Autoimmune urticaria: Pathogenesis, diagnosis, and management.

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Introduction

Autoimmune urticaria (AIU) is a chronic and often debilitating skin condition characterized by recurrent hives that arise due to an underlying autoimmune mechanism. Unlike common allergic urticaria, AIU is driven by autoantibodies targeting self-proteins involved in mast cell activation, leading to persistent inflammation and histamine release. This condition often overlaps with chronic spontaneous urticaria (CSU) and presents diagnostic and therapeutic challenges. Understanding its pathogenesis, diagnostic methods, and management strategies is crucial for improving patient outcomes [1].

AIU is primarily driven by autoantibodies, particularly immunoglobulin G (IgG) autoantibodies, that target high-affinity IgE receptors (FcεRI) on mast cells and basophils. These autoantibodies can directly trigger mast cell degranulation, leading to the release of histamine and other inflammatory mediators responsible for the development of hives. Another subset of AIU patients produces IgG autoantibodies against IgE itself, further amplifying immune activation. The presence of these autoantibodies distinguishes AIU from histamine-induced allergic reactions, which rely on external allergens rather than self-reactivity [2].

Furthermore, AIU has been linked to other autoimmune diseases, such as thyroid disorders (e.g., Hashimoto's thyroiditis and Graves' disease), systemic lupus erythematosus, and rheumatoid arthritis. This association suggests that dysregulated immune tolerance plays a crucial role in its development. Additionally, complement system activation has been implicated in AIU pathogenesis, further exacerbating mast cell activation and inflammation [3].

Patients with AIU experience recurrent episodes of urticaria lasting more than six weeks, often accompanied by angioedema. Unlike allergic urticaria, AIU hives are not triggered by external allergens but arise spontaneously. The lesions are typically raised, erythematous, and pruritic, appearing on different body areas without a consistent pattern. Some patients may experience burning sensations, indicating deeper inflammatory involvement [4].

A key clinical feature of AIU is its resistance to conventional antihistamines, as autoantibody-mediated mast cell activation is not easily suppressed by histamine blockade alone. Additionally, patients may report systemic symptoms such as fatigue, joint pain, and other autoimmune manifestations, especially when AIU coexists with systemic autoimmune diseases [5].

The diagnosis of AIU involves a combination of clinical evaluation, laboratory testing, and response to therapy. Standard blood tests, including complete blood count (CBC) and C-reactive protein (CRP), may indicate systemic inflammation, but they are not specific for AIU. More definitive diagnostic approaches include the autologous serum skin test (ASST) and the basophil activation test (BAT) [6].

The ASST involves injecting a patient's own serum intradermally and observing for a wheal-and-flare reaction, which suggests the presence of autoantibodies against mast cell or basophil receptors. The BAT measures basophil activation markers (e.g., CD63 and CD203c) in response to patient serum, providing further evidence of autoantibody involvement. Additionally, testing for thyroid autoantibodies and complement levels may help identify underlying autoimmune associations [7].

Effective management of AIU requires a stepwise approach that targets both symptom relief and immune modulation. First-line therapy consists of non-sedating H1-antihistamines, but in AIU, these drugs often provide incomplete relief due to the autoantibody-driven nature of the disease. When antihistamines fail, second-line treatments such as omalizumab, a monoclonal anti-IgE antibody, are considered [8].

The advent of biologic therapies has revolutionized AIU treatment. In addition to omalizumab, other targeted biologics, such as dupilumab (an anti-IL-4Rα monoclonal antibody) and rituximab (an anti-CD20 B-cell depleting agent), are being explored. These agents modulate immune responses by either reducing mast cell activation or directly targeting autoantibody-producing B cells. Clinical trials are ongoing to establish their efficacy and safety in AIU management [9].

In addition to pharmacological interventions, lifestyle modifications play a supportive role in AIU management. Identifying and avoiding potential exacerbating factors, such as stress, infections, and certain foods, may help reduce flare-ups. Some patients benefit from dietary changes, including low-histamine diets, although evidence supporting their effectiveness is limited [10].

Conclusion

Autoimmune urticaria is a complex condition driven by autoantibody-mediated mast cell activation, leading to chronic hives and angioedema. Its diagnosis requires specialized testing, such as the ASST and BAT, to confirm an

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autoimmune mechanism. Management involves a combination of antihistamines, biologic therapies like omalizumab, and immunosuppressants for severe cases. While AIU can be challenging to treat, emerging biologics and targeted immunotherapies offer hope for better disease control. Ongoing research is crucial to refine treatment approaches and improve patient outcomes in this autoimmune-driven dermatologic condition.

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