Chapter 2

Urticaria and Angioedema

Burhan Engin, Muazzez Çiğdem Oba and Server Serdaroğlu

Additional information is available at the end of the chapter

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Abstract

Urticaria is a common mast cell–mediated dermatosis presenting with pruritic erythematous superficial plaques also known as hives or wheals. Angioedema is an acute condition manifesting as localized edema affecting the skin and mucous membranes. In contrast with urticaria, itching is often absent, the skin appears normal and the edema occurs in deeper dermal and subcutaneous tissues in angioedema. Spontaneous urticaria can either be acute lasting less than 6 weeks or chronic with a duration of more than 6 weeks. In acute urticaria cases, an underlying cause, mostly medications, foods and infections, may be found in approximately 50% of patients. However, spontaneous urticaria is generally idiopathic. First-line treatment option for both acute and chronic urticaria is non-sedating H_1 antihistamines. Patients with recalcitrant disease are candidates for therapy with corticosteroids, immunosuppressives or omalizumab treatment. There are two different mechanisms causing angioedema. The first is mast cell mediated and is considered to be part of the spectrum of spontaneous or inducible urticarias. Patients present with angioedema alone or angioedema combined with urticaria. The second is bradykinin-induced angioedema, as observed in the hereditary angioedema and angiotensin-converting enzyme (ACE) inhibitor–induced angioedema.

Keywords: angioedema, spontaneous urticaria

1. Introduction

Urticaria is a common mast cell–mediated dermatosis presenting with pruritic erythematous superficial plaques also known as hives or wheals. There may be associated swelling in deep dermis or subcutaneous tissue leading to angioedema [1]. Angioedema is rather painful than pruritic and takes longer time to resolve in contrast to the wheals which usually disappear within 24 hours [2, 3]. The disease has considerable impact on patients' quality of life

with dissatisfaction in private life and work being frequent [4]. Non-sedating H_1 antihistamines are the first line therapy for both acute and chronic urticaria. Apart from angioedema which is part of the spectrum of urticaria, there is bradykinin-induced angioedema, such as that observed in the hereditary angioedema characterized by angioedema without wheals. Management of isolated angioedema differs from that of urticaria involving both preventive measures and treatment of acute attacks [5].

2. Classification

The current classification of urticaria is based upon the clinical course of the disease. Subtypes include spontaneous urticaria, physical urticarias and other urticaria types [2]. Spontaneous urticaria can either be acute lasting less than 6 weeks or chronic with a duration of more than 6 weeks. This arbitrary division for chronicity has been made as the etiologies and thus the clinical evaluation of acute and chronic urticaria vary considerably [3]. The physical and other urticaria types are elicited by external stimuli, such as heat, cold, pressure, vibration, friction, sunlight, water, etc. [6]. These two subtypes of urticaria are beyond the scope of this chapter.

3. Epidemiology

An episode of urticaria can occur in 15–25% of individuals at some point in their lifetime. Approximately 40% of patients with urticaria have wheals associated with angioedema and 1–13% of patients present with isolated angioedema [3, 7]. Socioeconomic status, ethnicity and education do not have any clear influence on the prevalence of the disease [3].

At first all cases of urticaria are acute; 30% of them progress to become chronic [7]. Acute episodic form of urticaria commonly presents in infancy and childhood, particularly in atopic subjects [1, 8]. Chronic urticaria peaks in adulthood between 20 and 40 years of age affecting women two times more frequently than men [1, 3, 4]. About 0.5–1% of population has chronic spontaneous urticaria at a specific point in time [3].

4. Etiology and pathogenesis

Drugs, foods, viral and parasitic infections, insect stings and contact allergens are present among the most common causes of acute urticaria [8]. Drugs most commonly implicated in acute urticaria are antibiotics (penicillins and sulfonamides), nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, opiates and narcotics. Foods, such as milk, eggs, nuts, fish and shellfish are common offenders, as well as food additives, such as tartrazine dyes, benzoic acid derivatives like sodium benzoate. Approximately 50% of cases of acute urticaria are idiopathic [5, 9].

The relationship between stress and chronic spontaneous urticaria is not fully understood. There are reports showing stressful life events, such as loss of close family member, financial problems, major personal illness preceded onset or exacerbation of the disease in a considerable subset of patients with chronic spontaneous urticaria [10, 11]. Although many patients report stress to exacerbate their disease, there is a lack of well-controlled studies on this subject [3].

In 35–40% of patients with chronic urticaria, circulating immunoglobulin G (IgG) autoantibodies against alpha subunit of the IgE receptors are found and in 5–10% of chronic urticaria patients, there is IgG antibody to IgE. This subtype of chronic urticaria is designated as chronic autoimmune urticaria [12]. The remainder of the patients with chronic urticaria is classified under the name of chronic idiopathic urticaria. In this form of urticaria, the mechanism for stimulation of mast cells is unknown [5].

Pathophysiological mechanisms leading to formation of urticaria and angioedema can be immune-mediated, complement-mediated, non-immune–mediated and autoimmune-mediated [13]. As in most cases of acute urticaria, immune-mediated urticaria is an IgE-mediated hypersensitivity reaction. This allergic reaction is commonly triggered in response to drugs, foods and insect bites [7, 13]. Complement activation leading to release of C3a, C4a and C5a can stimulate mast cells. Non-immune–mediated urticaria involves direct activation of mast cells by non-IgE mechanisms examples of which are physical stimuli, radiocontrast dyes, drugs, such as opiates and vancomycin. Autoimmune urticaria involves autoantibodies causing mast cell degranulation [12, 13]. As noted all mechanisms lead to activation of mast cells causing liberation of histamine, leukotriene C4 and prostaglandin D2. These vasoactive mediators cause vasodilatation and extravasation of plasma from postcapillary venules. In 4–5 hours, an inflammatory cytokine response including tumor necrosis factor, interleukin 4 and interleukin 5 recruits a perivascular inflammatory infiltrate. The result is the formation a pruritic urticarial plaque or angioedema [7].

5. Clinical features

Urticarial wheals consist of circumscribed erythematous plaques of various sizes with central swelling, with or without a surrounding flare (**Figure 1**). There is accompanying intense pruritus or occasional burning sensations. Lesions typically have round to oval shape but occasionally irregular, serpiginous or gyrate configurations may occur. Wheals are blanchable by diascopy. Individual lesions usually disappear within 1–24 hours without scarring but some lesions may take up to 48 hours to resolve [14–16]. Patients often report a poorly localized pruritus starting before the appearance of wheals [7]. Pruritus may impair sleep, private life and work leading to a diminished quality of life [4].

Angioedema is a descriptive term for abrupt onset of swellings of the deep dermis and subcutaneous tissue. In contrast to edema, angioedema is asymmetrical and can occur on non-dependent sites. Most common sites of involvement are the lips (**Figure 2**), tongue, eyelids and genitalia although any part of the body can be involved. Due to the tissue distention,

the lesions are usually painful rather than pruritic. Swellings of angioedema can be pink or skin-colored [9, 17, 18]. Involvement of the mucous membranes is a common feature. Stridor, abdominal pain, rarely intestinal obstruction may result from edema of respiratory or gastrointestinal tract. Lesions may take up to 72 hours to resolve [9, 18].

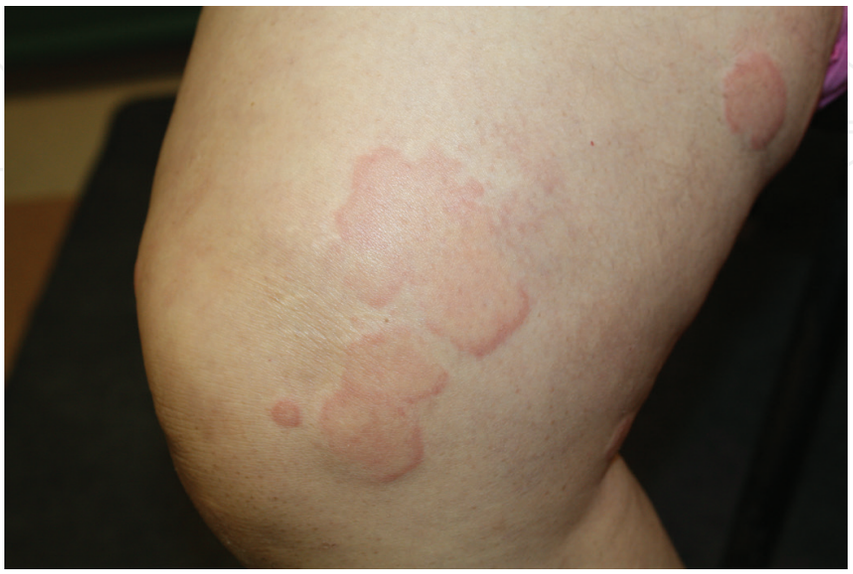

Figure 1. Typical urticarial plaques are observed on the leg of the patient.

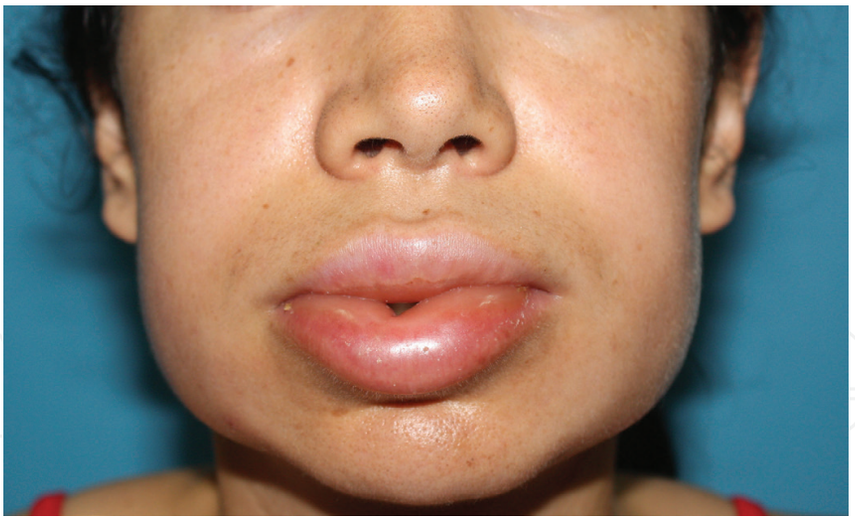

Figure 2. Angioedema involving the lips.

6. Prognosis

Cases of acute urticaria have a benign course with most patients being managed with conventional treatments [8].

Studies concerning duration of chronic spontaneous urticaria have yielded varying results. However, it is clear that many patients are affected for more than one year and an important proportion of patients have a long-term course of the disease exceeding 5 years [3].

In chronic spontaneous urticaria, there are four factors that potentially predict long disease duration, namely disease severity, presence of angioedema, autoreactivity and combination with physical urticaria. Patients with moderate to severe disease tend to have a more persistent disease as compared to patients with mild disease. Presence of angioedema with or without wheals in patients with chronic spontaneous urticaria predicts a longer course [3]. Autoreactivity, which is defined by a positive autologous serum skin test, reflects the finding of autoantibodies against IgE receptor or IgE. These patients have more severe disease with a longer duration and require higher doses of antihistamines to control disease activity than patients with negative autologous serum skin test [19]. Patients suffering from both chronic spontaneous urticaria and physical urticaria are likely to have longer disease duration in comparison with patients with chronic spontaneous urticaria alone [3].

7. Associated diseases

An increased prevalence of concomitant allergic diseases including rhinitis, asthma and atopic dermatitis is observed in cases of acute urticaria [8].

Chronic autoimmune urticaria is associated with antithyroid antibodies namely anti-microsomal and anti-thyroglobulin antibodies, observed in 27% of cases [12]. In patients with chronic urticaria, other autoimmune conditions such as vitiligo, type I diabetes mellitus, systemic lupus erythematosus and rheumatoid arthritis are more prevalent than in general population [5, 16].

Patients with chronic spontaneous urticaria often have concomitant physical urticaria that present with wheals lasting 2 hours or less [6].

Role of *Helicobacter pylori* infection in etiology of chronic autoimmune urticaria is still controversial [5]. However, it has been shown that *H. pylori* infection may contribute to the exacerbation of urticaria and that 2 weeks long triple therapy for eradication of the bacteria led to improvement of symptoms. As most patients infected with *H. pylori* are asymptomatic, screening of chronic urticaria patients for the presence of *H. pylori* infection by a non-invasive test, such as urea breath test or fecal antigen test is recommended [20].

8. Diagnosis

A through history is the most important tool in the diagnosis of urticaria. Duration, timing and localization of lesions, history of a recent viral infection, recent insect bite, medications, suspected foods, associated systemic symptoms, such as fever and arthralgia, and response to previous treatments should be questioned [5, 13]. In majority of cases of acute

urticaria, history taking and physical examination is sufficient for the diagnosis. Further investigations are generally not required in patients with acute urticaria except those with a clinical history or physical examination suggesting an underlying cause, such as upper respiratory tract infection, food- or drug-induced urticaria [8]. Skin prick tests and serum-specific IgE tests can be used to confirm allergic reaction to foods, latex and certain antibiotics [5].

In chronic urticaria, complete blood count, liver enzymes, urinalysis and thyroid function tests can be checked; however, these laboratory tests are of minor significance, if there is not a suspected underlying etiology for persistent urticarial lesions [13, 21].

Skin testing to aeroallergens can be of value only if the patient has concomitant allergic rhinitis and/or asthma. If the patient reports a specific food to be strongly related with the attacks, a serologic test to the specific food can be performed. Serologic testing would be more reliable than skin testing as an interpretation of wheal and flare response would be misleading in patients under recurrent bouts of urticaria [16].

Autologous serum skin test is a practical clinical test to detect circulating functional autoantibodies in patients with chronic urticaria. The test is performed by intradermal injection of patient's own serum obtained while the patient is symptomatic and injection of 0.9% saline on volar aspect of the forearm. It is of importance to stop antihistamines 2 days before application. A positive autologous serum skin test is defined as a red serum-induced wheal having a diameter greater than 1.5 mm than the saline-induced wheal at 30 min. The test is performed when an immunomodulatory treatment is planned for patients with severe chronic urticaria. However, this is a controversial issue as the presence or absence of autoantibodies does not predict efficacy to most therapies [5, 16]. Basophil histamine release assays, western blot analysis or ELISA are also used to detect autoantibodies. However, these tests are sophisticated tests not readily available to most clinicians [22].

Urticaria activity score (UAS) is commonly used to assess disease activity and treatment response in patients with chronic urticaria. UAS is calculated based on the daily number of wheals (1–3 points) and the intensity of pruritus (0–3 points) and ranges from 0 to 6 [23]. UAS7 is calculated by summing UAS recorded by the patient on 7 consecutive days. A UAS7 score of less than 7 indicates control of disease, whereas a score exceeding 28 indicates poorly controlled symptoms [24].

9. Histopathology

Skin biopsies of acute lesions demonstrate a minimal inflammatory infiltrate along with dilatation of small vessels, flattened rete pegs and swollen collagen fibers. Histology of chronic urticaria lesions reveals a perivascular cuffing by predominantly T lymphocytes and also monocytes, neutrophils, eosinophils and basophils [25].

Observation of fragmentation of neutrophils, red cell extravasation and swelling of endothelial cells in persistent lesions points to the diagnosis of leukocytoclastic vasculitis [13].

10. Differential diagnosis

Urticarial rash may be seen in the course of many diseases (**Table 1**). Urticaria and angioedema can be manifestations of underlying systemic diseases, such as collagenopathies, endocrinopathies, tumors and hemolytic diseases [1].

Urticarial vasculitis is a rare condition mainly affecting adult females in 4th decade of life. It may manifest with urticarial plaques, which generally persist for 48–72 hours. Pain and tenderness is a common complaint. The wheals may resolve leaving residual purpuric or hyperpigmented discoloration of the skin. Underlying pathogenesis is a type III hypersensitivity reaction mediated by immune complexes. It is mostly idiopathic, however cases associated with connective tissue diseases (systemic lupus erythematosus), infections (hepatitis B and hepatitis C), medications (diltiazem, fluoxetine, potassium iodide, etc.) and malignancies have been reported. In histopathology, leukocytoclastic vasculitis is seen with signs of vessel damage, such as leukocytoclasis and fibrinoid deposits around venules. In contrast to urticaria, immunofluorescence of the skin shows deposits of immunoglobulins and complement [26, 27].

Systemic mastocytosis is a rare disorder in which atypical mast cells proliferate in the liver, spleen, lymph nodes, bone marrow and other organs. Involvement of the skin manifests as wheals and itching [5].

Urticarial lesions that persist beyond 24 hours should warrant alternative diagnosis, such as erythema multiforme minor, morbilliform drug eruption, dermatitis herpetiformis and bullous pemphigoid [9]. Erythema multiforme minor is an acute condition that differs from urticaria with its persistent targetoid lesions, and is typically less pruritic than urticaria [13].

Urticarial rash in a young child accompanied by fever, edema of hands and feet and arthralgias should prompt a diagnosis of serum sickness-like reaction. In this condition, urticarial plaques usually have an associated ecchymotic pattern. Serum sickness-like reaction is a hypersensitivity reaction that is often due to medications or infections. It develops 1–3 weeks

Urticarial vasculitis
Systemic mastocytosis
Erythema multiforme minor
Morbilliform drug eruption
Dermatitis herpetiformis
Bullous pemphigoid
Serum sickness-like reaction
Urticaria multiforme
Cryopyrin-associated periodic syndromes

Table 1. Differential diagnosis of urticaria.

after the initial antigen exposure and has a self-limited course. Urticaria multiforme is also a hypersensitivity reaction marked with annular urticarial plaques and bruise-like areas similar to that seen in serum sickness-like reaction. The triggering factor is often a viral infection; urticarial lesions are preceded by 1–3 days of fever [28].

Cryopyrin-associated periodic syndromes are autoinflammatory diseases including familial cold autoinflammatory syndrome, Muckle-Wells syndrome and the neonatal onset multisystem inflammatory disease. They present often early in infancy with a variable severity of clinical manifestations. Main symptoms are fever, arthralgias and skin involvement with urticaria-like nonpruritic lesions. Histopathologically, the perivascular infiltration is composed of polymorphonuclear cells in contrast with classical urticaria [29].

11. Management

Management of acute urticaria should initially focus on avoidance of any triggering factors, such as foods, drugs, insect venoms and latex. First-line treatment agents are antihistamines, corticosteroids and immunomodulatory agents are reserved for patients resistant to antihistamines [5].

11.1. Antihistamines

For the first-line management of acute or chronic urticaria, second-generation H_1 antihistamines are used. Fexofenadine, desloratadine, loratadine, cetirizine and levocetirizine are the most commonly prescribed agents [5, 10]. Symptomatic relief with suppression of the pruritus and reduction of the number and size of wheals is the main goal of treatment. Loratadine and cetirizine can be used starting from 6 months of age and are also safe during pregnancy [9, 10]. Efficacy of antihistamines is often patient specific and none are consistently superior [16].

Antihistamines target H_1 receptors located on endothelial cells and sensory nerves. First-generation antihistamines (hydroxyzine, diphenhydramine and chlorpheniramine) can penetrate central nervous system and thus have sedating effects lasting longer than 12 hours. However relief of pruritus is much short-lived and lasts only up to 6 hours. Older first-generation antihistamines are not recommended for the management of chronic urticaria in the European Guidelines because they place patients at risk for serious side-effects and drug interactions. In contrast to first-generation antihistamines, the second-generation antihistamines are devoid of sedating and anticholinergic effects [30]. Similar to first-generation H_1 antihistamines, the use of H_2 receptor blockers (cimetidine and ranitidine) are not recommended in European Guidelines.

Updosing of antihistamines is safe in therapy resistant patients. Fourfold higher doses of licensed doses of antihistamines should be used before considering other treatments [30]. However, according to US guidelines treatment by updosing second-generation H_1 antihistamines can

substituted with an add-on treatment with other second-generation H_1 antihistamines, H_2 antagonists, leukotriene receptor antagonists or first-generation H_1 antihistamines as alternative second step treatment options [31].

11.2. Corticosteroids

Corticosteroids can be used in the management of antihistamine-resistant cases of acute urticaria and exacerbations of chronic spontaneous urticaria. Long-term therapy with corticosteroids is strictly dismissed because of the risk of side effects and development of tolerance. Oral corticosteroids such as 7 days of prednisone up to 40 mg/day are often used to alleviate symptoms unresponsive to antihistamines in chronic urticaria [5]. Likewise, addition of a brief course of prednisone to antihistamines in acute urticaria significantly improves symptom control [32].

11.3. Leukotriene receptor antagonists

Leukotriene receptor antagonists, such as montelukast and zafirlukast, may have a role in the management of chronic urticaria. According to European Guidelines, leukotriene receptor antagonists may be considered in patients who do not respond to updosing of H_1 antihistamines, although evidence is low as compared to cyclosporine or omalizumab [30, 33].

11.4. Immunosuppressives

Cyclosporine has been shown to be effective in the treatment of recalcitrant cases of chronic spontaneous urticaria in combination with second-generation antihistamines especially cetirizine. Its mechanism of action depends on the inhibition of anti-IgE–induced histamine release from basophils and skin mast cells. Cyclosporine at 3–5 mg/kg/day is administered with monitorization of diastolic blood pressure and levels of serum creatinine, serum potassium, serum bilirubin and liver enzymes at each visit [34, 35]. Common adverse effects of cyclosporine therapy include hypertension, fatigue, gastrointestinal problems and headache [33].

Immunosuppressive therapy with mycophenolate, tacrolimus and methotrexate can also be considered in recalcitrant cases [31].

11.5. Omalizumab

Omalizumab is a recombinant humanized monoclonal anti-immunoglobulin E antibody that prevents binding of IgE to the high-affinity IgE receptor and thus prevents urticaria and angioedema. This new biologic treatment, applied by monthly subcutaneous injections in a standardized protocol, provides a rapid and effective control of treatment-refractory urticaria patients. Omalizumab is generally well-tolerated and safe. Major risks of omalizumab treatment include anaphylaxis, increased risk of cardiac and neurovascular events, and a controversial increased risk of lymphoma [16, 36, 37].

11.6. Phototherapy

Efficacy of phototherapy, both narrowband UVB and PUVA, has been shown in several studies. Phototherapy is not recommended in urticaria guidelines; still it appears to be a safe and effective therapeutic modality for patients with refractory chronic urticaria [38–40].

12. Angioedema without wheals

As described previously in this chapter, angioedema is defined as swellings of the deep dermis and subcutaneous tissue. Clinically, there is non-pitting asymmetrically distributed edema usually involving the face. Angioedema typically resolves spontaneously in less than 72 hours [41].

Clinically a variety of conditions may cause swellings that resemble angioedema. Acute contact dermatitis develops after exposure to a foreign substance. When acute contact dermatitis involves the face, it is frequently misdiagnosed as angioedema. Abrupt onset of angioedema associated with diffuse maculopapular rash, fever, eosinophilia and lymphadenopathy is seen in drug rash with eosinophilia and systemic symptoms (DRESS) Syndrome. Periorbital edema of dermatomyositis may mimic angioedema [41]. Other diseases to consider in differential diagnosis of angioedema are superior vena cava syndrome, myxedema of hypothyroidism, photodermatitis, Crohn's disease of the mouth and lips, facial cellulitis and Melkersson-Rosenthal syndrome [18, 41].

Angioedema without wheals can be classified as hereditary angioedema, acquired angioedema, drug-induced angioedema and idiopathic angioedema [42].

12.1. Hereditary angioedema

12.1.1. Epidemiology

Hereditary angioedema is rare genetic disease with a prevalence of about 1:10,000–1:50,000. The inheritance is autosomal dominant. In 20% of cases, a positive family history of the disease cannot be obtained because these cases occur due to spontaneous mutations [42].

12.1.2. Etiology and pathogenesis

Two types of the disease have been defined, both concerning the inhibitor of the first component of human complement (C1). Type I accounts for 80–85% of cases and is characterized by low C1 inhibitor levels and function. Type II comprises the remaining 15–20% of cases and it is associated with normal levels of poorly functioning C1 inhibitor. Both types of hereditary angioedema result in low levels of C4; during acute attacks C2 levels may also decrease [42].

The recently described hereditary angioedema type III is not associated with C1 inhibitor deficiency or dysfunction. The etiology of this very rare type of hereditary angioedema is not fully understood. It mostly affects women. Estrogens and mutations in factor XII are thought be involved in pathogenesis [43, 44].

C1 inhibitor is the major regulator of complement and contact system activation. With the decreased activity of C1 inhibitor, unopposed activation of contact system leads to generation of bradykinin. Bradykinin induces relaxation in vascular smooth muscle and increases vascular permeability causing angioedema [42, 44].

Trauma, stress, infection, menstruation, oral contraceptives, hormonal replacement therapy and angiotensin-converting enzyme (ACE) inhibitors can trigger the attacks. However an underlying trigger cannot be found in most of the cases [42, 44].

12.1.3. Clinical features

Clinically angioedema mostly involves the face, tongue and lips, abdomen, larynx, extremities and genitalia [42]. Any part of the body can be affected including chest, joints, muscles, etc. Abdominal colicky pain, nausea and vomiting are manifestations of gastrointestinal involvement. Edema of the upper airway tract can be life threatening [42, 43]. The onset of disease is usually in childhood mostly between 8 and 12 years. Episodic swellings last 1–5 days before subsiding. A serpiginous rash called erythema marginatum, fatigue and muscle aches are prodromal symptoms reported by 50% of patients with hereditary angioedema [44].

12.1.4. Prophylaxis and treatment

Management of hereditary angioedema can be classified under three different categories, which are treatment of the attacks, short-term or procedural prophylaxis and long-term prophylaxis [43].

Management of acute attacks can be accomplished by replacement of C1 inhibitor or alternatively by using icatibant or ecallantide. Plasma-derived or recombinant C1 inhibitors are available for intravenous replacement of C1 inhibitor. Icatibant is bradykinin B2 receptor antagonist. Human C1 inhibitors and icatibant are approved for self-administration. These agents are most effective when given as early as possible during the attacks. Ecallantide works by reversible inhibition of kallikrein and is approved by FDA for use in patients older than 12 years of age. Application by a healthcare professional is imperative because of a high risk of developing anaphylactic reaction [43].

As noted above trauma is among the well-known triggers of an angioedema attack. Thus a short-term prophylaxis is indicated before interventions in the upper aerodigestive tract, such as intubation, bronchoscopy or esophagogastroduodenoscopy. For this purpose C1 inhibitors are the first-choice agents. Androgens, which have been the mainstay of management of patients with hereditary angioedema in the past, are no longer considered as first-line

options because of associated side effects and are only used when C1 inhibitor therapy is not available. Weight gain, hepatotoxicity, virilism and hypertension are among the various side effects of androgen therapy [43, 44].

Long-term prophylaxis can be initiated if treatment of acute attacks does not result in adequate symptom control. C1 inhibitor concentrates are recommended as first-line agents. Androgens and tranexamic acid are less favored because of high risk of adverse effects and low treatment efficacy, respectively [43].

12.2. Acquired angioedema

12.2.1. Etiology and pathogenesis

Acquired angioedema is an autoimmune disease characterized by autoantibodies against C1 inhibitor [44]. A lymphoproliferative disorder such as non-Hodgin lymphoma or monoclonal gammopathy or an autoimmune disease is found in many of the cases. These associations suggest that pathological B cell clones may be responsible for acquired angioedema [45].

Acquired angioedema is divided into two types. Type I acquired angioedema is due to massive consumption of C1 inhibitor, presumably by tumor-related immune complexes. Type II acquired angioedema occurs due to the production of anti-C1 inhibitor autoantibodies [25].

12.2.2. Clinical features

Clinical features of acquired angioedema are similar to those seen in hereditary angioedema. Abdominal involvement is less frequent [44]. Absence of family history and late onset of symptoms at 4th decade are distinguishing features [42]. Laboratory evaluation of patients with acquired angioedema reveals low C4 levels and decreased C1 inhibitor activity similar to hereditary angioedema; but also decreased levels of C1q [44].

12.2.3. Treatment

Treatment of acquired angioedema mostly depends on treatment of the underlying disease [42]. Although response rates are low, treatments used for hereditary angioedema are frequently applied. Acute attacks can be managed by administration of C1 inhibitor concentrate or alternatively by using icatibant or ecallantide. High-dose corticosteroid therapy is used in order to reduce production of autoantibodies but it is frequently ineffective and has many adverse effects. Rituximab has also been shown to be effective in decreasing autoantibody production against C1 inhibitor. Although several reports of patients successfully treated with rituximab exist, the responses can be inconsistent [44, 46].

12.3. Drug-induced angioedema

Drug-induced angioedema is most typically associated with the use of angiotensin-converting enzyme (ACE) inhibitors. Angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, fibrinolytics and oral contraceptives can also induce isolated angioedema [18].

Angioedema due to angiotensin-converting enzyme inhibitors occurs in 0.1–6% of patients under treatment with ACE inhibitors. It tends to develop more commonly in women, smokers and in patients of African American descent [47]. ACE inhibitor angioedema mostly develops at the first month of treatment but may also occur years after starting the medication [42].

As the underlying mechanism involves elevated levels of bradykinin, antihistamines and corticosteroids are not helpful in the management of drug-induced angioedema. Although not FDA-approved for this indication, bradykinin receptor antagonist icatibant and kallikrein inhibitors are effective treatment agents [42, 48].

12.4. Idiopathic angioedema

The term idiopathic angioedema is used when there is no identifiable cause for the recurrent angioedema attacks without wheals. Idiopathic angioedema is a diagnosis of exclusion. C1 inhibitor deficiency, factor XII mutation, treatment with ACE inhibitors must be ruled out [49]. The condition is mostly well-controlled with prophylactic antihistamines [5].

Author details

Burhan Engin*, Muazzez Çiğdem Oba and Server Serdaroğlu

*Address all correspondence to: burhanengin2000@yahoo.com

Dermatology Department, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

References

[1] Novembre E, Cianferoni A, Mori F, et al. Urticaria and urticaria related skin condition/disease in children. Eur Ann Allergy Clin Immunol 2008; **40**:5–13.

[2] Zuberbier T. Classification of urticaria. Indian J Dermatol 2013; **58**:208–210.

[3] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. Allergy. 2011; **66**:317–330.

[4] Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. Allergy 2003; **58**:621–623.

[5] Kanani A, Schellenberg R, Warrington R. Urticaria and angioedema. Allergy Asthma Clin Immunol 2011;**7**:9.

[6] Magerl M, Borzova E, Giménez-Arnau A, et al. The definition and diagnostic testing of physical and cholinergic urticarias—EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy. 2009; **64**:1715–1721.

[7] Amar SM, Dreskin SC. Urticaria. Prim Care 2008; **35**:141–157.

[8] Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. Demographic and clinical profiles in patients with acute urticaria. Allergol Immunopathol 2015; **43**:409–415.

[9] Krishnaswamy G, Youngberg G. Acute and chronic urticaria. Challenges and considerations for primary care physicians. Postgrad Med. 2001; **109**:107–108, 111–114, 119–123.

[10] Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J Dermatol Venereol Leprol 2008; **74**:594–599.

[11] Yang HY, Sun CC, Wu YC, Wang JD. Stress, insomnia, and chronic idiopathic urticaria–a case-control study. J Formos Med Assoc 2005; **104**:254–263.

[12] Kaplan AP. Chronic urticaria: pathogenesis and treatment. J Allergy Clin Immunol 2004; **114**:465–474.

[13] Baxi S, Dinakar C. Urticaria and angioedema. Immunol Allergy Clin North Am 2005; **25**:353–367.

[14] Frigas E, Park MA. Acute urticaria and angioedema: diagnostic and treatment considerations. Am J Clin Dermatol 2009; **10**:239–250.

[15] Dibbern DA Jr, Dreskin SC. Urticaria and angioedema: an overview. Immunol Allergy Clin North Am 2004; **24**:141–162.

[16] Fine LM, Bernstein JA. Guideline of chronic urticaria beyond. Allergy Asthma Immunol Res 2016; **8**:396–403.

[17] Greaves MW. Urticaria. Clin Allergy Immunol 2002; **16**:381–400.

[18] Kaplan AP, Greaves MW. Angioedema. J Am Acad Dermatol 2005; **53**:373–388.

[19] Poonawalla T, Kelly B. Urticaria: a review. Am J Clin Dermatol 2009; **10**:9–21.

[20] Abdou AG, Elshayeb EI, Farag AG, Elnaidany NF. *Helicobacter pylori* infection in patients with chronic urticaria: correlation with pathologic findings in gastric biopsies. Int J Dermatol 2009; **48**:464–469.

[21] Kozel MM, Bossuyt PM, Mekkes JR, Bos JD. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. J Am Acad Dermatol 2003; **48**:409–416.

[22] Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999; **140**:446–452.

[23] Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? Allergy 2008; **63**:777–780.

[24] Moolani Y, Lynde C, Sussman G. Advances in understanding and managing chronic urticaria. F1000Res. 2016; **5**:177.

[25] Huston DP, Bressler RB. Urticaria and angioedema. Med Clin North Am 1992; **76**:805–840.

[26] Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am 2004; **24**:183–213.

[27] Black AK. Urticarial vasculitis. Clin Dermatol 1999; **17**:565–569.

[28] Mathur AN, Mathes EF. Urticaria mimickers in children. Dermatol Ther 2013; **26**:467–475.

[29] Neven B, Prieur AM, Quartier dit Maire P. Cryopyrinopathies: update on pathogenesis and treatment. Nat Clin Pract Rheumatol. 2008; **4**:481–489.

[30] Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. Allergy. 2009; **64**:1427–1443.

[31] Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014; **133**:1270–1277.

[32] Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. Ann Emerg Med 1995; **26**:547–551.

[33] Staubach P, Zuberbier T, Vestergaard C, Siebenhaar F, Toubi E, Sussman G. Controversies and challenges in the management of chronic urticaria. J Eur Acad Dermatol Venereol 2016; **30**:16–24.

[34] Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P, Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. J Am Acad Dermatol. 2006; **55**:705–709.

[35] Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000; **143**:365–372.

[36] Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. J Dermatol Sci 2014; **73**:57–62.

[37] Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc 2013; **34**:446–452.

[38] Berroeta L, Clark C, Ibbotson SH, Ferguson J, Dawe RS. Narrow-band (TL-01) ultraviolet B phototherapy for chronic urticaria. Clin Exp Dermatol 2004; **29**:97–98.

[39] Engin B, Ozdemir M, Balevi A, Mevlitoglu I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy: a randomized controlled trial. Acta Derm Venereol 2008; **88**:247–251.

[40] Bishnoi A, Parsad D, Vinay K, Kumaran MS. Phototherapy using narrowband ultraviolet B and psoralen plus ultraviolet A is beneficial in steroid-dependent antihistamine-refractory chronic urticaria: a randomized, prospective observer-blinded comparative study. Br J Dermatol 2017; **176**:62–70.

[41] Andersen MF, Longhurst HJ, Rasmussen ER, Bygum A. How not to be misled by disorders mimicking angioedema: a review of pseudoangioedema. Int Arch Allergy Immunol 2016;**169**:163–170.

[42] Banerji A, Sheffer AL. The spectrum of chronic angioedema. Allergy Asthma Proc 2009; **30**:11–16.

[43] Greve J, Strassen U, Gorczyza M, et al. Prophylaxis in hereditary angioedema (HAE) with C1 inhibitor deficiency. J Dtsch Dermatol Ges 2016; **14**:266–275.

[44] Zeerleder S, Levi M. Hereditary and acquired C1-inhibitor-dependent angioedema: from pathophysiology to treatment. Ann Med 2016; **48**:256–267.

[45] Castelli R, Deliliers DL, Zingale LC, Pogliani EM, Cicardi M. Lymphoproliferative disease and acquired C1 inhibitor deficiency. Haematologica 2007; **92**:716–718.

[46] Branellec A, Bouillet L, Javaud N, et al. Acquired C1-inhibitor deficiency: 7 patients treated with rituximab. J Clin Immunol. 2012; **32**:936–941.

[47] Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin North Am 2006; **26**:725–737.

[48] Bas M. The angiotensin-converting-enzyme-induced angioedema. Immunol Allergy Clin North Am 2017; **37**:183–200.

[49] Cicardi M, Suffritti C, Perego F, Caccia S. Novelties in the diagnosis and treatment of angioedema. J Investig Allergol Clin Immunol 2016; **26**:212–221.