

Possible Immunological Mechanisms in COVID-19 Patients with Immune Thrombocytopenic Purpura

Mogući imunološki mehanizmi kod Covid-19 bolesnika s imunološkom trombocitopeničnom purpurom

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Summary

Millions of people around the world were, or are still involved with COVID-19 due to infection with SARS-CoV-2. In addition to hallmark symptoms, thrombotic problems, lymphopenia, and thrombocytopenia have also been reported in COVID-19 patients, of which ITP is the most common and occurs in more than one-third of COVID-19 patients. Hyperinflammation, cytokine storms, and generally immune dysregulation in a percentage of patients develop the main consequences of diseases such as ALI, ARDS and multiple organ failure. Some of the important events in the immunopathogenesis of this disease are disruption of T-cell effector differentiation and the destructive role of Th17 lymphocytes, neutrophil function and inflammatory macrophages. NLRP3-inflammasome hyperactivity causes serious dysfunction of innate immune cells and, consequently, T lymphocytes in many inflammatory disorders, most notably in the COVID-19. A closer look at the immunopathogenesis of ITP and COVID-19 brings us to common ground. The purpose of this study was to review and summarize the findings of various studies on the immunopathogenesis of ITP and its possible causes in COVID-19. Finally, enhanced differentiation of Th17 and Th1, the cell death called as pyroptosis, hyperinflammation and dysfunction of inflammatory neutrophils and macrophages, and NLRP3-inflammasome hyperactivity are important factors in the development of thrombocytopenia in patients with COVID-19. Further studies are needed to better understand immunopathogenesis and effective treatments for ITP, especially in inflammatory disorders.

Key words: COVID-19-SARS-CoV2; inflammasome; immune thrombocytopenic purpura; platelets; immune dysregulation

Sažetak

Diljem svijeta milijuni ljudi bili su, ili još uvijek jesu, zaraženi novom bolešću COVID-19, uzrokovanom infekcijom virusa SARS-CoV-2. Uz karakteristične simptome, kod ovih bolesnika prijavljeni su i trombotski problemi, te limfopenija i trombocitopenija, od kojih je imuna trombocitopenična purpura (ITP) najčešći problem i javlja se u više od jedne trećine pacijenata s COVID-19. Hiperinflamacija, citokinske oluje i općenito imunološka disregulacija u postotku bolesnika razvijaju glavne posljedice bolesti kao što su ALI, ARDS i višestruko zatajenje organa. Neki od važnih događaja u imunopatogenezi ove bolesti su poremećaj diferencijacije efektor T-stanica i destruktivna uloga TH17 limfocita, funkcija neutrofila i upalnih makrofaga. Hiperaktivnost NLRP3-inflamasoma uzrokuje ozbiljnu disfunkciju urođenih imunoloških stanica i, posljedično, T limfocita u mnogim upalnim poremećajima, ponajviše u COVID-19. Pažljiviji pogled na imunopatogenezu ITP-a i COVID-19 dovodi nas do zajedničkog stava. Svrha ove studije bila je pregledati i sažeti nalaze različitih studija o imunopatogenezi ITP-a i njegovim mogućim uzrocima u COVID-19. Konačno, pojačana diferencijacija Th17 i TH1, stanična smrt nazvana piroptoza, hiperinflamacija i disfunkcija upalnih neutrofila i makrofaga, te hiperaktivnost NLRP3-inflamazoma, važni su čimbenici u razvoju

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trombocitopenije u bolesnika s COVID-19. Potrebite su daljnje studije, kako bi se bolje razumjela imunopatogeneza i proveli učinkoviti tretmani za ITP, posebno kod upalnih poremećaja.

Ključne riječi: COVID-19-SARS-CoV2; inflamazom; imunološka trombocitopenična purpura; trombociti; imunološka disregulacija

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Introduction

Immune thrombocytopenia purpura (ITP) is an acquired disorder, diagnosed with the aid of only two criteria; 1- there should be only thrombocytopenia and other findings should be normal in complete blood count and peripheral blood slide, and 2- there should be no other clinical condition with manifestations similar to systemic lupus erythematosus, anti-phospholipid syndrome, and chronic lymphoid leukemia; patients with the above conditions are considered to have secondary ITP.¹ Because the exact etiology of ITP is unclear, the diagnosis should be made by differentiating it from other types of thrombocytopenia, such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, microangiopathic hemolytic anemia, and heparin-induced thrombocytopenia.^{2,3} The etiology of ITP is unknown, but it appears to be due to genetic and acquired factors.^{1,4} The ITP is a common acquired bleeding disorder, with a higher prevalence among children than adults. The annual prevalence of ITP in adults was 22 per million people.⁵ There is no marked difference in the clinical signs of ITP among patients, although ITP may start acutely and suddenly, but in most cases, it has an insidious onset. Bleeding in symptomatic patients can range from mild petechiae and bruising to severe hemorrhage, and symptoms of bleeding from thrombocytopenia often occur as mucocutaneous bleeding.⁶ The clinical manifestations of thrombocytopenia are highly age-related; older patients may exhibit the symptoms of severe hemorrhage such as gastrointestinal bleeding and intracerebral hemorrhage due to conditions such as hypertension. There is no gold standard test to confirm definitively the ITP detection, and the diagnosis is made by ruling out other causes of thrombocytopenia.⁷ Only patients with severe thrombocytopenia (platelets less than 20,000) should be treated. The treatment usually involves prednisolone at a dose of 1 mg/kg BW/day. Steroids help prevent bleeding and reduce platelet destruction.⁸ Most ITP patients respond to prednisolone treatment within two weeks and the major response is within the first week of treatment. Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection was officially declared a pandemic on March 11, 2020, and is still a major global threat, spreading to more than 200 countries. Although the main clinical manifestations of

coronavirus disease 2019 (COVID-19) are respiratory problems, the range of disorders and clinical manifestations of this disease is extensively wide, and many cases of neurological, gastrointestinal, hepatic, and cardiac disorders have been reported to varying degrees.⁹ On the other hand, the occurrence of biological disorders and laboratory parameters such as elevated liver enzymes, increased creatinine, electrolyte imbalance, a huge increase in CRP and hyperinflammation associated with COVID-19 is very common.¹⁰

The ITP in the patients with COVID-19

According to meta-analyses, various hematological disorders including thrombotic problems, lymphopenia, and thrombocytopenia have been reported in COVID-19, of which the ITP is very common, affecting more than one-third of COVID-19 patients.¹¹ Due to the importance of this subject in this pandemic, this study aimed to discuss the possible mechanisms in the occurrence of COVID-19-dependent ITP. As mentioned, the ITP has been reported in a significant number of patients with COVID-19. Hyperinflammation caused by SARS-CoV-2, like SARS-CoV-1, causes endothelial dysfunction/injury. It should be noted that this injury, along with the generation of autoantibodies against platelets, also increases the risk of thromboembolic disorders and exacerbates thrombocytopenia. According to previous case reports, the severity of SARS-CoV-2-induced thrombocytopenia appears to be related to age and more anti-platelet autoantibodies are developed in the elderly. The clinical signs of ITP are variable, which can be asymptomatic or accompanied by mild mucocutaneous bleeding or life-threatening hemorrhages. Although the COVID-19-associated thrombocytopenia is usually mild, very severe hemorrhage has been reported in a small number of patients.^{2,12-14} Based on a study by Sabin et al. on SARS-CoV-2-induced ITP, no association was found between hemorrhage severity and COVID-19 severity. In another study, Sue Pavord et al. found a sharp drop in platelets in the patients with end-stage COVID-19 due to multiple organ failure.¹⁵ According to a study of COVID-19-associated thrombocytopenic cases, the complication was generally found in people with a history of thrombocytopenia or underlying diseases

such as carcinoma, rheumatism, cardiovascular diseases such as hypertension, heart failure, and metabolic diseases such as type II diabetes and dyslipidemia. Some patients also received chemotherapy and immunosuppressants. According to studies of COVID-19-associated thrombocytopenia cases, the most common clinical manifestations were epistaxis and mucosal hemorrhage, petechia and purpura, and occasionally hematuria or subarachnoid and intracerebral hemorrhage.^{2,11,16,17}

Immunopathogenesis of ITP

In the immunopathogenesis of ITP, there is a disorder in the T cell population so that this dysregulation develops autoantibodies against platelets and megakaryocytes, and the cytotoxic CD8+ T cells cause platelet and megakaryocyte lysis. These two mechanisms can occur parallelly or separately; thus, the induction of apoptosis in platelets or megakaryocytes and their subsequent phagocytosis by macrophages and dendritic cells increases platelet clearance and decreases platelet count.^{18,19} In the ITP, the CD4+ T cell imbalance also occurs in which the Th1/Th2 ratio increases in favor of the Th1 phenotype, and since Th1 is responsible for the response to intracellular pathogens, its overexpression can lead to autoimmune diseases. The CD4 cells are essential for the conversion of B cells to plasma cells, and this increase in the Th1 ratio causes the production of autoreactive B cells and the secretion of autoantibodies. The Th17 is another inflammatory T cell that is elevated in ITP, which in turn disrupts the Th1/Th2 ratio and increases autoantibodies.^{20,21} Another mechanism proposed in the ITP is to disrupt the proportion of cytotoxic CD8+ T cell subtypes, which induces platelet apoptosis and inhibits thrombopoiesis in megakaryocytes.²² The primary cause of these autoimmune responses is unclear and may be related to genetic and environmental factors. Infections with HIV, HCV, CMV, HSV, Ebola virus and EBV appear to induce secondary ITP. There have also been reports of thrombocytopenia due to SARS-CoV-1 infection, which was generally mild. Several possible mechanisms have been proposed for the development of ITP due to infection with viruses, which briefly include molecular mimicry of platelet membrane glycoproteins, direct attack on megakaryocytes, induction of apoptosis, and activation of inflammasomes in platelets.²³ Stimulation of platelet membrane glycoproteins by viruses induces CD4+ T cell-assisted B cell response, leading to the production of antibodies generally of the IgG type and against the GP IIb/IIIa receptor that target both viruses and

platelets. In addition, this molecular mimicry activates CD8+ T-cells, which directly causes platelet lysis.

Direct attack on megakaryocytes, and induction of apoptosis

Another possible mechanism for the development of ITP, such as that seen in HIV-associated thrombocytopenia, is the direct attack of the virus on megakaryocytes and the induction of apoptosis in them and reduced platelet production. The differentiation of the two mechanisms of platelet destruction or reduction due to the direct viral attack on the megakaryocyte can be predicted by measuring thrombopoietin level, which is the most important regulator of thrombopoiesis.^{24,25} A. Scaradavou evaluated the incidence of thrombocytopenia in HIV patients and monitored thrombopoietin levels, and found that the lower the plasma level of thrombopoietin, the more normal the mass of megakaryocytes in the bone marrow, and the predominant mechanism of ITP is platelet destruction, while the higher the level of thrombopoietin, the lower the mass of megakaryocytes and the predominant mechanisms are lower platelet production and bone failure.^{3,25}

NLRP3-inflammasome

The NOD-like receptor family pyrin domain-containing 3 (NLRP3)-inflammasome is a multiprotein complex with a key role in the detection of a variety of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The activation of the NLRP3-inflammasome results in an inflammatory cell death called pyroptosis, as well as the production of an active form of cytokines such as IL1beta and IL-18.^{26,27} Unlike the previous outlook, today one cannot imagine a boundary between innate and adaptive immune systems. In fact, one of the main tasks of the innate immune system is to regulate and shape adaptive immune system responses. Today, hyperactivity and dysregulation of inflammasome function, especially NLRP3-inflammasome, is recognized as a key mechanism in the immunopathogenesis of many inflammatory disorders such as neurodegenerative diseases, gout, and metabolic syndromes.²⁸

NLRP3-inflammasome and COVID-19

Based on extensive studies on beta-coronaviruses at the onset of COVID-19 outbreaks, cytokine storms occur significantly in COVID-19 patients due to NLRP3-inflammasome hyperactivity and dysregulation.^{29,30} A study by evaluating the effects of

inflammasome activation and pyroptosis in COVID-19 patients with lymphopenic liver reported that the inhibition of NLRP3-inflammasome and pyroptosis developed liver failure, thus highlighting their potential therapeutic targets in the treatment of COVID-19 patients.³¹ In a study, a single-cell mathematical model was developed to evaluate the pyroptosis caused by SARS-CoV-2 and the anti-inflammatory response to the drug Tranilast, the results of which showed a delay in the NLRP3-inflammasome formation via tranilast and thus a decrease in pyroptosis.³²

The inflammasome activation in the ITP

Studies have shown significant effects of NLRP3-inflammasome on the T-cell responses. A study clearly showed that the level of NLRP3 gene and protein expression in active ITP patients was significantly higher than that in healthy controls and ITP patients in remission. ASC and Caspase-1 as other major components of NLRP3-inflammasome also showed a higher expression in the active ITP group compared to the control group. NLRP3 and ASC expression had a significant correlation in the active ITP group, confirming the destructive role of NLRP3-inflammasome in the occurrence of ITP. Interestingly, the plasma IL-18 levels were higher in the active ITP patients compared with controls. On the other hand, this rate had returned to normal levels in the survived individuals. Overall, the findings of this study suggested that the NLRP3-inflammasome activation could be a potential mechanism in ITP immunopathogenesis.¹² A study reported an increase in NLRP3, NLRC4 and NLRP6-inflammasomes in patients with primary ITP.¹⁴ The association of increased HMGB1 as an early detection marker, especially in pediatric ITP, with NLRP3-inflammasome activation has been demonstrated.³³ In a study, the polymorphisms in a number of inflammation-related genes associated with ITP were examined. In addition to SNPs of genes associated with inflammation, the NLRP3 gene polymorphism was also studied. Although no significant association was observed in this study between most SNPs, the protective role of rs10499194 was reported in the ITP.³⁴ Another study showed that platelets regulate NLRP3-inflammasome activation and IL1-beta production in a variety of pathways, such as platelet-derived lipid mediators, purines, nucleic acids, and a large number of platelet-derived cytokines. Therefore, any abnormality in platelet count can be associated with NLRP3-inflammasome dysregulation.¹⁰ These studies are important due to the occurrence of

extensive cytopenia such as ITP in patients with COVID-19. Evidence of NLRP3-inflammasome hyperactivity and the occurrence of ITP in patients with COVID-19 and the results of previous studies underscore the need for further studies in this area in order to better understand the immunopathogenesis of COVID-19 and find more missing parts of the mysterious puzzle of this disease and eventually achieving more effective therapeutic interventions. One type of cell death is pyroptosis, which is caused by the activation of an inflammasome complex. Although the exact role of inflammasome involvement in the development of ITP is not fully understood, increased NLRP3-inflammasome expression in platelets and its associated inflammatory cytokines has been observed in patients with ITP and some other autoimmune diseases. Cell destruction by HIV and many other viruses is due to the activation of the inflammasome and the subsequent occurrence of pyroptosis.³⁵ Therefore, this protein complex could be one of the possible mechanisms of ITP development after viral infections such as SARS-CoV-2. In addition to establishing homeostasis in innate and acquired immune systems, the platelets play an active role in controlling infections and causing inflammatory reactions. In conditions such as sepsis, malaria, or infection with viruses such as HIV, the platelets have been shown to produce a chain of inflammatory responses by activating the inflammasomes (predominantly NLRP3 inflammasome).¹⁰ The platelet-secreted IL-1 β through the activation of IL-1R on endothelial cells causes the expression of VCAM-1 in endothelial cells and consequently increases their permeability and plasma leakage, which is primarily a defense reaction for the migration of neutrophils and immune cells, but the hyperactivity can lead to thrombocytopenia. The IL-18, also known as IFN- γ , is another important inflammatory cytokine; one of the effects of its overactivity is its increased proliferation and cytotoxic activity of CD8+ T-cells, which cause platelet or megakaryocyte lysis.²⁰ This cytokine can also change the Th1/Th2 ratio in favor of Th1. As previously stated in the pathogenesis of ITP, this imbalance is associated with autoreactive B cells and the secretion of autoantibodies. Therefore, the activation of inflammasome and related cytokines is necessary to control pathogens and as a protective effect, but their activity must be controlled and their overexpression leads to autoimmune complications. Studies to date have shown that SARS-CoV-2 is significantly able to activate the NLRP3-inflammasome^{29-31,36,37} and this may be a possible explanation for the occurrence of cytokine storm and Hyperinflammation in patients with COVID-19.

Management of ITP

The ITP management in patients with SARS-CoV-2 depends on the patient's underlying condition and the extent of platelet depletion. The first line of treatment for COVID-19-associated thrombocytopenia is the administration of intravenous immune globulin (IVIG, 1g/kg) combined with systemic corticosteroids such as prednisolone or dexamethasone.¹¹ To avoid the risk of secondary infection, it is best to keep the dose and duration of steroid treatment to a minimum and the taper should be started after a maximum of two weeks. More than 70% of patients respond well to first-line treatment, and a small percentage are resistant. The second-line treatment is the use of immunosuppressants such as rituximab or splenectomy. Thrombopoietin Receptor Agonists (TPO-RAs), such as Eltrombopag, provoke the platelet production by stimulating thrombopoietin (TPO) receptors on megakaryocytes, but they are prescribed only when the patient does not respond well to any of the first- and second-line treatments due to the risk of thrombosis and increased liver enzymes.¹⁵ As mentioned earlier, there is a risk of thrombosis in patients with COVID-19; therefore, the balance between thrombosis and bleeding must be considered to select the appropriate treatment option for ITP, and the platelet transfusion should be performed alone or simultaneously with other treatments only if there is severe and life-threatening bleeding in the patient.^{15,38}

Conclusion

COVID-19 and the ITP are two diseases with very complex immunopathogenesis, and the immune response dysregulation and dysfunction are the key factors in both. Despite extensive studies, the complex puzzle of immunopathogenesis of both diseases still has many missing pieces. To date, various SARS-CoV-2-associated hematological disorders have been observed and reported among the clinical symptoms of this infection, the most important of which is thrombocytopenia affecting more than one third of hospitalized patients. The ITP is different from other types of thrombocytopenia and occurs due to an increased rate of platelet depletion or decreased platelet production in the bone marrow following immune responses. Co-occurrence of COVID-19 and ITP at a time when nearly 40 million people around the world are affected and there is still no clear vision for the development of a definitive vaccine and drug could be an opportunity to gain an accurate understanding of how these diseases occur. Accordingly, a greater focus on the cause of ITP risk during COVID-19 not only

helps to better understand immunopathogenesis and the effective treatment of COVID-19, but also provides a new perspective on the causes of ITP, especially in other inflammatory disorders similar to COVID-19. Unregulated immune responses, especially by T lymphocytes, are of the main mechanisms involved in the development of ITP. Reviewing and interpreting previous studies, we suggest that the pathological effects of NLRP3-inflammasome hyperactivity, such as Hyperinflammation through overproduction of interleukin-1 β and IL-18, pyroptosis, increased Th17 level and the destructive role of IL-17 and generally immune dysregulation, may be a justification for severe thrombocytopenia and lymphopenia in COVID-19 patients. More detailed studies, on the one hand, and a greater focus on the common denominators of ITP and COVID-19 immunopathogenesis and other severe inflammatory disorders, on the other hand, could establish a new approach to ITP treatment in the future.

Abbreviations

- Immune thrombocytopenia purpura (ITP)
- Severe acute respiratory syndrome coronavirus (SARS-CoV-2)
- Coronavirus disease 2019 (COVID-19)
- Pathogen-associated molecular patterns (PAMPs)
- Damage-associated molecular patterns (DAMPs)
- NOD-like receptor family pyrin domain-containing 3 (NLRP3)

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