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Invited Review

Thrombocytopenia in Patients with Systemic Lupus Erythematosus

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Abstract

Thrombocytopenia can be one of the first manifestations of systemic lupus erythematosus and occurs in up to 40% of patients. Additionally, approximately 2% of patients with primary immune thrombocytopenia may develop systemic lupus erythematosus. Systemic lupus erythematosus is a highly heterogeneous disease, and in some patients, it may present mainly with hematological findings. Thrombocytopenia associated with systemic lupus erythematosus is also diverse, ranging from asymptomatic to severe, acute, or chronic cases. Several studies suggest that the coexistence of immune thrombocytopenia and systemic lupus erythematosus may be linked to a shared genetic background among various autoimmune diseases. Studies have reported correlations between thrombocytopenia and increased disease activity as well as kidney and central nervous system involvement in systemic lupus erythematosus. Severe thrombocytopenia is considered a poor prognostic factor in systemic lupus erythematosus. Despite this knowledge, the exact cause of reduced platelet count in systemic lupus erythematosus remains relatively unknown. Mainly, an excess of platelet destruction and/or reduced production from megakaryocytes are considered the primary factors contributing to systemic lupus erythematosus-associated thrombocytopenia. Given the prognostic significance of thrombocytopenia, there is a possibility of a pathogenic mechanistic role of thrombocytopenia and platelets in systemic lupus erythematosus. In systemic lupus erythematosus, platelets are activated and play a role in promoting autoimmune and inflammatory responses by interacting with both the innate and adaptive immunity. There is no randomized clinical trial in the treatment of systemic lupus erythematosus-related thrombocytopenia. Treatment approach of thrombocytopenia in lupus is almost similar to the treatment of immune thrombocytopenia. Considering the role of platelets in both inflammation and tissue injury, platelet activation and platelet–immune cell interaction might be important therapeutic strategies in the treatment of systemic lupus erythematosus.

Keywords: Systemic lupus erythematosus, thrombocytopenia, platelets

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects multiple systems in the body, and it predominantly affects women of childbearing age.[1] The prevalence of SLE is observed to be rising due to improved recognition and enhanced survival rates.[2] It is noteworthy that SLE is more prevalent in minority populations in the USA, and these individuals often experience more severe disease course.[3] Despite significant improvements in survival rates, SLE remains one of the leading causes of mortality among young females, as reported by the Centers for Disease Control and Prevention (CDC).[4]

Systemic lupus erythematosus is a highly heterogeneous disease, with some patients experiencing only mild symptoms, while others presenting with significant organ involvement.[5] Life-threatening manifestations of SLE often include lupus nephritis, central nervous system (CNS) involvement, and hematological disorders such as severe thrombocytopenia and hemolytic anemia.[4] Thrombocytopenia associated with SLE also exhibits a wide range of presentations, including acute, severe, chronic, or even asymptomatic cases.[1] Immune thrombocytopenia is a distinct hematological manifestation of lupus and is included in the hematological classification criteria.[6] In this review article, we aimed to evaluate thrombocytopenia and associated factors in SLE.

Epidemiology of Thrombocytopenia

Thrombocytopenia is characterized by platelet counts below 100×10^9/L and can be observed in 10%-40% of SLE patients.[7,8] Severe thrombocytopenia affects approximately 3%-20% of individuals with SLE and is often associated with a chronic disease course.[9] Thrombocytopenia can present as an initial clinical

finding in approximately 5%-16% of patients with SLE.[10] According to a recent meta-analysis, SLE can develop in nearly 2% of patients with primary immune thrombocytopenia (ITP).[11] In primary ITP, female gender and positive antinuclear antibody (ANA) status are considered risk factors for the development of future lupus.[11]

It has been suggested that ANA-positive primary ITP patients should be regarded as a distinct clinical entity.[12] Immune thrombocytopenia, being a prototypic organ-specific autoimmune disease, shares etiopathogenic mechanisms reminiscent of systemic autoimmune diseases such as SLE.[6] Several studies have proposed that the coexistence of ITP and SLE may be attributed to a shared genetic background among various autoimmune diseases.[13] Additionally, some studies suggest that certain patients with SLE may represent incomplete forms of the disease, with ITP being a "blood-dominant" form of SLE.[14] Non-rheumatologist physicians may overlook lupus-related symptoms that do not develop concurrently with thrombocytopenia. Therefore, lupus specialists recommend evaluating SLE serology and antiphospholipid (APS) antibodies in all primary ITP patients and considering hydroxychloroquine treatment if positive ANA or other features suggestive of SLE are present but do not meet the complete classification criteria.[6] Although SLE and ITP share some common genetic background, it remains unclear whether their molecular signatures are similar or distinct.

Multiple studies have reported correlations between thrombocytopenia and increased disease activity, disease severity, as well as kidney and CNS involvement in SLE.[15] Furthermore, severe thrombocytopenia is recognized as a poor prognostic factor in SLE and is associated with a higher mortality rate.[10] A particular study focused on thrombocytopenia in lupus and discovered that it is not directly linked to end-organ damage and mortality. However, it identified a subgroup of patients with higher comorbidity, suggesting that thrombocytopenia should be considered a reliable prognostic marker, indicating a subset of patients whose disease course may be worsened by end-organ damage.[16]

Main Points

- Immune thrombocytopenia can be a first presenting finding of systemic lupus erythematosus (SLE).
- Severe thrombocytopenia is a poor prognostic factor in patients with SLE.
- Major contributing factors for SLE-associated thrombocytopenia are increased platelet destruction and decreased production from megakaryocytes.
- Platelets are activated in SLE, and they interact with other immune cells and play a role in the pathogenesis of lupus.
- There are no randomized controlled trials in the treatment of SLE-associated thrombocytopenia.

Pathogenesis of Thrombocytopenia in Systemic Lupus Erythematosus

While the prognostic value of thrombocytopenia and its correlation with disease activity in SLE are recognized, the exact cause of reduced platelet count in SLE remains largely unknown.[10] Excessive platelet destruction and/or reduced production from megakaryocytes are considered major factors contributing to SLE-associated thrombocytopenia.[17] Elevated levels of antiplatelet antibodies and/or APS antibodies are often detected in SLE patients with thrombocytopenia.[15,17] However, it is worth noting that many SLE patients without thrombocytopenia may also have these autoantibodies.[10,15] An association between antiplatelet antibodies and SLE disease activity has been observed in SLE patients without thrombocytopenia.[18] In contrast to ITP, where platelet glycoproteins are specific antigenic targets for antiplatelet antibodies, the exact antigens involved in SLE-associated thrombocytopenia are less well defined.[15] To date, no study has investigated the specific antigenic targets of antiplatelet antibodies in SLE patients. A recent study conducted in a lupus mouse model demonstrated that immune complexes (ICs) and platelets are sequestered in certain vascular beds, particularly in the lung and brain microvasculature, suggesting that platelet sequestration may contribute to thrombocytopenia in SLE.[19] CD8+ T cells also participate in platelet destruction and can inhibit platelet production.[17] Other potential causes of thrombocytopenia in SLE include APS antibodies and certain medications.[16]

Pathogenesis of Systemic Lupus Erythematosus

Considering the prognostic role of thrombocytopenia and its association with disease severity, there is a possibility of thrombocytopenia and platelets playing a mechanistic role in the pathogenesis of SLE.[17] Thrombocytopenia in SLE is thought to involve multiple and overlapping pathogenic mechanisms. When examining the pathogenesis of SLE, the loss of immune tolerance and the production of pathogenic autoantibodies are key events.[1,2] The development of SLE involves interactions between genes, environmental factors, and female hormones with the innate and adaptive immune system. Environmental exposures, such as ultraviolet light, infections, and chemicals, can increase the rate of apoptosis.[1,16] Normally, the immune system cannot get access to nuclear antigens due to effective and rapid clearance mechanisms. However, increased rates of apoptosis and defective clearance can lead to the presence of abundant nucleic acid-containing autoantigens. Neutrophil apoptosis, particularly neutrophil extracellular trap (NET) formation, contributes to the increased load of apoptotic cells. The persistence of these autoantigens can activate nucleic acid recognition receptors, such as Toll-like receptors (TLRs), triggering an inflammatory response.[5] The innate immune response, especially type I interferon (IFN) production, is strongly associated with the activation of nucleic acid recognition receptors.[1,5] Type I IFN response and other inflammatory cytokines interact with the adaptive immune response, contributing to the loss of immune tolerance.[2]

Abnormalities in the adaptive immune system have long been recognized in lupus. T cells play a role in providing help for the differentiation of autoreactive B cells and the production of autoantibodies.[1,5] Autoreactive B cells can respond to nucleic acids, leading to the development of high-affinity, somatically mutated pathogenic autoantibodies. These autoantibodies, along with ICs, can enter tissues and cause IC deposition and tissue damage. These events may lead to chronic inflammation and irreversible end-organ damage.

Platelets and Pathogenesis of Systemic Lupus Erythematosus

Platelets are small subcellular fragments that circulate in the blood.[17] They are highly abundant in the bloodstream, representing the second largest cellular component after erythrocytes.[20] Despite their abundance, platelets have a relatively short life span of around 8-10 days, and our body produces nearly 100 billion platelets daily.[21] However, the majority of platelets do not participate in hemostatic processes and are eliminated by the reticuloendothelial system.[22] While the primary function of platelets is to prevent bleeding, recent research supports their role in modulating immune responses and inflammation.[17] Platelets have the capacity to synthesize various molecules that can influence both adaptive and innate immune responses. Additionally, upon activation, platelets release their contents and

engage in interactions with other immune cells. Molecules released by platelets, such as CD40 ligand, interleukin-1 (IL-1), serotonin, and danger-associated molecular patterns, actively contribute to the pathogenesis of SLE.[15]

Platelet activation in Systemic Lupus Erythematosus

In SLE, platelets are activated by ICs through the Fc receptor FcRIIA.[15,17] Additionally, C1q accentuates platelet activation by ICs. The complement system also plays a role in IC clearance, and there is a balance between complement-mediated IC clearance and platelet activation. Antiphospholipid antibodies contribute to platelet activation in SLE by promoting C4d deposition and complement activation on platelets. Various TLRs can also activate platelets in SLE. These activated platelets actively participate in the pathogenesis of SLE.[17,18] Activated SLE platelets promote the upregulation of endothelial ICAM1 and chemokines through the production of IL-1B. This leads to the activation of endothelial cells (ECs), which express E-selectin, VCAM1, and ICAM1, promoting platelet adhesion. Activated platelets also interact with leukocytes, and elevated levels of circulating platelet–leukocyte aggregates are detected in SLE patients.[15] Furthermore, platelet CD40L activates ECs and stimulates the adaptive immune system by supporting T cell-mediated B cell responses, including antibody production.[18] Platelet-derived microparticles containing cytokines, microRNA, and mRNA can contribute to the autoantigenic load in the circulation and have been associated with lupus activity.[15] Platelets release mitochondria and mitochondrial DNA, which induce neutrophil activation and the production of NETs and autoantigen release.[17,18] CD40L and soluble CD40L are expressed on activated platelets and stimulate B cell responses and the production of autoantibodies. Platelets can also shed membrane vesicles known as microparticles, which carry inflammatory mediators and disseminate mitochondrial antigens for the formation of ICs. Additionally, several platelet-produced mediators, such as S100A8/A9 proteins, serotonin, soluble CD40L, and HMGB1, have been associated with SLE pathogenesis.[15,17] Apart from APS antibodies, the ligation of FcGRIIA and increased complement deposition on platelets may also be associated with an increased risk of thrombosis in SLE.[15,18]

Platelets play a significant role in promoting autoimmune and inflammatory responses by interacting with both the innate and adaptive immune systems. They also contribute to the pathogenesis of organ damage in SLE.[17] In an experimental autoimmune encephalomyelitis mouse model, platelets have been found to be involved in the recruitment of inflammatory cells to the CNS. Depletion of platelets prevented the invasion of T cells and subsequent CNS damage. Additionally, in the microcirculation of the kidneys, activated platelets can potentially cause thrombus formation and contribute to kidney damage in SLE.[15] An intriguing study explored the role of platelets in the resolution of inflammation. The findings indicated that platelets contribute to the resolution of inflammation by directly recruiting T regulatory cells to the inflamed area and by transcriptionally reprogramming alveolar macrophages toward an anti-inflammatory phenotype. While platelets may potentially play a role in the resolution of SLE-related inflammation within tissues, no study has specifically evaluated this aspect thus far.[20,23]

Treatment of Thrombocytopenia in Systemic Lupus Erythematosus

Primary ITP and SLE-associated thrombocytopenia are typically treated initially with similar medications. Steroids, immunosuppressive drugs, intravenous immunoglobulin, and rituximab are commonly used as mainstay therapies for thrombocytopenia in SLE.[6] However, treatment strategies specifically for SLE-related thrombocytopenia are primarily based on small case series and studies focusing on other organ involvement. To date, there have been no randomized clinical trials specifically addressing the treatment of SLE-related thrombocytopenia.

Considering the role of platelets in both inflammation and tissue injury, targeting platelet activation and platelet–immune cell interactions may represent important therapeutic strategies in the treatment of SLE.[15,24] Some small studies targeting platelet activation have shown promising results in SLE.[15] Targeting platelets therapeutically may be a useful approach to prevent the development and propagation of inflammation-mediated organ damage in SLE.

Conclusion

Platelets not only play an active role in primary hemostasis but also contribute to the pathogenesis of SLE. Studies have demonstrated that platelets are activated in lupus and actively interact with the innate and adaptive immune systems.[15,17] Thrombocytopenia in SLE has been found to correlate with disease activity, major organ involvement, and poor prognosis, indicating a potential role in the pathogenesis of SLE. Despite several possible mechanisms, the exact cause of thrombocytopenia in lupus remains unknown. Population-based studies have revealed a close relationship between ITP and SLE. This association may be attributed to a shared common genetic background or the possibility that ANA-positive ITP represents an incomplete presentation of a "blood-dominant" form of lupus.[6] While many SLE cohort studies have examined the prognostic role of various clinical findings, including thrombocytopenia, limited studies have specifically focused on thrombocytopenia alone. Thrombocytopenia associated with SLE is managed using similar medications as those used for other systemic manifestations of lupus.[6] However, there is currently a lack of controlled studies specifically focused on the treatment of lupus-related thrombocytopenia. Considering the data that support the role of platelets in promoting inflammation and tissue injury in SLE, alternative treatment approaches targeting platelets have shown promise. Preclinical and clinical studies have demonstrated that therapies aimed at targeting activated platelets and modulating platelet–immune cell interactions may hold potential for the management of thrombocytopenia in SLE.

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