Dermatology. **Lecture: 4**
Dr. Intisar Ahmed **Stage: 5**

Urticaria

*Is a common disease with many different clinical presentations, characterized by short-lived swellings of the skin and mucosa due to plasma leakage.
*Weals (hives) is the descriptive term for transient, well-demarcated, superficial erythematous or pale swellings of the dermis, which are very itchy and are associated with a surrounding red flare initially.
*Angio-oedema is swellings affect the deeper dermal, subcutaneous and submucosal tissues, painful rather than itchy, poorly defined, and pale or normal in colour.
*Anaphylaxis, is an acute, severe, life-threatening, generalized or systemic hypersensitivity reaction. It consists of a combination of symptoms and signs, including diffuse erythema, pruritus, urticaria and angiooedema, hypotension and difficulty in breathing.
*May occur at any age; up to 20% of the population will have at least one episode.

Clinical Classification of Urticaria:

1.Ordinary urticaria (recurrent or episodic urticaria not in the categories below)
2.Physical urticaria (defined by the triggering stimulus)

- Adrenergic urticaria
- Aquagenic urticaria
- Cholinergic urticaria
- Cold urticaria
- Delayed pressure urticaria
- Dermographism
- Exercise-induced anaphylaxis
- Localized heat urticaria
- Solar urticaria

3.Contact urticaria (induced by biologic or chemical skin contact)
4.Urticarial vasculitis (defined by vasculitis as shown by skin biopsy specimen)
5.Angioedema (without wheals)

Pathophysiology:

*Histamine is the most important mediator of urticaria.
*Histamine is produced and stored in mast cells (primary cell responsible for urticaria)

*A variety of stimuli cause histamine release by process called degranulation through two mechanism:

1. Immunologic mechanisms:

-Autoimmune (autoantibodies against FcεRI or IgE).
-Immune complex (vasculitic).
-Complement-dependent (C1 esterase inhibitor deficiency).

2. Non-immunologic mechanisms:

-Drugs: opiate derivatives (morphine and codeine), vancomycin, polymyxin, aspirin, non steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors.
-Chemical: radiocontrast media.
-Foods: strawberries.
-Vasoactive stimuli: nettle stings.

*Histamine causes localized capillary vasodilatation, which allows vascular fluid to leak between the cells through the vessel wall, contributing to tissue edema and wheal formation.

Ordinary urticaria:

Clinical features:

*Itching erythematous macules develop into weals consisting of pale to pink, oedematous, raised areas of the skin often with a surrounding red flare.
*Occur any where on the body, including scalp, palms and soles.
*Variable numbers and sizes, ranging from a few millimetres to large areas.
*Varying shapes including rounded, annular, serpiginous and bizarre patterns due to confluence of adjacent lesions.
*Very rarely, bullae may form when oedema is intense.
*Weals last a few hours and resolve within **24 h**, leaving the skin with a normal appearance.
*They are very itchy, particularly at night.
*Patients tend to rub rather than scratch, so excoriation marks are unusual.
*May be associated with angio-oedema in 50% of patients.
*May be preceded by vomiting and be associated with systemic symptoms of malaise, loss of concentration, low mood, feeling hot and cold, headache, abdominal pain, diarrhoea, arthralgia, dizziness, syncope and, in its most severe acute form, with anaphylaxis.

Acute Urticaria:

*Urticaria is present daily or almost daily for less than **6 weeks**.
*More common in children and young adults.
***Aetiology of Acute urticaria:**

1. Idiopathic.
2. Infectious.
-Upper respiratory tract infection.
-Streptococcal infection.
-Hepatitis B infection.
3. Allergy (immediate hypersensitivity).
-Foods.
-Drugs.
-Inhalants.
4. Non-allergic.
-Histamine liberators (e.g. codeine).
-Pseudoallergens: *Aspirin and other non-steroidal anti-inflammatories.
*Dietary (food additives, natural salicylates).
*Radiocontrast media.

Chronic Urticaria:

*Hives lasting for **6 weeks or more.**
*The etiology is often unclear, and determined in less than 5% to 20% of cases.
*More common in middle -aged women, infrequent in children.
***Aetiology of chronic urticaria:**
1. Idiopathic.
2. Autoimmunity: functional autoantibodies.
3. Pseudoallergy: salicylates, food colours, preservatives, antioxidants.
4. Infection: bowel parasites, helicobacter pylori, bowel candidiasis, chronic sepsis (e.g. dental abscess).

Associations with chronic ordinary urticaria.

1.Autoimmune disease: thyroiditis, vitiligo, pernicious anaemia, systemic lupus erythematosus, coeliac disease.
2.Infection: helicobacter pylori gastritis.
3.Malignancy.

Physical Urticarias:

*Physical urticarias are induced by physical and external stimuli.
*They typically affect young adults.
*More than one type of physical urticaria can occur in an individual.
*Most physical urticaria forms persist for about 3 to 5 years or longer.

Dermographism:

*Most frequent.
*This involves the triple response that arise from firm stroking of the skin (local erythema followed by oedema and a surrounding flare), accompanied by itching.

*Most common in young adult.
*Starts in minutes, lasting 2 -3 hours.
*No systemic symptoms.
*Darier's sign (wealing following friction) positive.
*Rx: Antihistamine, NBUVB, PUVA.

Delayed pressure urticaria:

*Frequent.
*Wealing occurs at sites of sustained pressure applied to the skin after a delay of 30 min to 9 h, but usually 4–8 h, and lasts 12–72 h
*Weals occur frequently under tight clothing, on hands after manual work, on buttocks and lower back after sitting and on feet after walking.
*Lesions may be itchy, but are often tender or painful, particularly on the soles and scalp.
*May be accompanied by systemic symptoms of malaise, flu-like symptoms, arthralgia, myalgia and leukocytosis.
*Rx: Oral steroids, Topical steroid under occlusion.

Cholinergic Urticaria:

*Very frequent.
*Cholinergic urticaria occurs in response to sweating caused by an increase in core temperature, also can be triggered by emotional and gustatory sweating.
*The patient complains of itching weals that starts in 2-20 minutes, lasting ½ - 2 h.
*The weals are small, 1–3 mm across, with or without a well-marked flare.
*Anaphylaxis and angioedema may occur.
*Rx: Anticholinergics, Antihistamines, Tranquillizers.

Exercise-induced anaphylaxis:

*Patients develop pruritus, urticaria, respiratory distress, and hypotension after exercise.
*Exercise acts as a physical stimulus provokes mast cell degranulation and elevated serum histamine levels.
*Lesions are large and are not produced by hot showers, pyrexia, or anxiety.
*Rx: H 1 antihistamines, epinephrine by auto-injector may be required.

Cold urticaria:

*Cold urticaria syndromes are a group of disorders characterized by urticaria, angioedema, or anaphylaxis that develops after cold exposure.
-Primary acquired cold urticaria: Occurs in children and young adults, local whealing and itching occur within a few minutes of applying a solid or fluid cold stimulus to the skin and lasts for about a half hour. Spontaneous improvement occurs in an average of 2 to 3 years.

-Secondary acquired cold urticaria: Occurs in about 5% of patients with cold urticaria. Wheals are persistent, may have purpura, and demonstrate vasculitis on skin biopsy.

Solar urticaria:

Hives occur in sun-exposed areas minutes after exposure to the sun and disappear in less than 1 hour.

Evaluation and Management of Urticaria:

1. History and physical examination.
2. Ix: CBP , ESR, GSE, GUE, urine and blood sugar, liver and renal function tests
3. Skin test: commonly used in patient with chronic urticaria.
4. Tx

1. Non-pharmacological:

-Avoid aggravating and provoking factors.

-Medications that exacerbate the hives (usually NSAIDs, aspirin, or beta blockers) should be stopped until the urticaria resolves.

2. Pharmacological:

-**First line (antihistamines):**

• Second generation H1 antihistamine (loratadine,desloratdin).
• Add sedating antihistamine (diphenhydramine , hydroxyzine).
• Increase above licensed dose.
• Add H2 antihistamine (ranitidine, famotidine).

-**Second line (targeted treatments):**

• Steroids (short term only for delayed pressure urticaria and urticaria vasculitis or single doses for severe exacerbations of ordinary urticaria.
• Epinephrine for throat angio-oedema.
• C1 esterase inhibitor for hereditary angio-oedema swellings.
• Doxepin (for anxiety).
• Montelukast for aspirin sensitivity.
• Dapsone for urticarial vasculitis and delayed pressure urticaria.

-**Third line (immunodulatory):**

• Ciclosporin.
• Mycophenolate.
• Methotrexate.
• Intravenous immunoglobulins.
• Therapeutic monoclonals.

***Note/** In acute sever urticaria we can start treatment by IM antihistamine , IVsteroid (hydrocortisone) and S.C. adrenaline.
***Note/** We must exclude certain disease commonly associated with chronic urticaria as chronic infection especially sinus infection, UTI, connective tissue diseases, intestinal warms, internal malignancy and lymphoma.

Urticarial vasculitis:

*Is a subset of vasculitis characterized clinically by urticarial lesions, histologically by necrotizing vasculitis.
*Immune complexes are lodge in small blood vessels with activation of complement, mast cell degranulation, infiltration by acute inflammatory cells, fibrin deposition, and blood vessel damage.
*Two types:
-Normocomplementemic urticarial vasculitis: Skin-limited, idiopathic.
-Hypocomplementemic vasculitis: Highly associated with systemic disease.
*Females >50 y most commonly affected.
*Systemic symptoms include angioedema, arthralgias, pulmonary disease, and abdominal pain.
*Lesion last more than 24 hours, painful or burning, resolve with purpura or hyperpigmentation.
*Treatment:
-Primary: antihistamines, oral steroids, indomethacin.
-Alternatives: dapsone, colchicine, hydroxychloroquine.
-Severe: Rituximab, IVIG.

Angioedema:

*Angiooedema: swellings affect the deeper dermal, subcutaneous and submucosal tissues. usually painful rather than itchy, poorly defined, and pale or normal in colour.
*Occur on the face; eyelids and lips, and any other area such as ears, neck, hands, feet and genitalia.
*Mucosal swellings occur inside the oral cavity on the buccal mucosa, tongue and pharynx but laryngeal involvement is fortunately rare.
*May be preceded by an itching or tingling sensation, but it is not always itchy and may be painful.
*The lesions may last for several days.

Classification:

1. Acquired.

-Idiopathic.

-Drug-related: Angiotensin converting enzyme inhibitors, Non-steroidal anti-inflammatory drugs.

-Physical: Exercise-induced angio-oedema, Vibratory angio-oedema.

-Acquired C1 esterase inhibitor deficiency: Lymphoproliferative disease, C1 inhibitor autoantibody.

2. Hereditary angio-oedema:

-C1 esterase inhibitor deficiency.

Type I (reduced absolute level of C1 esterase inhibitor).

Type II (reduced functional inhibitor but normal or increased level)

-Normal C1 esterase inhibitor.

Type III (oestrogen-dependent)

Vasculitis

*Inflammation within the vessel wall, with endothelial cell swelling, necrosis or fibrinoid change.

*The clinical manifestations depend upon the size of the blood vessel affected.

Classification:

1. Large vessel vasculitis: Giant cell arteritis, Takayasu's arteritis.
2. Medium-sized vessel vasculitis: Polyarteritis nodosa, Kawasaki disease.
3. Mixed small and medium vessel vasculitis: Mixed cyroglobulinemia, ANCA-associated.
4. Small vessel vasculitis: Henoch-Schönlein purpura, Acute hemorrhagic edema of infancy, Urticarial vasculitis.

Small vessel vasculitis: (Henoch-Schönlein purpura)

*Most common vasculitis.

*90% of cases occur in children<10 yr with male predominance.

*Seasonal variation, with winter predominance.

Pathophysiology:

*Immune complexes may lodge in the walls of blood vessels (principally the postcapillary venules), activate complement and attract polymorphonuclear leucocytes.

*Enzymes released from these can degrade the vessel wall.

*Antigens in these immune complexes include: drugs, autoantigens, and infectious agents such as viruses and bacteria.
*Ab is of IgA type.
*Occurs 1–2 weeks after URI or Streptococcus infection and other infections as Bartonella henselae, Parvovirus B19, S. aureus, H. pylori, and Coxsakie virus.
*Drug exposure reported in a minority of patients.

Clinical presentation:

***Skin**: crops of painful palpable purpura in dependent areas (buttocks and lower extremities, forearm and flanks).
***Musculoskeletal**: athralgias, arthritis of the knees and ankles.
***GI**: colicky abdominal pain, diarrhea, melena.
***Renal**: hematuria and risk of nephritis, ESRF (1%–3%).

Course:

*Resolution following removal of the precipitant.
*10% may have repeated episodes.
*The presence of nephritis predicts a worse prognosis.

Investigations:

*physical examination.
*Chest X-ray.
*ESR.
*Biochemical tests monitoring the function of various organs.
*Urine analysis, checking for proteinuria and haematuria, is the most important.
*Blood pressure checking.
*Skin biopsy confirm the diagnosis.

Treatment:

*Supportive measure as bed rest, antihistamine as it is self limited disease in weeks to months.
*NSAIDs for painful skin lesions and associated arthralgias but should be avoided if there is renal involvement.
*Colchicine or dapsone may shorten duration and help with skin finding.
*Patients with kidney involvement may need systemic corticosteroids or immunosuppressive agents such as cyclophosphamide.