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DIAGNOSTIC DIFFERENTIATION AND MANAGEMENT OF URTICARIA-LIKE SYNDROMES: A PATHWAY-BASED APPROACH

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Abstract: Urticaria is a heterogeneous disorder characterized by transient wheals and/or angioedema, resulting from complex pathophysiological mechanisms (EAACI, 2021; Matos et al., 2022). Based on pathogenesis, urticaria can be broadly classified into mast cell–mediated and non–mast cell–mediated forms (Schettini et al., 2023). Chronic spontaneous urticaria (CSU) represents an autoimmune or idiopathic mast cell–driven process, while inducible urticarias arise from physical triggers such as pressure, cold, or heat, leading to mast cell activation (EAACI, 2021). Urticarial vasculitis (UV) is an immune complex–mediated condition, with vascular inflammation and possible systemic involvement (Krause et al., 2023). Other forms include drug-induced and autoinflammatory urticaria, which involve distinct immunological pathways, including IgE- or complement-mediated mechanisms (Matos et al., 2022; Schettini et al., 2023). Accurate classification according to pathogenesis is critical for guiding diagnostic evaluation, laboratory testing, and targeted therapy (EAACI, 2021). Integrating recent evidence and international guidelines, this review provides a comprehensive overview of urticaria subtypes, emphasizing their underlying mechanisms, clinical features, and implications for management (EAACI, 2021; Krause et al., 2023).

Introduction

Urticaria is a common dermatological disorder characterized by transient, pruritic wheals and/or angioedema, affecting up to 20% of individuals at least once in their lifetime (Schettini et al., 2023). Although most cases are self-limiting, urticarial lesions can significantly impair quality of life due to persistent itching, sleep disturbance, and psychosocial impact (EAACI, 2021). Clinically, urticaria is often categorized by duration: acute (<6 weeks) and chronic (≥6 weeks), with chronic urticaria further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (EAACI, 2021).

The pathogenesis of urticaria is heterogeneous. Mast cell–mediated mechanisms are central to most forms, including CSU and inducible urticarias, where degranulation of mast cells releases histamine, cytokines, and other inflammatory mediators, leading to increased vascular permeability and wheal formation (Matos et al., 2022). In contrast, urticarial vasculitis (UV) is primarily immune complex–mediated, involving activation of complement pathways and vascular inflammation, which can result in lesions lasting more than 24 hours and leaving residual hyperpigmentation or purpura (Krause et al., 2023). Other rarer subtypes, such as drug-induced urticaria and autoinflammatory urticaria, involve distinct immunological pathways, including IgE-mediated hypersensitivity and innate immune dysregulation (Schettini et al., 2023; Matos et al., 2022).

Accurate classification of urticaria according to underlying pathogenesis is critical. It informs clinical evaluation, guides laboratory testing—including complement levels, autoantibodies, and histopathology—and directs therapy ranging from second-generation H1-antihistamines to biologics or immunosuppressive agents in refractory or systemic cases (EAACI, 2021; Krause et

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al., 2023). Despite advances, misdiagnosis remains common, as multiple conditions can mimic urticaria, highlighting the need for careful differential diagnosis and standardized clinical algorithms (Matos et al., 2022).

This review aims to integrate recent literature and international guideline recommendations to provide a comprehensive overview of urticaria subtypes, emphasizing pathogenesis-based classification, diagnostic evaluation, and implications for clinical management (EAACI, 2021; Schettini et al., 2023).

Clinical Features of Conditions Mimicking Urticaria

Conditions that can mimic urticaria are increasingly recognized as part of diverse pathophysiological pathways, each with characteristic clinical features and associated disorders (Matos et al., 2022).

Autoinflammatory Urticarial Syndromes (AUS) are driven by dysregulation of the interleukin-1 (IL-1) pathway and hyperactivation of the inflammasome, leading to neutrophilic infiltration of the skin and systemic inflammation (Schettini et al., 2023). Clinically, AUS presents with slightly itchy or non-pruritic wheals, typically lasting 24–48 hours, often symmetrically distributed on the trunk and extremities. Systemic symptoms such as fever, fatigue, and arthralgia are common. Examples of AUS include neutrophilic urticarial dermatosis (NUD), which manifests as recurrent erythematous macules and papules with dermal neutrophilic infiltrates; cryopyrin-associated periodic syndromes (CAPS), encompassing familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular syndrome (CINCA/NOMID); Schnitzler's syndrome, characterized by urticarial rash, recurrent fever, and monoclonal IgM gammopathy; adult-onset Still's disease (AOSD), presenting with salmon-pink rash and arthralgia; systemic-onset juvenile idiopathic arthritis (SoJIA), with fever and pink macular eruptions; mevalonate kinase deficiency (MKD/HIDS), which includes recurrent fever, maculopapular rash, and lymphadenopathy; and TNF-receptor-associated periodic syndrome (TRAPS), featuring migrating erythema, urticarial plaques, and abdominal or chest pain (Matos et al., 2022; Schettini et al., 2023).

Immune-Mediated Conditions are caused by dysregulated adaptive immune responses, often associated with lymphocytic infiltration or immune-complex deposition (Krause et al., 2023). Lesions usually persist for more than 24 hours and may present with papules, plaques, or eczematous changes. Systemic involvement can also occur. Representative conditions include urticarial dermatitis (UD), which presents with itchy wheals and eczematous patches; urticarial vasculitis (UV), characterized by painful or burning wheals, residual hyperpigmentation, and leukocytoclastic vasculitis; and cutaneous lupus erythematosus (CLE), presenting as malar rash, annular or papulosquamous lesions, and photosensitivity (Krause et al., 2023; Matos et al., 2022).

Autoimmune Disorders involve autoantibody-mediated tissue injury or T-cell dysregulation, often resulting in intensely pruritic lesions (Schettini et al., 2023). Vesicles or bullae may develop on an urticarial base, and systemic features are sometimes observed. Notable examples include bullous pemphigoid (BP), with tense bullae on an erythematous base; pemphigoid gestationis (PG), which is pregnancy-specific; dermatitis herpetiformis (DH), a gluten-related eruption of papulovesicular lesions on extensor surfaces; and autoimmune progesterone

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dermatitis (APD), with cyclical urticaria-like eruptions during the luteal phase (Matos et al., 2022; Schettini et al., 2023).

Hyperproliferative Diseases arise from clonal proliferation or overactivation of immune cells, such as mast cells, resulting in chronic skin lesions (Krause et al., 2023). These present as persistent or recurrent papules and macules, sometimes pigmented, with Darier's sign often positive. Mastocytosis, both cutaneous and systemic, demonstrates maculopapular lesions and, in systemic forms, multi-organ involvement. Hypereosinophilic syndrome (HES) can also present with pruritic erythematous papules or plaques, with potential organ damage (Matos et al., 2022).

Drug-Related Eruptions are triggered by either immunologic (IgE-mediated) or non-immunologic mechanisms (direct histamine release) (Schettini et al., 2023). Clinical features include maculopapular rashes or urticarial wheals, symmetrical distribution, mild fever, and pruritus. Fixed drug eruption (FDE) presents as well-demarcated, dusky-red patches recurring at the same site upon re-exposure (Matos et al., 2022).

Other Inflammatory Conditions are characterized by eosinophilic or neutrophilic infiltration due to immune dysregulation (Krause et al., 2023). Edematous plaques, often associated with burning or tenderness, can mimic urticaria initially but evolve differently. Examples include Wells syndrome (eosinophilic cellulitis), presenting with erythematous, edematous plaques and eosinophilic dermal infiltrates; Sweet syndrome (acute febrile neutrophilic dermatosis), with painful red papules or plaques and fever; and polymorphic eruption of pregnancy (PEP or PUPPP), which manifests as pruritic erythematous papules and plaques in the third trimester, often within striae (Schettini et al., 2023; Matos et al., 2022).

Diagnostic Differentiation of Conditions Mimicking Urticaria

While clinical features provide initial guidance, precise diagnosis requires targeted investigations, as several disorders can present with urticaria-like lesions (EAACI, 2021; Matos et al., 2022). Diagnostic differentiation is typically organized according to underlying pathophysiological pathways.

Autoinflammatory Urticarial Syndromes (AUS) are primarily differentiated by laboratory markers of systemic inflammation and genetic testing (Schettini et al., 2023). Common laboratory findings include elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA). Genetic testing can confirm mutations in genes such as NLRP3 (CAPS), MEFV (familial Mediterranean fever), or MVK (mevalonate kinase deficiency) (Matos et al., 2022). Skin biopsy demonstrates neutrophilic dermal infiltrates without evidence of vasculitis. Additional supportive tests may include serum IL-1 levels or therapeutic response to IL-1 inhibitors, which can be both diagnostic and therapeutic (Schettini et al., 2023).

Immune-Mediated Conditions are differentiated by histopathology and immunologic markers (Krause et al., 2023). Urticarial vasculitis (UV) shows leukocytoclastic vasculitis on skin biopsy, with fibrinoid necrosis of vessel walls and perivascular neutrophilic infiltrates; hypocomplementemic UV is associated with low serum C3 and C4. Cutaneous lupus erythematosus (CLE) requires direct immunofluorescence showing granular deposition of IgG, IgM, or C3 along the dermoepidermal junction ("lupus band"), alongside antinuclear antibody

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(ANA) positivity. Urticarial dermatitis (UD) demonstrates spongiosis and superficial perivascular lymphocytic infiltrates on histopathology without vasculitis (Matos et al., 2022; Krause et al., 2023).

Autoimmune Disorders are differentiated by autoantibody profiles and histopathology (Schettini et al., 2023). Bullous pemphigoid (BP) shows subepidermal blisters with eosinophilic infiltrates; direct immunofluorescence reveals linear IgG and C3 deposition along the basement membrane. Pemphigoid gestationis (PG) is diagnosed similarly, in the context of pregnancy, and dermatitis herpetiformis (DH) shows granular IgA deposits at the dermal papillae, with gluten sensitivity confirmed by serology for anti-tTG or anti-endomysial antibodies. Autoimmune progesterone dermatitis (APD) is differentiated clinically by cyclical recurrence, sometimes confirmed via intradermal progesterone testing (Matos et al., 2022).

Hyperproliferative Diseases rely on histopathology, bone marrow evaluation, and serum markers (Krause et al., 2023). Mastocytosis shows dermal infiltration of mast cells, often highlighted by Giemsa or toluidine blue staining, with elevated serum tryptase supporting systemic involvement. Hypereosinophilic syndrome (HES) requires sustained eosinophilia (>1.5 × 10^9/L for >6 months) and exclusion of secondary causes; tissue biopsies reveal eosinophilic infiltration in affected organs (Matos et al., 2022).

Drug-Related Eruptions are primarily differentiated by detailed history and, when necessary, drug challenge or patch testing (Schettini et al., 2023). Fixed drug eruptions (FDE) are identified by recurrent lesions at the same site after drug exposure; histology shows necrotic keratinocytes, pigment incontinence, and lymphocytic infiltrates (Matos et al., 2022).

Other Inflammatory Conditions are distinguished by specific histopathologic patterns and systemic involvement (Krause et al., 2023). Wells syndrome (eosinophilic cellulitis) demonstrates “flame figures” composed of eosinophil granule deposition in the dermis. Sweet syndrome (acute febrile neutrophilic dermatosis) shows dense dermal neutrophilic infiltrates without vasculitis and is associated with fever and leukocytosis. Polymorphic eruption of pregnancy (PEP) is primarily diagnosed clinically, supported by histology showing superficial perivascular lymphocytic infiltrate with edema, and occurs in the third trimester without systemic involvement (Matos et al., 2022; Schettini et al., 2023).

Treatment Approach According to Differential Diagnosis

Effective management of urticaria-like conditions requires a stepwise approach, addressing both symptoms and the underlying pathophysiology (EAACI, 2021; Matos et al., 2022). Treatment strategies differ depending on whether the condition is autoinflammatory, immune-mediated, autoimmune, hyperproliferative, drug-related, or another inflammatory disorder (Schettini et al., 2023).

In autoinflammatory urticarial syndromes, such as CAPS, the primary goal is to control systemic inflammation and prevent organ damage. IL-1 inhibitors, including anakinra and canakinumab, are often the first-line therapy, while NSAIDs or colchicine may be used for milder manifestations. Regular laboratory monitoring of CRP, ESR, and serum amyloid A helps track inflammatory activity (Matos et al., 2022; Schettini et al., 2023).

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In immune-mediated conditions like urticarial vasculitis, mild cases can be managed with NSAIDs, antihistamines, or short courses of corticosteroids, whereas severe or hypocomplementemic disease may require systemic corticosteroids, immunosuppressants such as azathioprine or mycophenolate mofetil, or biologics like rituximab in refractory cases (Krause et al., 2023). Cutaneous lupus erythematosus is treated with topical corticosteroids or calcineurin inhibitors for localized lesions, systemic hydroxychloroquine for widespread disease, and immunosuppressants if needed (Matos et al., 2022).

Autoimmune disorders such as bullous pemphigoid and pemphigoid gestationis are managed primarily with systemic corticosteroids, with adjunctive therapy including topical steroids or immunosuppressants for chronic or refractory disease (Schettini et al., 2023). Dermatitis herpetiformis requires a lifelong gluten-free diet and symptomatic control with dapsone, while autoimmune progesterone dermatitis may respond to antihistamines for acute flares and hormonal modulation to suppress cyclical symptoms (Matos et al., 2022).

Hyperproliferative diseases, including mastocytosis, are treated mainly for symptom control with H1 and H2 antihistamines, while epinephrine is indicated for patients at risk of anaphylaxis and cytoreductive therapy for systemic disease with organ involvement (Krause et al., 2023). Hypereosinophilic syndrome is initially managed with corticosteroids, with targeted therapy such as mepolizumab for eosinophil-driven disease, and ongoing monitoring for organ involvement (Matos et al., 2022).

Drug-related eruptions require immediate cessation of the offending agent, symptomatic relief with antihistamines and topical corticosteroids, and systemic corticosteroids in severe or bullous reactions (Schettini et al., 2023). Prevention involves patient education and documentation of culprit drugs, with patch testing if necessary (Matos et al., 2022).

Other inflammatory conditions, such as Wells syndrome, respond to topical or systemic corticosteroids, while Sweet syndrome requires systemic corticosteroids and immunosuppressants in refractory cases (Krause et al., 2023). Polymorphic eruption of pregnancy is managed symptomatically with topical corticosteroids and antihistamines, typically resolving postpartum (Schettini et al., 2023). Across all urticaria-like conditions, treatment should prioritize targeting the underlying mechanism, with antihistamines providing adjunctive symptom relief. Monitoring for systemic involvement is essential in autoinflammatory, hyperproliferative, and autoimmune diseases, and interdisciplinary collaboration with dermatology, rheumatology, or hematology is often necessary for complex cases (EAACI, 2021; Matos et al., 2022).

Conclusion

Urticaria-like conditions encompass a complex and heterogeneous spectrum of disorders, unified by the presence of transient or persistent wheals but distinguished by diverse underlying immunologic, inflammatory, or proliferative mechanisms (Schettini et al., 2023; Matos et al., 2022). The clinical overlap among these conditions often poses diagnostic challenges, emphasizing the necessity of a structured, mechanism-based approach to patient assessment (EAACI, 2021; Krause et al., 2023). Comprehensive evaluation—including detailed clinical history, identification of potential triggers, targeted laboratory investigations, and, when

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indicated, histopathologic examination—facilitates accurate differentiation between histamine-mediated, autoimmune or autoinflammatory, drug-induced, mast cell–driven, and connective tissue–associated presentations (Matos et al., 2022; Schettini et al., 2023).

From a therapeutic perspective, tailoring interventions to the specific pathophysiologic pathways is paramount. Empiric management with antihistamines alone may be insufficient in conditions driven by autoimmunity, systemic inflammation, or mast cell proliferation, underscoring the importance of mechanistic insight in guiding targeted pharmacologic strategies (EAACI, 2021; Krause et al., 2023). Moreover, recognizing the potential systemic involvement in certain urticaria-like syndromes.

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