URTICARIA AND ANGIOEDEMA

chapter 1

LEARNING OBJECTIVES

- Diagnose a case of urticaria and classify it based on trigger factors, clinical features and duration.
- Diagnose a case of angioedema and enlist causative factors.
- Differentiate a case of spontaneous urticaria from physical /contact urticarial and urticarial vasculitis.
- Work-up a case of urticaria and angioedema with an attempt to elicit a possible underlying etiology (by history taking and judicious use of investigations).
- Enumerate treatment modalities and institute treatment strategies for urticaria and angioedema.

INTRODUCTION

Urticaria is a heterogenous group of disorders characterised by eruption of *wheals* (syn. hives, 'nettle rash') Illustration 1 which are transient, itchy, well-demarcated, superficial erythematous or pale swellings of the dermis. Angioedema (syn. Angioneurotic oedema, Quinckeís oedema) is swelling that affects the deeper dermis, subcutaneous and submucosal tissues mainly of the dependent areas.

EPIDEMIOLOGY

Urticaria is a fairly common problem with an estimated cumulative lifetime prevalence of 1-5% for chronic urticaria. It may be seen at any age with slight female preponderance. Around 50% patients with urticaria have associated angioedema.

The characteristic lesion of urticarial is a wheal. This is a transient, raised, round, oval or bizarre lesion with a pale centre and erythematous margins. (Fig 14.1a and b) The size may range from a few millimetres to large confluent lesions, and the number of lesions is highly variable. Lesions are very pruritic and often evoke rubbing rather than scratching and excoriation marks are usually not found. Acute urticaria may present as an anaphylactic reaction, especially following intake of certain drugs and stings by bees and wasps.

Angioedema (AE) is a swelling that involves the deeper dermis, subcutaneous/submucosal tissue and is characterised by localized, episodic, non-erythematous and usually mildly pruritic but painful swelling involving areas with lax skin or mucosae such as eyelids, lips, upper respiratory tract and genitalia. (Fig 14. 2) It may be associated with anaphylaxis and edema involving the larynx and tracheobronchial tract with symptoms of dyspnoea and dysphagia which may be life threatening.

Illustration 1: Nettle leaf

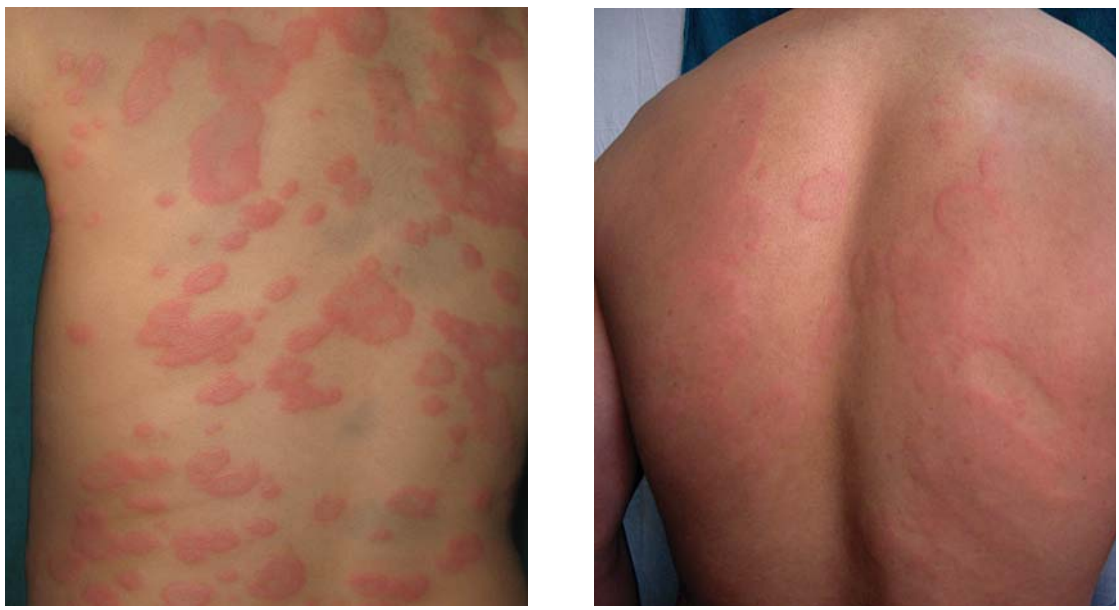

Figure 14.1a and b: Classical wheal

Figure 14. 2: Angioedema – Periorbital

CLASSIFICATION OF URTICARIA

Urticarias can be classified based on trigger factors, clinical features and duration (Table 1).

SPONTANEOUS URTICARIA

This term is used when physical urticaria, contact urticaria and urticarial vasculitis have been excluded. Wheals erupt spontaneously and usually subside within few minutes to hours and do not persist beyond 24 hours. Based on duration of the disease, spontaneous or ordinary urticaria may be:(can be put in tint box)

TABLE 1 Classification of urticaria

- Spontaneous urticaria

Acute, Chronic (Idiopathic or autoimmune), Episodic

- Contact urticaria
- Physical urticarias

- Acute: Wheals occur daily or almost daily for less than 6 weeks. More than 80% cases of first-time acute urticaria resolve within 2 weeks.
- Chronic: Urticaria persists for more than 6 weeks. An etiology is difficult to determine in most cases and more than 50% cases resolve spontaneously within 6 months.
- Episodic: Occurrence of recurrent episodes of acute urticaria (each episode lasting less than 6 weeks).

ETIOLOGY AND PATHOGENESIS OF ACUTE URTICARIA

Clinical features

1. Allergic – Mast cells are the major effector cells of urticaria. The pathogenesis of acute urticaria involves the interaction of an allergen with specific IgE

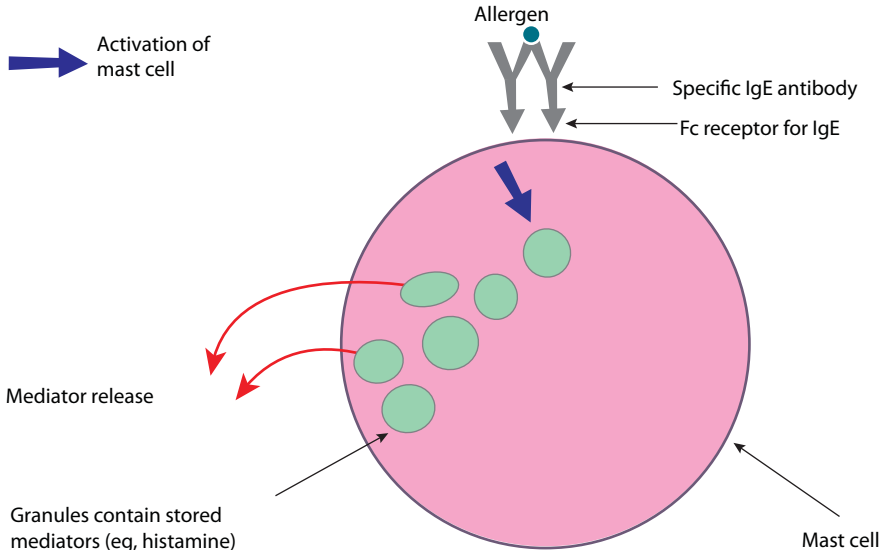

Illustration 2: Pathophysiology of Urticaria

antibodies which are bound to the mast cells. This antigen-IgE complex cross-links two FcεRIα receptors, which are high-affinity IgE receptors present on the mast cell surface, resulting in their activation and subsequent degranulation with the release of various mediators and cytokines (Illustration 2). This results in vasodilatation, local increase in permeability of capillaries and venules and leakage of plasma proteins and clinical manifestation of wheal formation. Histamine is the major mediator, acting via H1 and to a lesser extent H2 receptors. Eosinophils play a role in the persistence of wheals by generating leukotrienes and releasing major basic proteins.

Various allergens implicated are:

- Drugs- penicillins, cephalosporins, insulin, vaccines, blood products. Drug induced urticaria manifests within 36 hours of exposure to the drug.
- Foods- fish, milk, nuts especially peanuts, sesame seeds, beans, celery, parsley, carrots, spices, rice, bananas, apples, oranges
- Insect stings- bees and wasps of the order Hymenoptera
- Contactants - latex in rubber products such as gloves etc.
- Inhalants- pollens, animal dander, mould spores, house dust

2. Non-allergic – This occurs by direct histamine release from mast cells or due to other mechanisms such as pro-inflammatory lipo-oxygenase pathway products.
   - Drugs – aspirin, other NSAIDS, polymyxin, vancomycin, morphine, codeine, tubocurarine, iodine-based radiocontrast dyes, dextran-based plasma expanders.
   - Foods – Peanuts, cheese, meat, tomatoes, pineapple, avocados, strawberries, scromboid fish, shell fish and prawns, food dyes and preservatives-tartrazine
3. Infections – Dental, vaginal and urinary tract infections, streptococcal throat infection, hepatitis B, Epstein-Barr and rarely campylobacter jejuni infection.
4. Idiopathic – No cause can be identified in 50% patients with acute urticaria,.

ETIOLOGY AND PATHOGENESIS OF CHRONIC URTICARIA

It is difficult to determine an etiological cause. Around 50-60% cases of chronic urticaria qualify for chronic autoimmune urticaria and have circulating autoantibodies in their sera. Severe, longer-lasting or persistent lesions are seen and frequently associated with systemic symptoms, often non-responsive to anti-histamines. Patients show positive autologous serum skin test (ASST) in which a wheal develops when patient is injected with their own serum.

Remaining cases are labelled as chronic idiopathic urticaria (CIU) though there are certain known aggravating factors such as drugs, specific foods and food additives, inhalants, infections (dental sepsis, urinary tract and gall bladder infections, *Helicobacter pylori* infection, *Candida*), intestinal parasitic infestation (protozoa and helminths), implants (dental prosthesis, dental amalgam) and psychological stress. Association of chronic urticaria with collagen vascular diseases (lupus erythematosus, Sjogrenís syndrome) and autoimmune thyroid disease is well known.

CONTACT URTICARIA

Urticaria occurs following skin contact with substances like certain foods, preservatives, cosmetics and medicaments. It is of two types:

- Immunological contact urticaria (ICU), mediated by IgE (Type 1 hypersensitivity)
- Non-immunologic contact urticaria (NICU), mediated by prostaglandins rather than histamine.

In both types, lesions appear within minutes to an hour of contact with the provoking substances. While ICU occurs on secondary exposure to the substance in a pre-sensitized individual, NICU occurs on the first contact itself. In ICU, the reaction may evolve into generalised urticaria and anaphylactic shock.

PHYSICAL URTICARIAS

These are induced by a specific physical stimulus and usually have a chronic course. They account for up to 30% cases of all urticaria. Co-existence of a physical and ordinary urticaria in the same person is of common occurrence. The various types include:

Dermographism: The word 'dermographism' means skin-writing. It is the most common physical urticaria, frequently seen in young adults. It is induced by stroking of skin and lesions are often linear or may assume the shape of eliciting stimulus. (Fig 14. 3) Local erythema is followed by edema and surrounding flare. Dermographism may be seen as an exaggerated physiological response in 5% individuals (simple dermographism), who do not require any therapy.

Pressure urticaria: It results from sustained pressure e.g. at sites of tight clothing (like the waistline), pressure over buttocks after sitting, pressure of walking on feet, leaning against furniture etc. It can be immediate (onset within minutes and lasting for 30 min to few hours) or delayed (onset after a delay of 4-8 hours and lasting for 12-72 hours).Lesions are itchy, but may be painful and tender and often accompanied with systemic symptoms like arthralgia and myalgia.

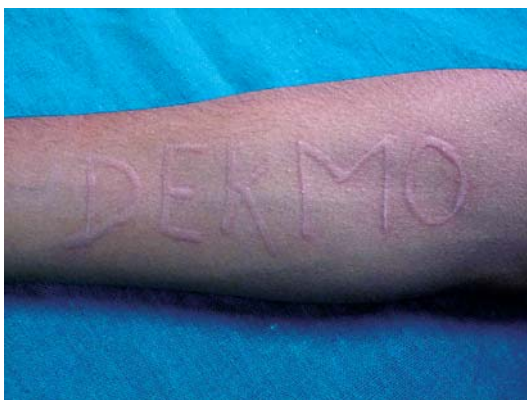

Figure 14.3: Dermographism

Cholinergic urticaria: It occurs as a consequence to sweating induced by rise in core temperature (exercise, hot bath), emotions or gustatory stimuli (spicy foods) and is characterized by the eruption of very small (1-3 mm) punctuate weals that appear within minutes of exertion.

Localized heat urticaria: A rare form in which wheals appear within a few minutes and last for up to 3 hours at sites of contact with heat.

Adrenergic urticaria: An extremely uncommon variant in which multiple small wheals are induced by **stress**, but not by heat or exercise.

Exercise induced anaphylaxis: Exercise (like jogging and active sports) induces anaphylactic symptoms. It usually starts with itching, followed by urticaria and often angioedema persisting for upto 4 hours. 'Food and exercise induced anaphylaxis' is another condition in which angioedema and/or anaphylaxis occur within minutes of exercise if it follows a heavy meal or prior ingestion of a specific food (wheat, shellfish, celery, nuts).

Solar urticaria: A rare entity, seen mostly in young adults following sun exposure. Wheals develop over photo exposed parts (most commonly chest and shoulders) within minutes of exposure and last for up to 2 hours. Face and back of hands are less commonly involved due to chronic light exposure-induced photo-tolerance.

Aquagenic urticaria: Contact with water leads to small wheals resembling cholinergic wheals, but lesions are few in number. Most common sites involved are upper trunk and neck and it is usually seen in young adults.

Cold urticaria: It is caused by cold exposure – cold winds, rain, cold water. Wheals appear within minutes and last for up to 1 hour. Angioedema of the lips may occur following sipping cold water.

Vibratory angioedema: A rare entity induced by vibratory stimuli (typing, vigorous towelling, use of lawn-mowers and pneumatic instruments). Wheals appear within minutes and lasts for less than a few hours.

URTICARIAL VASCULITIS

It is characterised by occurrence of urticarial wheals that persist beyond 24 hours. The lesions may burn as well as itch, are often tender or painful and resolve with residual staining. It is a type III hypersensitivity reaction with antigen-antibody complex formation and evidence of vasculitis on histology. Though most cases are idiopathic, association with viral and bacterial infections, connective tissue diseases like lupus erythematosus and Sjogrenís syndrome, and drugs has been reported. An attempt should always be made to distinguish ordinary urticaria from urticarial vasculitis since management of the two conditions differs (Table 2).

URTICARIA ASSOCIATED WITH OTHER SYNDROMES

Schnitzlerís syndrome: Urticarial vasculitis is associated with monoclonal gammopathy.

Muckle-Wells/ familial cold urticaria syndrome: It is characterized by fever, urticaria, chills, sensory deafness, and neuropathy due to amyloidosis.

Familial Mediterranean fever: It is characterized by fever, urticaria, erysipelas-like lesions, renal amyloidosis, serositis, and synovitis.

TABLE 2 Differences between urticaria and urticarial vasculitis

Feature	Urticaria	Urticarial vasculitis
Duration of wheals	<24 hours (few min. to hrs)	>24 hours
Symptoms	Itching only	Itching, burning, pain and tenderness
Resolution	No residual staining	Residual staining or bruising often seen
Systemic symptoms	Uncommon	Arthralgia, abdominal pain, nausea, microscopic proteinuria, hematuria
Skin histology	Dermal oedema, vascular and lymphatic dilatation, mixed peri-vascular infiltrate.	Evidence of vasculitis (endothelial swelling, fibrinoid deposits in and around blood vessels, leukocytoclasia)
Etiology	Type I hypersensitivity	Type III hypersensitivity reaction
Management	Antihistaminics	Steroids, dapsone, colchicine, anti-malarials

CLASSIFICATION OF ANGIOEDEMA

Angioedema is classified based upon the presence or absence of wheals.

Angioedema with wheals: This is a type 1 hypersensitivity reaction. The reaction is triggered within few minutes by foods (e.g. fish, shellfish, and nuts), contact with latex, or drugs (most commonly beta-lactam antibiotics) and is more common in atopic individuals. It may also occur due to aspirin and other NSAIDS due to the inhibition of cyclo-oxygenase pathway of arachidonic acid metabolism. Similar to physical urticarias, AE may be triggered by physical stimuli in susceptible individuals.

Angioedema without wheals: This can be of two types.

- Angiotensin-converting enzyme inhibitor associated – It may occur at any time after commencing treatment, but usually manifests within 3 weeks.
- C1 esterase inhibitor deficiency associated: This may be hereditary or acquired. Hereditary form is an autosomal dominant-inherited trait characterised by deficiency of C1 esterase inhibitor (C1INH) or presence of dysfunctional C1INH. Components of complement (C2, C4 and CH50), especially C4 are low. Attacks are often associated with nausea, vomiting, colicky abdominal pain and urinary symptoms. Acquired form is due to increased catabolism of C1INH by different mechanisms resulting in its low levels. Associated conditions include B-cell lymphomas, lymphocytic leukaemias, paraproteinemias, connective tissue disorders like SLE and carcinomas. The clinical presentation is similar to that of hereditary form, but onset is at a later age.

Idiopathic angioedema: No specific cause is identifiable and the role of histamine and mediators like leukotrienes in the pathogenesis is likely.

APPROACH TO A PATIENT WITH URTICARIA AND ANGIOEDEMA

History: A detailed history and eliciting the nature of the wheals and trigger factors forms the most important aspect of management. The following details should be considered:

- Onset, duration and course of wheals – Acute or chronic, any physical stimulus involved, and to differentiate ordinary urticaria from urticarial vasculitis. The wheals lasting longer than 24 hours should raise suspicion about urticarial vasculitis.
- Location, number and shape of wheals: characteristic small, monomorphic wheals of cholinergic urticaria and linear wheals of dermographism.
- Enquiry about systemic symptoms- these are often seen in urticarial vasculitis and may be seen in delayed pressure and cold urticaria too. History of abdominal symptoms and family history is suggestive of hereditary angioedema.
- Possible precipitating or aggravating factors – Physical stimuli, recent acute infection, drug intake, or intake of a particular food/ preservative/ additives.

INVESTIGATIONS

Acute urticaria – Skin prick testing with suspected allergens may be done cautiously since anaphylaxis may be precipitated in a sensitive individual. A panel of semi-quantitative radio-allergosorbent test (RAST) or fluoro-immunoassay that measure antigen-specific antibody in the serum for some antigens like suspected food substances can be undertaken. However, it is an expensive test done at few centres only.

Chronic urticaria – A total and differential blood count (TLC/DLC) is performed routinely; eosinophilia may be indicative of parasitic infestation. An elevated erythrocyte sedimentation rate (ESR) suggests possibility of an underlying systemic disease like urticarial vasculitis, lupus erythematosus, and screening for thyroid autoantibodies may be worthwhile. Antinuclear antibody titres are done in suspected urticarial vasculitis.

Other tests: urine (for infection) and stool examination (for ova and cysts), complement levels, serum immunoglobulins, serum IgE levels, RAST, skin tests, etc.

Autologous serum skin test (ASST) helps to detect autoimmune urticaria.

Skin biopsy may be helpful if wheals persist beyond 48 hours and do not respond to antihistamines, suggesting the possibility of urticarial vasculitis or delayed pressure urticaria. Skin biopsy reveals leucocytoclastic vasculitis and increased number of neutrophils.

Screening tests for C1INH deficiency includes plasma complement C4 levels. Quantitative and qualitative studies of C1esterase inhibitors can be undertaken if C4 levels are low.

TREATMENT

General Measures – Elucidation of any specific triggering or precipitating factors and their elimination is the most important, but least amenable practically. Avoidance of certain non-specific triggers such as NSAIDS may help a few, but not all patients with CU.

Food diary: The patient is instructed to make a list of foods that are suspected to be allergenic. This can then be subjected to diet elimination test or re-challenge.

PHARMACOLOGICAL MEASURES IN URTICARIA

First-line therapy – H1-antihistamines are the cornerstone of urticaria management, as nearly all symptoms are primarily mediated by histamine via H1-receptors. Antihistamines are required for a short period of time (<6 weeks) in acute urticaria while CU needs prolonged use of antihistamines for indefinite periods.

H1-antihistamines are divided into three generations relating to their development and properties. In general, the second and third generation antihistamines are preferred due to their less likelihood of causing sedation, minimal anti-cholinergic effects and less frequent dosing schedules resulting in better patient compliance. Antihistamines can be used in the following ways:

- Use of a single antihistaminic drug to achieve control – the second and third generation antihistaminics (Cetirizine 5-10 mg, loratadine 10 mg, ebastine 10-20 mg, levocetrizine 5mg, desloratadine 5mg, fexofenadine 30-180 mg) should be preferred over the first generation compounds (Diphenhydramine 25-50 mg, promethazine 25-50 mg, chlorpheniramine 2-4 mg, pheniramine 25 -50mg, hydroxyzine 25-50 mg).
- Use of combination of antihistamines vs incremental doses of a single agent – In cases not responding to a single agent, a combination of agents- one first generation and one second or third generation drug may be used e.g. cetirizine with chlorpheniramine, or loratidine with fexofenadine. Higher doses (four fold times) of non-sedating antihistamines have been used successfully.
- Addition of H2-antihistamines – An H2-antihistaminic (ranitidine, famotidine) added to a regimen of H1-antagonists may be beneficial in some cases.
- Use of dual-receptor (H1 + H2) blocker antihistamines such as doxepin (10-50 mg at night) or cyproheptadine (4 mg upto thrice a day) may be tried.

Safety issues with prolonged antihistamines have been outlined in Table 3.

Second-line therapy – Systemic steroids –A short tapering course of oral prednisolone (0.5-1.0 mg/kg/day) may be required in severe acute, recalcitrant CU and severe urticarial vasculitis. Parenteral steroids along with parenteral antihistamines are indicated for acute control of anaphylaxis.

Leukotriene antagonists – Montelukast (10 mg once a day), and zafirlukast (20 mg twice a day) are newer drugs with good

TABLE 3 Safety issues with antihistamines

Sedation	Avoid driving, or engage in any machinery-related work to prevent accidents, especially with first generation drugs.
Anti-cholinergic effect	Dry mouth, precipitation of glaucoma, urinary retention in patients with prostatic hypertrophy (elderly males)
Cardiac	Terfenadine and astemizole have been reported to cause prolongation of Q-Tc interval triggering torsades de pointes, a fatal cardiac arrhythmia
Pediatric and geriatric	Paradoxical excitation can occur in children and elderly, with first generation drugs.
Pregnancy	Though no H1-antangonist has been found to be teratogenic, they should preferably be avoided in pregnancy. Chlorpheniramine appears to be the least risky. Loratidine is found useful.
Lactation	First generation drugs may cause irritability, drowsiness or rarely respiratory depression in the breast-fed babies.
Drugs and alcohol	Anti-depressants and alcohol add to the sedative effect of antihistamines.
Liver and Kidney failure	First generation antihistamines and mizolastine are avoided in liver disease while fexofenadine and desloratadine can be used. In renal impairment, cetirizine and levocetirizine are avoided, while loratadine and desloratadine can be used with caution.

efficacy and safety and may be used as adjuvant to antihistamines to achieve better control.

Others – Calcium channel blocker nifedipine and phototherapy (PUVA and narrow band UVB) have been used as adjuvant to antihistamines.

Third-line therapy – These are required only for patients with severe unremitting urticaria not responding to aforesaid therapies. Plasmapheresis, intravenous immunoglobulin (IVIG) infusions (0.4g/kg/day for 5 days), cyclosporin-A (2.5-4 mg/kg/day up to 3 months) and methotrexate have been shown to be effective in some studies.

PHARMACOLOGICAL MEASURES IN URTICARIAL VASCULITIS

Antihistamines, oral steroids, NSAIDS, colchicine, dapsone, hydroxychloroquine have been used in mild cases. In severe and refractory cases, immunosuppressives may be required such as methotrexate, cyclophosphamide, azathioprine, cyclosporin and mycophenolate mofetil. Other therapies tried include pentoxyfilline, thalidomide, interferon and plasmapharesis.

PHARMACOLOGICAL MEASURES IN ANGIOEDEMA

Mild cases can be controlled with antihistamines and short tapering course of oral steroids. Parenteral steroids and antihistamines are indicated in severe angioedema. In cases of anaphylaxis and laryngeal edema, subcutaneous epinephrine should be immediately given. Tracheostomy is required if edema is severe enough to compromise the airway. (Fig 14. 4)

In cases of C1INH deficiency, C1INH concentrates in severe cases, androgenic drugs like danazol and stanozolol; antifibrinolytic drugs such as ε-aminocaproic acid and tranexamic acid are used. Plasmapheresis and cytotoxic drugs may be needed in refractory cases. Patients with acquired C1INH deficiency should undergo treatment of the underlying condition.

Figure 14.4: Angioedema of lips with laryngeal edema

KEY POINTS

Urticaria is a common skin disease characterized by wheal formation and can be acute (< 6 weeks), chronic (> 6 weeks) or episodic in nature.

Various allergens have been implicated to trigger urticaria such as foods, drugs, infections and infestations, contact allergens, inhalants. However, approximately 50% cases remain idiopathic.

Urticarias are classified as spontaneous, physical and contact urticaria and need to be differentiated from urticarial vasculitis.

Angioedema is characterized by swelling involving areas with lax skin or mucosae such as eyelids, lips, upper respiratory tracts, genitalia and can be associated with urticaria; anaphylaxis is a life threatening complication.

Identifying the cause, anti-histamines and steroids form the mainstay of management in urticaria and angioedema.

FURTHER READING

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