

Role of Platelet Activation Factor in Patients with Hypersensitive Vasculitis, Autoimmune and Allergic Urticaria

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Abstract. Cutaneous syndrome is a relevant issue not only among allergic diseases but also among autoimmune disorders. Urticaria is a widespread problem, as its prevalence among the population can reach up to 9%. The main goal of the article is to analyze the role of platelet-activating factor in patients with hypersensitive vasculitis, autoimmune, and allergic urticaria. Urticarial rash is at the intersection of allergic and autoimmune diseases, where is observed active immunopathogenetic influence of platelet-activating factor in the initiation and maintenance of systemic vasculitis, including hypersensitive/urticarial and cryoglobulinemic vasculitis Considering the significant role of

this factor in the pathogenesis of hypersensitive vasculitis and allergic reactions, selective targeting of platelet-activating factor represents a promising therapeutic approach. These include platelet-activating factor receptor antagonists such as rupatadine and apafant, as well as platelet-activating factor acetylhydrolase inhibitors, enzymes responsible for platelet-activating factor degradation. Targeted intervention on platelet-activating factor holds promise for the improving the quality of life of patients with hypersensitive vasculitis, autoimmune disorders, and allergic urticaria.

Keywords: platelet activation factor, hypersensitive vasculitis, urticaria.

Introduction. Currently, cutaneous syndrome is a relevant issue not only among allergic diseases but also among autoimmune disorders. Urticaria, commonly known as hives, is a widespread problem, as its prevalence among the population can reach up to 9% [1].

After reviewing a considerable amount of contemporary scientific literature, including the results of multicenter studies [2], our attention was drawn to one of the potent phospholipid mediators involved in various physiological and pathological processes, including inflammation, immune reactions, and allergic responses in the human body – platelet-activating factor.

The purpose of the study was to analyze the role of platelet-activating factor in patients with hypersensitive vasculitis, autoimmune, and allergic urticaria.

Materials and methods. Analysis and synthesis of the existing body of research and review articles regarding the significance of platelet activation factor in the immunopathogenesis of hypersensitive vasculitis, autoimmune, and allergic urticaria.

The research of the article is a fragment of research works of the Department of clinical immunology and allergology at Lviv National Medical University named after Danylo Halytskyi on the topic "Post-COVID syndrome and Post-traumatic stress disorder: immune dysregulation and patient management tactics (state registration number 118U00010, implementation period 2023-2027).

Results and discussion. Platelet-activating factor was initially described by Jacques Benveniste in 1974 as a mediator secreted by IgE-mediated basophils capable of inducing platelet aggregation. Platelet-activating factor is a lipid mediator synthesized in two stages. Firstly, membrane phosphocholine is converted into lyso-platelet-activating factor by cytosolic phospholipase A2; subsequently, platelet-activating factor is synthesized from its precursor, lyso-platelet-activating factor, by acetyl-CoA lyso-platelet-activating factor acetyltransferase. Platelet-activating factor can be rapidly released (within 30 seconds) upon cell stimulation, but it is also produced in the late phase of allergic reactions. Platelet-activating factor has a short half-life (3-13 minutes), and its degradation is catalyzed by platelet-activating factor acetylhydrolase. Deficiency of platelet-activating factor acetylhydrolase has been associated with allergic diseases, and a correlation has been described between serum platelet-activating factor acetylhydrolase levels and the severity of anaphylaxis [3].

Platelet-activating factor is released by several types of cells, including mast cells, eosinophils, platelets, neutrophils, monocytes, basophils, epithelial, and endothelial cells. Platelet-activating factor actively participates in the immunopathogenesis of autoimmune processes, including rheumatoid arthritis, systemic lupus erythematosus, and systemic (including urticarial/hypersensitive) vasculitis. This factor significantly contributes to the dysregulation of the immune response by inducing the synthesis of pro-inflammatory cytokines and chemokines, sustaining the chronic inflammatory process. The mechanism of action of platelet-activating factor is complex due to the wide range of processes it mediates [3,4].

Overall, the mechanism of platelet-activating factor action involves receptor-mediated activation of intracellular signaling pathways, leading to a wide range of cellular responses that play a crucial role in inflammation, immune response, and vascular homeostasis. Dysregulation of platelet-activating factor signaling pathways may contribute to the pathogenesis of various inflammatory and vascular diseases, underscoring the importance of understanding the mechanism of platelet-activating factor action for therapeutic intervention [3,5].

The mechanism of development of urticaria is associated with inflammation and involvement of small blood vessels, particularly capillaries, which can be characterized as allergic capillaritis. The role of platelet-activating factor in this case is significant, as it contributes to the pathogenesis and clinical manifestations of this process [6].

Mast cells are an important source of platelet-activating factor in the case of allergic capillaritis. After contact with allergens or other triggering factors, mast cells release platelet-activating factor along with other inflammatory mediators such as histamine and cytokines. Platelet-activating factor, in turn, can further activate mast cells, creating a positive feedback loop that sustains and enhances the inflammatory response in the case of allergic capillaritis [7].

Among allergic diseases, a special place belongs to urticaria - a very common pathology that often requires personalized assistance. Urticaria is a pathological process characterized by the appearance of wheals (urticarial rash) and/or angioedema. Over the past 20 years, the incidence of the disease has tripled [1, 8].

Depending on the duration, urticaria is divided into two forms: acute urticaria and chronic urticaria. The prevalence of acute urticaria in the general population is about 15-20% of cases over a person's lifetime. Acute urticaria more often has allergic origins and is found in cases of atopy [9,10].

The prevalence of chronic urticaria, defined as episodic or daily episodes of urticarial rash lasting 6 weeks or more, is approximately 1.8% among the adult population. Additionally, chronic urticaria is observed in 0.1-0.3% of children. The presence of urticaria negatively affects the quality of life of affected individuals, causing prolonged interruptions in schooling and work. In 50% of those who have experienced this disease, its exacerbation may occur again even after a long remission. Women suffer from urticaria more often than men, and children suffer more often than adults [1].

It is believed that active symptoms of urticaria are primarily associated with the activation of mast cells in the skin. As for autoimmune urticaria, indirect evidence that chronic urticaria may have an autoimmune nature has existed for many years. Thus, as early as 1983, Leznof et al. established a connection between autoimmune thyroiditis and CC, and in 1989, the same authors identified a combined syndrome – autoimmune thyroid disease and chronic urticaria in 15% of patients [1, 7].

Autoimmune urticaria occurs as a result of a targeted pathological attack by the immune system on the body's own tissues, which is also accompanied by hyperproduction of pro-inflammatory cytokines, chemokines, and platelet-activating factor [3, 9, 10].

At the same time, allergic inflammation (including in urticaria) consists of two stages: early and late phase, during which mast cells are activated, and synthesis of pro- and anti-inflammatory cytokines occurs. One of such components synthesized in large quantities is platelet-activating factor, which belongs to humoral mediators of inflammation. Platelet-activating factor can induce the formation of wheals and itching even without histamine involvement, regardless of mast cell degranulation [4, 10].

Moreover, platelet-activating factor contributes to the recruitment of eosinophils and other immune cells to the site of allergic inflammation, further enhancing the allergic response.

It is also important to note the impact of platelet-activating factor on the vascular wall, which is significant and contributes importantly to various physiological and pathological processes. Previous findings have shown that pro-inflammatory agonists, including platelet-activating factor, contribute to increased permeability of the endothelial barrier [11].

Urticarial rash is at the intersection of allergic and autoimmune diseases, with an IgE-mediated mechanism underlying it. In addition, according to Western scientists, platelet-activating factor also plays a significant role in the initiation and maintenance of systemic vasculitis, including hypersensitive/urticarial and cryoglobulinemic vasculitis [11, 12].

It acts as a potent mediator of vascular permeability, leading to the extravasation of inflammatory cells into the vessel walls. Furthermore, platelet-activating factor promotes the expression of adhesion molecules on endothelial cells, facilitating the migration of leukocytes to the site of inflammation. These actions lead to tissue damage and clinical manifestations observed in hypersensitive and cryoglobulinemic vasculitis [11].

Therefore, the key pathways of the pathogenesis of cutaneous syndrome in patients with urticaria and urticarial vasculitis are today's and future therapeutic targets. Thus, inhibiting platelet-activating factor will have a positive effect on the clinical manifestations of these diseases, considering the main pathophysiological effects of platelet-activating factor: increasing vascular permeability; binding to platelet-activating factor receptors expressed on mast cells; increasing tissue sensitivity to histamine and bradykinin; increasing histamine synthesis; recruiting and activating granulocytes and monocytes.

Platelet-activating factor is a key mediator of inflammation associated with hypersensitive/urticarial vasculitis, autoimmune diseases, and allergic urticaria. Its multifaceted role in promoting vascular permeability, immune cell activation, and inflammatory mediator release underscores its significance in the immunopathogenesis of these pathological conditions.

Targeted intervention on platelet-activating factor holds promise for the development of new therapeutic interventions aimed at alleviating disease severity and improving the quality of life of patients with hypersensitive vasculitis, autoimmune disorders, and allergic urticaria. Further research is needed to investigate the mechanisms of action of second-generation antihistamines on platelet-activating factor and to assess the safety and efficacy of their use in clinical practice.

Conclusions. Considering the significant role of platelet-activating factor in the pathogenesis of hypersensitive vasculitis, autoimmune disorders, and allergic reactions, selective targeting of platelet-activating factor represents a promising therapeutic approach. Pharmacological agents that inhibit platelet-activating factor synthesis or block its receptors have shown efficacy in preclinical and clinical studies. These include platelet-activating factor receptor antagonists such as rupatadine and apafant, as well as platelet-activating factor acetylhydrolase inhibitors, enzymes responsible for platelet-activating factor degradation. By attenuating platelet-activating factor - mediated inflammation, these agents demonstrate potential advantages in reducing disease activity and improving clinical outcomes in patients with hypersensitive vasculitis, autoimmune disorders, and allergic urticaria.

Conflict of interest. The authors have approved the article for publication and declare that the research was conducted in the absence of any conflict or potential conflict of interest.

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