering platelet activation.

All adenovirus-vector vaccines against SARS-CoV-2 exhibit high affinity for PF4. The adenovirus vector capsid has a strongly electronegative surface that electrostatically interacts with positively charged PF4.

For instance, the Oxford vaccine contains higher levels of impurities, such as human proteins generated during

2024 • Vol. 18 • № 6
Obstetrics, Gynecology and Reproduction

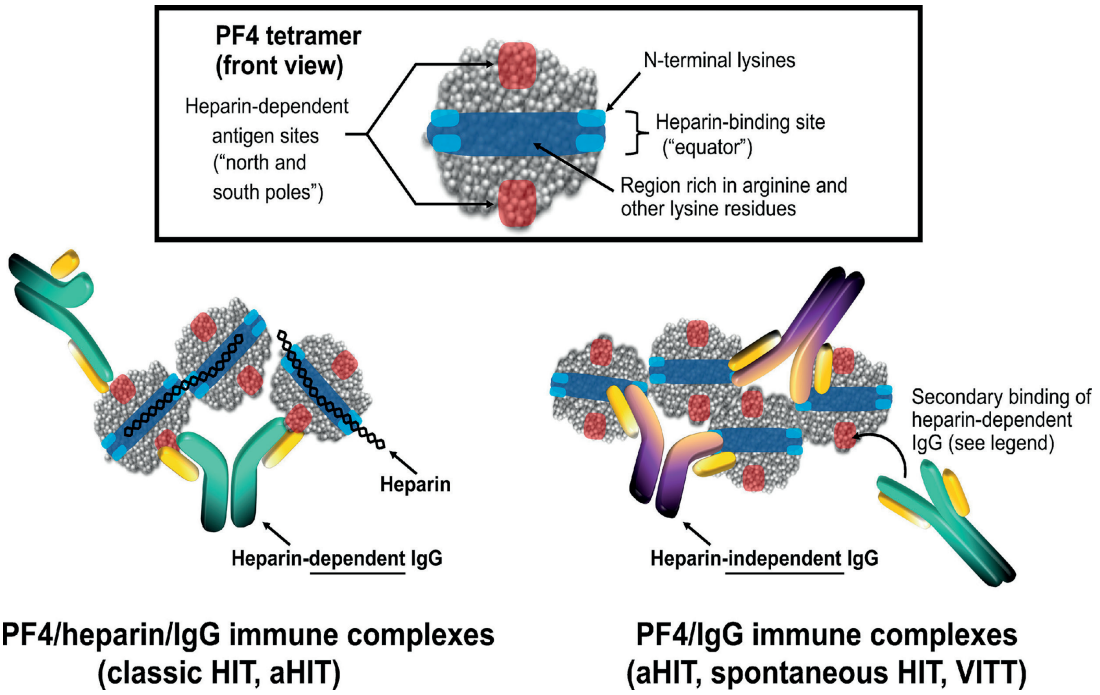

Figure 6. Heparin-dependent and heparin-independent antigenic sites on platelet factor 4 surface [24].

Note: *PF4 – platelet factor 4; HIT – heparin-induced thrombocytopenia; aHIT – autoimmune heparin-induced thrombocytopenia; VITT – vaccine-induced immune thrombotic thrombocytopenia.*

Рисунок 6. Гепарин-зависимые и гепарин-независимые антигенные сайты на поверхности фактора тромбоцитов 4 [24].

Примечание: *PF4 – тромбоцитарный фактор 4; HIT – гепарин-индуцированная тромбоцитопения; aHIT – аутоиммунная гепарин-индуцированная тромбоцитопения; VITT – вакцин-индуцированная иммунная тромботическая тромбоцитопения.*

the production process, compared to other vaccines. These impurities may contribute to the formation of PF4 complexes and a potentially higher incidence of immune responses against PF4.

A two-stage mechanism of VITT pathogenesis has been proposed: shortly after vaccination (days 1–2), neoantigens are generated through interactions between positively charged PF4 and negatively charged viral DNA or other vaccine components that have entered the bloodstream, forming antigenic complexes that bind to platelet surfaces.

These "platelet-PF4-vaccine component" complexes are then transported to the spleen, where they are phagocytosed by macrophages, triggering B-cell activation, which is further amplified by inflammatory co-signals induced by vaccine protein contaminants (an immunological "danger signal"). Later (days 5–20), in some vaccine recipients, the activated B-cells produce high titers of anti-PF4 autoantibodies, which engage platelets via FcγRIIA binding. The cross-interaction between PF4, activated platelets, and VITT antibodies leads to neutrophil activation, resulting in NETs formation and thrombosis.

The activation of immune platelets in HIT is mediated by the interaction between IgG Fc fragment and FcγRIIA receptor on platelet surface. HIT pathogenesis involves circulating PF4/heparin/antibody complexes that bind to FcγRIIA on platelets and other blood cells bearing Fc receptors, such as monocytes and neutrophils. FcγRIIA activation induces platelet activation, leading to the release of granule contents and the formation of procoagulant microparticles.

Additionally, platelet-neutrophil interactions triggered by HIT antibodies can activate vascular endothelium. PF4/heparin immune complexes directly activate endothelial cells without involving FcγRIIA, inducing increased expression of adhesion molecules such as P- and E-selectins and promoting vWF release.

The combined effect of direct platelet activation by immune complexes through FcγRIIA and monocyte-mediated activation, along with thrombin released from endothelial cells, enhances phosphatidylserine expression on platelet surfaces and promotes factor Xa binding to platelets. Such events result in increased thrombin generation, which elevates the risk of thrombotic vascular occlusions.

Long COVID / Длительный COVID

Long COVID is a public health emergency affecting millions worldwide, characterized by heterogeneous

symptoms across multiple organ systems. There is growing evidence linking thromboinflammation to the post-acute sequelae of COVID-19. Studies have revealed persistent vascular damage with elevated circulating markers of endothelial dysfunction, coagulation abnormalities, and increased thrombin generation potential. The neutrophil phenotype in long COVID patients resembles that seen in acute COVID-19, with heightened activation and NETs formation. This hypercoagulable state may lead to microvascular thrombosis, as indicated by the presence of microclots, elevated D-dimer levels in the bloodstream, and perfusion defects in the lungs and brain of long COVID patients. Additionally, COVID-19 survivors exhibit an increased incidence of both arterial and venous thrombotic events [25].

At least three significant, potentially interconnected hypotheses have been discussed to explain thromboinflammation in long COVID:

- persistent structural changes, primarily endothelial damage, caused during the initial infection;
- the presence of a viral reservoir;
- immune dysregulation resulting from malfunctioning immune responses.

Conclusion / Заключение

Almost 5 years after the onset of the COVID-19 pandemic, the medical community has made marked progress in understanding both the major pathogenetic disease links and a number of fine mechanisms in developing complications.

The previously ignored role for thrombotic syndromes in COVID-19 has become a key in predicting the disease outcome, early and late post-COVID complications. Such advancement was facilitated by multiple clinical studies aimed at exploring the mechanisms and features underlying formation of microthrombosis, DIC, TMA.

Special attention is paid to development of vaccination-associated thrombotic syndromes and heparin use. A number of studies indicate a prominent role for immunothrombosis in development of adverse drug reactions.

Currently, the attention of medical community is focused on a phenomenon such as long COVID, in which similar hemostasis disorders are noted. Nevertheless, fine pathogenesis mechanisms of this condition remain a subject of study in basic and clinical medicine.

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