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Urticarial Syndromes

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Abstract

Urticaria is a common dermatological condition that can occur in acute and chronic forms. Common urticaria is generally easy to diagnose; however, urticarial syndromes should be considered in cases where lesions persist for greater than 24–36 h, the location of lesions has bilateral symmetry, urticarial lesions are accompanied by additional elementary lesions, and/or the patient presents with additional systemic symptoms. Additionally, urticarial syndromes should be considered for patients with typical urticarial lesions that do not respond to systemic antihistamine treatment. Hyperpigmentation or bruising can be observed following resolution of urticarial syndromes. Many cutaneous and systemic diseases can cause urticarial syndromes. Systemic causes of urticarial syndromes can affect multiple organ systems and may be accompanied by systemic symptoms such as fever, asthenia, and arthralgia. Clinicopathologic correlation is essential for the accurate diagnosis of urticarial syndromes. In this chapter, cutaneous and systemic etiologies of urticarial syndromes are reviewed.

Keywords: urticaria, common urticaria, urticarial syndromes, cutaneous urticarial syndromes, systemic urticarial syndromes

1. Introduction

Urticaria is a disease with a lifetime prevalence of 25–30% and is characterized by itchy urticarial lesions and/or angioedema [1, 2]. Although its physiopathology is not well understood, cutaneous mast cells are the main causative factor that is responsible for the release of histamine and other mediators [3, 4]. The disease is divided into acute and chronic depending on whether the duration is less or more than 6 weeks. While acute urticaria is often limited and the cause can be determined in most patients, chronic urticaria is a long-term disease, and further investigation is required in terms of accompanying disorders or autoimmunity [5]. The diagnosis of common urticaria is usually made easily. However, some difficulties in terms

of response to treatment, accompanying lesions, and systemic findings can be seen in some patients. Various disorders, both cutaneous and systemic, are included in the spectrum called urticarial syndrome (**Table 1**). In general, lesions lasting longer than 24–36 h, showing bilateral symmetric involvement, with elementary lesions other than urticaria and accompanying systemic symptoms should bring urticarial syndromes to mind. Clinicopathologic correlation is essential in the diagnosis of urticarial syndromes [1, 5]. Cutaneous and systemic disorders that may cause the urticarial syndrome will be reviewed in this section.

Cutaneous urticarial syndromes	Systemic urticarial syndromes
Urticarial dermatitis	Vasculitides
Contact dermatitis	<ul style="list-style-type: none"> • Urticarial vasculitis
Papular urticaria	<ul style="list-style-type: none"> • Other vasculitides
Mastocytosis	Immunologic disorders
Exanthematous drug eruption	<ul style="list-style-type: none"> • Connective tissue diseases
Autoimmune bullous disorders	<ul style="list-style-type: none"> • SLE, Sjogren syndrome, dermatomyositis • Juvenile rheumatoid arthritis
<ul style="list-style-type: none"> • Bullous pemphigoid • Gestational pemphigoid 	Hematologic diseases
<ul style="list-style-type: none"> • Linear IgA dermatosis • Dermatitis herpetiformis • Epidermolysis bullosa acquisita 	<ul style="list-style-type: none"> • Waldenstrom macroglobulinemia • Schnitzler syndrome • Hypereosinophilic syndromes
Pruritic urticarial papules and plaques of pregnancy	<ul style="list-style-type: none"> • Polycythemia vera
Rare cutaneous urticarial syndromes	<ul style="list-style-type: none"> • Non-Hodgkin lymphoma (B cell)
<ul style="list-style-type: none"> • Autoimmune progesterone/estrogen dermatitis • Wells syndrome • Interstitial granulomatous dermatitis • Neutrophilic eccrine hidradenitis • Urticaria-like follicular mucinosis 	Autoinflammatory syndromes
	<ul style="list-style-type: none"> • Hereditary periodic fever syndromes • Cryopyrin-associated periodic syndromes • Other autoinflammatory syndromes

Table 1. Cutaneous and systemic urticarial syndromes.

2. Cutaneous urticarial syndromes

Various skin disorders can cause urticarial lesions and can be confused with common urticaria.

2.1. Urticarial dermatitis

Urticarial dermatitis is a clinical picture where urticarial plaques and edematous lesions are combined and is usually seen in the elderly. Urticarial dermatitis is quite itchy and often

characterized by diffuse and symmetrical involvement of the body and proximal extremities. Facial and palmoplantar region involvement is usually not present. Existing lesions may persist for days or even weeks. Excoriations and lichenification due to the severe itching may be observed in time. It usually has a chronic relapsing course and spontaneous regression is very rare [5, 6]. Most pathologists describe urticarial dermatitis as a “dermal hypersensitivity reaction.” Papillary dermal edema and minimal epidermal spongiosis with superficial perivascular lymphocytic and eosinophilic infiltration are seen on histopathologic examination [6, 7]. While the etiologic agents most commonly held responsible are drugs, detecting the triggering agent can sometimes be difficult [6]. Low to moderate doses of systemic steroids can provide relief in patients’ resistant to topical steroids and systemic antihistamines [5, 8].

2.2. Contact dermatitis

Contact dermatitis (CD) develops after contact with allergic and/or irritant agents and is fairly common. The sensitizers that most commonly cause allergic CD are poison ivy, nickel, formaldehyde, and fragrances that are included in many cosmetics. Irritant CD is also called non-immunologic contact dermatitis and is most commonly due to fragrances, flavoring agents, and preservatives [9–11]. While CD usually causes itchy eczematous lesions, urticarial lesions may rarely be seen due to dermal edema. The border between CD and contact urticaria is not clear. Dermal edema is seen more commonly in contact urticaria, and this is accepted as the most important difference with CD. Histopathologic investigation is usually not required in CU as it develops in the region that contacts the allergic and/or irritant agent. However, if performed, a spongiotic dermatitis picture characterized by a mixed inflammatory infiltrate formed of lymphocytes, histiocytes, and eosinophils is often observed in CD. Only dermal changes are seen in CU and epidermal spongiosis is not seen [12, 13]. A patch test and/or specific IgE investigation is recommended to detect the agent causing the problem.

2.3. Papular urticaria

Papular urticaria is a kind of allergic hypersensitivity reaction developing after arthropod bites. It is most common in children at the age of 2–10 years [14]. It usually develops in open regions of the body such as the arms, lower leg, and face due to insect bites from fleas, mosquitoes, or bedbugs especially in the summer [15]. The genital, perianal, and axillary regions are generally protected. Vesicles, excoriation, and post-inflammatory hyperpigmentation can be gradually observed in the middle of the lesion that starts as an itchy papule. Mostly, acute-type localized insect bites have urticarial features [16]. Diagnosis is usually clinical but can rarely be confused with other disease such as varicella, miliaria rubra, and Gianotti-Crosti syndrome [17]. Nonsedating antihistamines and moderate-potency topical corticosteroids for itching are usually adequate for treatment [14].

2.4. Exanthematous drug eruptions

Exanthematous drug eruptions, also called morbilliform or maculopapular drug eruptions, are the most common drug hypersensitivity reaction [18]. They are present in form of erythematous fixed macules, papules, or wheal-like lesions with a bilateral and symmetrical

distribution especially on the body after an average of 1 week following drug administration. The lesions become confluent in time and improve by leaving transient hyperpigmentation while regressing [5]. The mucous membranes are usually not involved. However, the mucous membranes (oral, conjunctival, nasal, or anogenital) and skin appendages (hair and nails) may be involved in patients with severe drug eruption. Mild fever can be seen. The medication history is essential in the diagnosis. Histopathologic diagnosis is not always required. Biopsy sometimes does not help in the diagnosis because it does not contain specific signs. Skin biopsy is generally recommended in the case of drug use that may cause a drug eruption, fever $>38^{\circ}\text{C}$, and the presence of erythroderma, blisters, and purpura or pustules and mucous membrane involvement [19]. Discontinuing the suspected drug immediately is recommended in the treatment. Topical corticosteroids and systemic antihistamines are recommended for symptomatic treatment. However, short-term moderate-high dose (prednisone 1–2 mg/kg/day) systemic corticosteroid treatment can be recommended in those with a severe exanthematous drug reaction [20].

2.5. Cutaneous mastocytosis (*Urticaria pigmentosa*)

Mastocytosis is a group of disorders characterized by the accumulation of mast cells in one or more organs. It is divided into two main groups as cutaneous and systemic [21]. *Urticaria pigmentosa* (UP) is the most common type of cutaneous mastocytosis both in childhood and adulthood. It presents with brown macules and papules, especially in the trunk or limbs. However, it can be seen as an urticarial rash that can affect the entire body in children. Dermographism-urticaria (Darier finding) development after skin rubbing is present in most cases [21, 22]. Healing is usually with post-inflammatory hyperpigmentation. The number of lesions is variable. The most common symptoms are itching and flushing. However, bulla development, recurrent syncope, and even anaphylaxis can be seen. Regression in symptoms is seen in the majority of the patients until adolescence with full improvement in 50% [23]. Although clinicopathologic correlation is recommended for the diagnosis, histopathologic characteristics may not always be obvious. The treatment is usually symptomatic in children. Phototherapy is the primary treatment in widespread maculopapular lesions seen in adults [24].

2.6. Autoimmune bullous disorders

Bullous pemphigoid, gestational pemphigoid, linear IgA dermatosis, and epidermolysis bullosa acquisita are disorders due to autoantibodies toward various basal membrane components and characterized by subepidermal bulla formation related to these antigens. Another common characteristic of these disorders is the possibility of urticarial lesions.

2.6.1. *Bullous pemphigoid*

Bullous pemphigoid (BP) is an autoimmune bullous disorder that is especially observed in elderly people and often accompanied by severe itching. It presents with tense bullae following a prodromal stage lasting weeks or even months. Bulla development may not be observed

in some patients. Pruritic eczematous and papular or urticaria-like skin lesions are commonly observed in the prodromal period [25–27]. They may develop on a non-inflammatory base or an urticarial-erythematous base [28]. The body, extremity flexures, and axillary and inguinal folds are the main regions involved. Bilateral symmetrical involvement is usually present [25, 26, 28]. BP may not be considered in patients with a long-term prodromal period. The gold standard in the diagnosis is histopathology and direct immunofluorescence. Detection of autoantibodies in the serum with indirect immunofluorescence has become the standard for the diagnosis at many centers [29].

2.6.2. *Gestational pemphigoid*

Gestational pemphigoid is a rare autoimmune skin disorder seen during pregnancy. It is characterized by a severe itchy and bullous eruption due to damage in the basement membrane of the skin by autoantibodies developing against placental BP180 (BPAG2/collagen XVII) [30]. However, urticarial and eczematous lesions may be seen before and/or during bulla development in some cases. The onset is usually with severe itching around the belly. Red papules, urticarial plaques, or erythema multiforme-like targetoid lesions develop. However, cases where the urticarial or targetoid lesions lasted longer have also been reported. Histopathology, direct immunofluorescence, and indirect immunofluorescence are important in the diagnosis [5, 29, 31].

2.6.3. *Linear IgA bullous dermatosis*

Linear IgA bullous dermatosis (LABD) is a mucocutaneous autoimmune subepidermal vesiculobullous disorder. Although the etiopathogenesis is not fully known, it is thought to be associated with drugs, infections, autoimmune diseases, gastrointestinal diseases, and malignancies [32, 33]. There can be clear or hemorrhagic lesions, tense vesicles, or bullae appearing on an erythematous or urticarial base [34]. When erythematous or urticarial lesions last a long time, the diagnosis of bullous disorders can be missed. The diagnosis is made with clinical, histopathologic, and immunologic data as in other autoimmune disorders.

2.6.4. *Epidermolysis bullosa acquisita*

Epidermolysis bullosa acquisita (EBA) is a rare acquired, chronic subepidermal bullous disease of the skin and mucous membranes. It is characterized by antibodies developing against type VII collagen, which is the major component of anchoring fibrils. Clinical presentation is usually in the form of non-inflammatory bullous lesions that improve with scarring and milia formation in trauma-prone acral regions. However, in addition to the classic presentation, BP-like presentation, cicatricial pemphigoid-like presentation, Brunsting-Perry pemphigoid presentation, and LABD-like disease can also be seen. Urticarial lesions can be observed with various durations, especially with a BP-like and LABD-like presentation. Clinical, histopathologic, and immunologic investigations are required in the diagnosis. Colchicine, dapsone, plasmapheresis, photopheresis, infliximab, and intravenous immunoglobulin are the most commonly used treatment agents. However, treatment satisfaction is usually low [5, 35].

2.7. Pruritic urticarial papules and plaques of pregnancy

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is the itchiest dermatosis of pregnancy. PUPPP is seen in the form of erythematous, urticarial plaques, and papules and usually starts from the abdomen and extends to the thighs, legs, back, buttocks, arms, and breasts. However, the periumbilical region is protected. The lesions usually regress within 6 weeks in the postpartum period [36, 37]. In addition to erythematous and urticarial plaques, targetoid and vesicular lesions can be seen in approximately half of the patients as the disease progresses. Moisturizers, topical corticosteroids, and antihistamines can be recommended for symptomatic relief in patients with severe itching [36].

2.8. Rare cutaneous urticarial syndromes

Autoimmune progesterone/estrogen dermatitis, interstitial granulomatous dermatitis, eosinophilic cellulitis (Wells syndrome), neutrophilic eccrine hidradenitis (NEH), and urticaria-like follicular mucinosis are rare cutaneous urticarial syndromes.

2.8.1. Autoimmune progesterone/estrogen dermatitis

Autoimmune progesterone dermatitis (APD) is a rare dermatosis that causes inflammation at the luteal phase of the menstrual cycle and presents with several skin findings. Skin signs include urticarial, eczematous and vesiculopustular eruption, targetoid lesions, and angioedema [38, 39]. Urticaria is seen in about half of patients [5]. There is no specific diagnostic test. A history of premenstrual exacerbation, prevention of lesions with ovulation inhibition, and a positive reaction to intradermal progesterone injection are helpful in the diagnosis [39]. Autoimmune estrogen dermatitis has also been identified in the literature but only in low numbers [5].

2.8.2. Interstitial granulomatous dermatitis

Interstitial granulomatous dermatitis (IGD) is a rare dermatosis and accepted as a separate histopathologic entity [40]. Papules, nodules, plaques, and an urticarial rash can be observed in the disorder that is more common in women and the elderly people. Of the cases identified until today, two-thirds have had a chronic course and the remaining a recurrent and episodic course. Recognizing IGD is quite important in order to indicate the underlying autoimmune disorders [5, 40]. Clinicopathological correlation is essential for the diagnosis.

2.8.3. Wells syndrome (eosinophilic cellulitis)

Wells syndrome is a rare dermatosis that presents as acute, recurrent, itchy, erythematous, and edematous lesions [41]. Although it brings bacterial cellulitis to mind first in the clinic, not responding to systemic antibiotics is an important indicator in the diagnosis. Another differential diagnosis is urticaria due to the presence of urticarial lesions. In addition to bacterial cellulitis and urticaria, it can be confused with insect bite, contact dermatitis, angioedema, and hypereosinophilic syndrome [42]. Clinicopathologic correlation is important in the diagnosis.

Dermal edema, eosinophilic dermal infiltration, and free eosinophilic granules coating collagen bundles (“flame figures”) are observed histopathologically. However, the histopathologic signs change in time. Peripheral eosinophilia may also be present in the acute phase [41, 42].

2.8.4. *Neutrophilic eccrine hidradenitis*

Neutrophilic eccrine hidradenitis (NEH) is a very rare dermatosis seen in patients with malignancy or those receiving chemotherapy. The majority of the cases are acute myelogenous leukemia patients receiving chemotherapy [43]. It clinically presents with fixed erythematous and edematous papules and plaques. It is usually accompanied by fever. Histopathologic signs are important in the diagnosis. It is histopathologically characterized by neutrophilic infiltration accompanied by necrosis around eccrine glands and secretory coils. No specific treatment is required as it is usually self-limiting. However, systemic corticosteroid treatment has been reported to shorten the duration of the lesions and the fever [5, 44].

2.8.5. *Urticaria-like follicular mucinosis*

Urticaria-like follicular mucinosis (ULFM) is a very rare disease that presents with itching, urticarial papules, and plaques on an erythematous base, usually in the head and neck. It is usually seen in middle-aged men. Spontaneous improvement is common. However, recurrence can be seen. Histopathological characteristics are important in the diagnosis. Cystic spaces filled with mucin in the outer sheath of hair follicles are histologically seen [45].

3. Systemic urticarial syndromes

In addition to skin disorders, many systemic diseases can cause urticarial lesions. The differential diagnosis with ordinary urticaria should consider that systemic urticarial syndromes may cause elementary skin lesions such as papules, vesicles, hemorrhages, necrosis, and crusts in addition to urticarial skin lesions and also many systemic symptoms such as fever, asthenia, and arthralgia. Lesions usually last longer than 24–36 h, show bilateral and symmetrical distribution, and recover with hyperpigmentation and bruising [46, 47]. Systemic diseases causing urticarial skin lesions will be reviewed in this section.

3.1. Vasculitides

3.1.1. *Urticarial vasculitis*

Urticarial vasculitis (UV) is a separate clinicopathologic entity characterized by recurrent urticarial episodes, histopathologically showing leukocytoclastic vasculitis characteristics [48]. It is the most common clinical picture causing systemic urticarial syndrome. UV has been reported in 2–20% of the patients diagnosed with chronic urticaria [49]. It causes painful and burning skin lesions rather than itching. Urticarial lesions continue longer than 24–36 h. Central clearing of lesions is seen in time and they are accompanied by palpable purpura. Necrosis and ulceration are less common skin findings [50]. The lesions regress with a residual

hyperpigmentation [47, 51]. Histopathology is essential in the diagnosis. The correct choice of the lesion is important in order to reveal true vasculitic changes. Leukocytoclastic vasculitis of the small dermal vessels characterized by a neutrophilic perivascular infiltrate, the typical findings for UV, is observed in fully developed lesions. Additionally, neutrophil fragmentation, nuclear dust, erythrocyte extravasation, and fibrin deposition in and around the vessels are observed [50, 52].

Urticarial vasculitis is mostly idiopathic. However, an association with various drugs, sun, cold, connective tissue diseases, infections, and various malignancies (paraneoplastic) has been identified [50, 51, 53]. Among connective tissue diseases, it is most commonly seen with systemic lupus erythematosus (SLE) [53]. The most common laboratory findings in idiopathic UV are elevation of the erythrocyte sedimentation rate and reduction of serum complement levels [48]. UV is divided into two groups as mainly normocomplementemic UV (NUV) and hypocomplementemic UV (HUV), based on complement levels [51, 54]. Systemic involvement is usually absent or minimal and the prognosis is better in NUV patients. However, there is a propensity to more severe multi-organ involvement in HUV patients [48]. The most common systemic manifestations are in the joints, kidneys, and lungs [52, 54]. Gastrointestinal and neurologic involvement can also be seen [50, 52]. Antinuclear antibody (ANA) positivity has also been reported in up to 78% of HUV patients [52, 54].

Several agents are used for UV treatment and the treatment response is variable. Systemic corticosteroids are the basis of the treatment in UV where antihistamines are usually not sufficient. UV can be controlled with prednisone at a dose of 1 mg/kg/day but can recur after the dose is decreased. Steroid-sparing agents are used in the treatment to avoid the side effects of long-term corticosteroids. Dapsone, colchicine, hydroxychloroquine, mycophenolate mofetil, interferon-alpha, cyclosporine A, azathioprine, cyclophosphamide, rituximab, intravenous immunoglobulins, anakinra, and plasmapheresis are treatment agents that can be used alone or in combination with corticosteroids [50–52].

3.1.2. *Other vasculitides*

Urticarial lesions can be seen in the Churg-Strauss syndrome, Wegener granulomatosis, and polyarteritis nodosa, which are characterized by vasculitis.

The Churg-Strauss syndrome is a rare allergic granulomatous polyangiitis that usually affects middle-aged men. The most common sign is asthma. However, hay fever, rash, gastrointestinal bleeding, and pain can also be seen. Urticarial lesions have been identified in less than 10% of the patients [55].

Polyarteritis nodosa (PAN) is a vasculitis affecting medium-sized vessels and is very rare. Although it can affect any tissue in the body, it most commonly affects the muscles, joints, intestines, nerves, and skin. Urticarial lesions have been identified in about 6% of PAN patients [56].

3.2. Immunologic disorders

Many immunologic disorders can cause urticarial lesions. Connective tissue diseases and mainly SLE, Sjogren syndrome, dermatomyositis, and mixed connective tissue disease are

important among these. It is important to know that urticarial lesions can also be seen in addition to the existing lesions in connective tissue diseases. Although rare, urticarial lesions can also be present in juvenile rheumatoid arthritis [51].

3.3. Hematologic diseases

A wide variety of hematologic diseases can cause urticarial lesions.

3.3.1. Schnitzler syndrome

Schnitzler syndrome is characterized by an urticarial rash and monoclonal gammopathy clinically and neutrophil-mediated inflammation histologically [57]. An urticarial rash and usually IgM but rarely IgG monoclonal gammopathy are present with a chronic pattern in all the patients. Recurrent fever, bone or joint pain, increased bone density, hepato- or splenomegaly, lymphadenopathy, and elevated acute-phase reactants are also accepted as minor criteria [58]. Approximately, 300 cases have been identified in the literature [57]. Risk of developing a lymphoproliferative disorder at an approximate rate of 15% has been reported in the 10-year follow-up, although the syndrome usually has a benign course. The most commonly developing lymphoproliferative disease is Waldenstrom macroglobulinemia. Treatment is usually unsatisfactory, but high doses of corticosteroids, systemic antihistamines, oral cyclosporine, intravenous pulse cyclophosphamide, and pefloxacin mesylate are the therapeutic agents used [58].

3.3.2. Waldenstrom macroglobulinemia

Waldenstrom macroglobulinemia is a chronic indolent lymphoproliferative disorder [59]. Increased levels of IgM paraprotein in the circulation and infiltration of the bone marrow with lymphocytes and plasma cells are seen. Urticarial lesions can be seen in addition to purpura, edema, and ulceration [60].

3.3.3. Hypereosinophilic syndromes

This is a group of myeloproliferative disorders characterized by multiple organ damage caused by persistent eosinophilia. It is more common in young and middle-aged patients but can be seen at any ages. Their classification is complicated. Three factors are mainly included in the diagnostic criteria. These are eosinophilia longer than 6 months ($>1500/\mu\text{l}$), no identifiable etiology for eosinophilia, and signs and symptoms of organ involvement. The most commonly involved organs are the skin, heart, lungs, and the central and peripheral nervous systems. Skin findings are usually common and are in the form of eczematous, urticarial, and angioedema-like findings [61, 62].

3.4. Autoinflammatory syndromes

Autoinflammatory syndromes are a group of heterogeneous single-gene disorders causing recurrent febrile episodes and inflammatory cutaneous, mucosal, serosal, and osteoarticular

manifestations [63, 64]. No infectious, autoimmune, or neoplastic reason has been shown. Excessive activation of the interleukin 1 beta (IL-1 β) pathway is most commonly held responsible in the etiopathogenesis [64].

Many syndromes such as familial Mediterranean fever (FMF), Tumor necrosis factor (TNF) receptor-associated periodic syndrome, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndromes have been identified among the autoinflammatory syndromes. A monogenic defect has been found but only in some of these disorders. However, all have been included within the autoinflammatory syndromes as they show similar inflammatory features [63].

Autoinflammatory syndromes mostly start in infancy or during childhood. Although most cases are familial, some are sporadic. Recurrent episodes of inflammation with fever, elevation in acute-phase reactants, and skin rash can be seen in the absence of an infectious or autoimmune etiology. Although joint and skin involvement can be seen in various forms, fever is almost always present. These symptoms can also be accompanied by systemic findings such as abdominal pain, myalgia, ocular involvement, serositis, amyloidosis, and neurological signs [63, 65].

The skin signs show variety. Urticarial lesions are the predominant skin signs, especially in cryopyrinopathies, and occur in the first year of life. They are more commonly seen as erysipelas-like plaques in the lower extremities in FMF. Erythematous macules and urticarial lesions are seen in HIDS [51, 65].

Autoinflammatory disorders can pose a significant challenge for primary care physicians, pediatricians, dermatologists, rheumatologists, and infectious disease specialists in terms of wide-ranging clinical spectrum. A perivascular and interstitial neutrophil-rich infiltration suggesting neutrophilic urticarial dermatoses is observed in the histopathologic evaluation of skin lesions. Leukocytoclastic vasculitis-like signs can also be seen [65, 66]. However, these signs are not specific. The diagnosis of autoinflammatory disorders is usually made with the clinical features and then supported by either genetic testing or the patient's response to IL-1 inhibition or other specific therapies [63].

4. Conclusion

Ordinary urticaria is a clinical picture frequently encountered by dermatologists and usually presents no diagnostic difficulty. However, cutaneous and systemic urticarial syndromes should be considered in the case of persistence of urticarial lesions, bilateral and symmetrical location, healing with hyperpigmentation or bruising, the presence of other elementary lesions, not responding to systemic antihistamines, and being accompanied by systemic findings. The differential diagnosis of ordinary urticaria and urticarial syndromes is not easy. A detailed clinical evaluation should therefore be performed. Clinicopathologic correlation and, if necessary, further studies should be conducted in the presence of findings suggesting urticarial syndromes.

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References

- [1] Kaplan A. Urticaria and angioedema. In: Adkinson NFJ, Buss WW, Bochner BS, et al., editors. *Middleton's allergy principles and practice*. 6th ed. Philadelphia (PA): Mosby; 2003. pp. 1537–1558.
- [2] Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, et al. Epidemiology of urticaria in Spain. *J Investig Allergol Clin Immunol*. 2004;14:214–220.
- [3] Schocket AL. Chronic urticaria: pathophysiology and etiology, or the what and why. *Allergy Asthma Proc*. 2006;27:90–95.
- [4] Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy*. 2009;39:777–787.
- [5] Peroni A, Colato C, Schena D, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part I. Cutaneous diseases. *J Am Acad Dermatol*. 2010;62:541–555.
- [6] Kossard S, Hamann I, Wilkinson B. Defining urticarial dermatitis: a subset of dermal hypersensitivity reaction pattern. *Arch Dermatol*. 2006;142:29–34.
- [7] Kossard S, Hamann I. A clinician's view of urticarial dermatitis. Reply. *Arch Dermatol*. 2006;142:932–933.
- [8] Fung MA. The clinical and histopathologic spectrum of "dermal hypersensitivity reactions," a nonspecific histologic diagnosis that is not very useful in clinical practice, and the concept of a "dermal hypersensitivity reaction pattern". *J Am Acad Dermatol*. 2002;47:898.
- [9] Belsito DV. Occupational contact dermatitis: etiology, prevalence, and resultant impairment/disability. *J Am Acad Dermatol*. 2005;53:303–313.
- [10] Templet JT, Hall S, Belsito DV. Etiology of hand dermatitis among patients referred for patch testing. *Dermatitis*. 2004;15:25–32.
- [11] Mowad CM. Contact dermatitis: practice gaps and challenges. *Dermatol Clin*. 2016;34:263–267.

- [12] Mowad CM, Marks JG Jr. Allergic contact dermatitis. In: Bologna JL, Jorizzo JL, Rapini RP, editors. *Dermatology*. St Louis: Mosby; 2003. pp. 227–240.
- [13] Cohen DE, Bassiri-Tehrani S. Irritant contact dermatitis. In: Bologna JL, Jorizzo JL, Rapini RP, editors. *Dermatology*. St Louis: Mosby; 2003. pp. 241–249.
- [14] Hernandez RG, Cohen BA. Insect bite-induced hypersensitivity and the SCRATCH principles: a new approach to papular urticaria. *Pediatrics*. 2006;118:189–196.
- [15] Steen CJ, Carbonaro PA, Schwartz RA. Arthropods in dermatology. *J Am Acad Dermatol*. 2004;50:819–842.
- [16] Moffit JE, Golden DBK, Reisman RE, Lee R, Nicklas R, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol*. 2004;114:869–886.
- [17] Steen CJ, Janniger CK, Schutzer SE, Schwartz RA. Insect sting reactions to bees, wasps, and ants. *Int J Dermatol*. 2005;44:91–94.
- [18] Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf*. 2007;30:1011–1030.
- [19] Justiniano H, Berlingeri-Ramos AC, Sánchez JL. Pattern analysis of drug-induced skin diseases. *Am J Dermatopathol*. 2008;30:352–369.
- [20] Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol*. 2008;58:33–40.
- [21] Briley LD, Phillips CM. Cutaneous mastocytosis: a review focusing on the pediatric population. *Clin Pediatr*. 2008;47:757–761.
- [22] Yanagihori H, Oyama N, Nakamura K, Kaneko F. C-kit mutations in patients with childhood-onset mastocytosis and genotype-phenotype correlation. *J Mol Diagn*. 2005;7:252–257.
- [23] Akoglu G, Erkin G, Cakir B, Boztepe G, Sahin S, Karaduman A, et al. Cutaneous mastocytosis: demographic aspects and clinical features of 55 patients. *J Eur Acad Dermatol Venereol*. 2006;20:969–973.
- [24] Gobello T, Mazzanti C, Sordi D, Annessi G, Abeni D, Chinni ML, et al. Medium versus high dose ultraviolet A1 phototherapy for urticaria pigmentosa: a pilot study. *J Am Acad Dermatol*. 2003;49:679–684.
- [25] Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 1: clinical manifestations. *J Dtsch Dermatol Ges*. 2011;9:844–856.
- [26] Schmidt E, della Torre R, Borradori L. Clinical features and practical diagnosis of bullous pemphigoid. *Dermatol Clin*. 2011;29:427–438.
- [27] Kasperkiewicz M, Zillikens D, Schmidt E. Pemphigoid diseases: pathogenesis, diagnosis, and treatment. *Autoimmunity*. 2012;45:55–70.

- [28] Di Zenzo G, Marazza G, Borradori L. Bullous pemphigoid: physiopathology, clinical features and management. *Adv Dermatol*. 2007;23:257–288.
- [29] Karpati S. Dermatitis herpetiformis: close to unraveling a disease. *J Dermatol Sci*. 2004;34:83–90.
- [30] Huilaja L, Mäkikallio K, Tasanen K. Gestational pemphigoid. *Orphanet J Rare Dis*. 2014;9:136.
- [31] Boulinguez S, Bedane C, Prost C, Bernard P, Labbe L, Bonnetblanc JM. Chronic pemphigoid gestationis: comparative clinical and immunopathological study of 10 patients. *Dermatology*. 2003;206(2):113–119.
- [32] Chanal J, Ingen-Housz-Oro S, Ortonne N, Duong TA, Thomas M, Valeyrie-Allanore L, et al. Linear IgA bullous dermatosis: comparison between the drug-induced and spontaneous forms. *Br J Dermatol*. 2013;169:1041–1048.
- [33] Chen S, Mattei P, Fischer M, Gay JD, Milner SM, Price LA. Linear IgA bullous dermatosis. *Eplasty*. 2013;13:49.
- [34] Guide SV, Marinokovich MP. Linear IgA bullous dermatosis. *Clin Dermatol*. 2001;19:719–727.
- [35] Gupta R, Woodley DT, Chen M. Epidermolysis bullosa acquisita. *Clin Dermatol*. 2012;30:60–69.
- [36] Rudolph CM, Al-Fares S, Vaughan-Jones SA, Mullegger RR, Kerl H, Black MM. Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181 patients. *Br J Dermatol*. 2006;154:54–60.
- [37] Matz H, Orion E, Wolf R. Pruritic urticarial papules and plaques of pregnancy: polymorphic eruption of pregnancy (PUPPP). *Clin Dermatol*. 2006;24:105–108.
- [38] Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy*. 2004;2:10.
- [39] Stranahan D, Rausch D, Deng A, Gaspari A. The role of intradermal skin testing and patch testing in the diagnosis of autoimmune progesterone dermatitis. *Dermatitis*. 2006;17:39–42.
- [40] Ahmed ZS, Joad S, Singh M, Bandagi SS. Interstitial granulomatous dermatitis successfully treated with etanercept. *Am J Case Rep*. 2014;15:94–96.
- [41] Gandhi RK, Coloe J, Peters S, Zirwas M, Darabi K. Wells syndrome (eosinophilic cellulitis): a clinical imitator of bacterial cellulitis. *J Clin Aesthet Dermatol*. 2011;4:55–57.
- [42] Weiss G, Shemer A, Confino Y, Kaplan B, Trau H. Wells' syndrome: report of a case and review of the literature. *Int J Dermatol*. 2001;40:148–152.
- [43] Bachmeyer C, Aractingi S. Neutrophilic eccrine hidradenitis. *Clin Dermatol*. 2000;18:319–330.

- [44] Bhanu P, Santosh KV, Gondi S, Manjunath KG, Rajendaran SC, Raj N. Neutrophilic eccrine hidradenitis: a new culprit-carbamazepine. *Indian J Pharmacol.* 2013;45:91–92.
- [45] Crovato F, Nazzari G, Nunzi E, Rebora A. Urticaria-like follicular mucinosis. *Dermatologica.* 1985;170:133–135.
- [46] Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy.* 2009;64:1417–1426.
- [47] Buck A, Christensen J, McCarty M. Hypocomplementemic urticarial vasculitis syndrome: a case report and literature review. *J Clin Aesthet Dermatol.* 2012;5:36–46.
- [48] Venzor J, Lee WL, Huston DP. Urticarial vasculitis. *Clin Rev Allergy Immunol.* 2002;23:201–216.
- [49] Grotz W, Baba H, Becker J, Baumgartel MW. Hypocomplementemic urticarial vasculitis syndrome. An interdisciplinary challenge. *Dtsch Arztebl Int.* 2009;106:756–763.
- [50] Brown NA, Carter JD. Urticarial vasculitis. *Curr Rheumatol Rep.* 2007;9:312–319.
- [51] Peroni A, Colato C, Schena D, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. *J Am Acad Dermatol.* 2010;62:557–570.
- [52] Dincy CVP, George R, Jacob M, Mathai E, Pulimood S, Eapen EP. Clinicopathologic profile of normocomplementemic and hypocomplementemic urticarial vasculitis: a study from South India. *J Eur Acad Dermatol.* 2008;22:789–794.
- [53] DeAmicis T, Mofid MZ, Cohen B, Nousari HC. Hypocomplementemic urticarial vasculitis: report of a 12-year-old girl with systemic lupus erythematosus. *J Am Acad Dermatol.* 2002;47:273–274.
- [54] Tosoni C, Lodi-Rizzini F, Cinquini M, Pasolini G, Venturini M, Sinico RA, et al. A reassessment of diagnostic criteria and treatment of idiopathic urticarial vasculitis: a retrospective study of 47 patients. *Clin Exp Dermatol.* 2009;34:166–170.
- [55] Tlacuilo-Parra A, Soto-Ortiz JA, Guevara-Gutierrez E. Churg-Strauss syndrome manifested by urticarial plaques. *Int J Dermatol.* 2003;42:386–388.
- [56] Chang S, Carr W. Urticarial vasculitis. *Allergy Asthma Proc.* 2007;28:97–100.
- [57] Gusdorf L, Asli B, Barbarot S, Masseau A, Puechal X, Gottenberg JE, et al. Schnitzler syndrome: validation and applicability of diagnostic criteria in real-life patients. *Allergy.* 2017;72:177–188.
- [58] Eiling E, Schröder JO, Gross WL, Kreiselmaier I, Mrowietz U, Schwarz T. The Schnitzler syndrome: chronic urticaria and monoclonal gammopathy—an autoinflammatory syndrome? *J Dtsch Dermatol Ges.* 2008;6:626–631.

- [59] Vogt RF, Marti GE. Overview of monoclonal gammopathies of undetermined significance. *Br J Haematol.* 2007;139:687–689.
- [60] Chan I, Calonje E, Whittaker SJ. Cutaneous Waldenstrom's macroglobulinaemia. *Clin Exp Dermatol.* 2003;28:491–492.
- [61] Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol.* 2010;126:45–49.
- [62] Liao W, Long H, Chang CC, Lu Q. The eosinophil in health and disease: from bench to bedside and back. *Clin Rev Allergy Immunol.* 2016;50:125–139.
- [63] Cush JJ. Autoinflammatory syndromes. *Dermatol Clin.* 2013;31:471–480.
- [64] Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, et al. In vivo regulation of interleukin 1a in patients with cryopyrin-associated periodic syndromes. *J Exp Med.* 2009;206:1029–1036.
- [65] Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases. Clinical and genetic advances. *Arch Dermatol.* 2008;144:392–402.
- [66] Kanazawa N, Furukawa F. Autoinflammatory syndromes with a dermatological perspective. *J Dermatol.* 2007;34:601–618.

