2) Disorders of Abnormal Keratinization - Dr. Ali

Disorder of Keratinization

- In the normal epidermis, as the keratinocytes move from the basal-cell layer to the surface, the process of terminal differentiation and cornification involves complex metabolic changes.
- Disorder of keratinization: a group of different skin diseases, which are due to abnormality in keratinization.

Types:

- Ichthyoses
- Keratosis pilaris
- Keratosis follicularis
- Palmoplantar Keratoderma
- Corns
- Callosities

Ichthyosis

- The word ichthyosis comes from the Greek word for a fish.
- **Ichthyosis**: is a group of disorders that are characterized by a persistent, non-inflammatory scaling disorder of the skin surface. It is caused by abnormality in keratinization and exfoliation of the horny cell layer.
- The skin is covered with what appear to be fish-like scales.
- Scales may vary in size, color, and body site.
- The clinical manifestations of the different forms of ichthyosis and their disease course are extremely variable.
  - **Non syndromic ichthyosis**: isolated cutaneous features
  - ** Syndromic ichthyosis**: associated with extra-cutaneous symptoms

Types of non syndromic ichthyosis

a) Congenital ichthyosis
   - Ichthyosis vulgaris
   - X-linked ichthyosis
   - Bullous congenital ichthyosiform erythroderma (BCIE)
   - Nonbullous congenital ichthyosiform erythroderma (NBCIE)
   - Lamellar ichthyosis

b) Acquired ichthyosis
   - Acquired ichthyosis

Types of syndromic ichthyosis

- Sjögren-Larsson syndrome
- Netherton syndrome
- KID syndrome
- Refsum syndrome
- Rud syndrome
Ichthyosis vulgaris

- It is the common inherited disorder of keratinization. Inheritance is autosomal dominant (AD).
- **Etiology:** It is caused by mutation in the gene coding for filaggrin, a key protein involved in skin barrier function.
- **Pathogenesis:** As a result of a decrease in the production of filaggrin, which moisturizes the epidermis, there is abnormal exfoliation and dryness and scaling.
- **Histopathology (H/P):** There is thickening of the horny cell layer reduction or loss of granular cell layer.
- **Age of onset:** appearing in the first months of life.
- **C/F:** This is the mildest form of ichthyosis.
  - The main symptoms are dryness and scaling of the skin (fine scale).
  - Which present, mostly on the extensor surfaces of extremities and trunk. (back > abdomen, extensor surface > flexor surface)
  - The flexures of joints is spare.
  - Some cases of ichthyosis are associated with atopic dermatitis or Keratosis pilaris
  - The symptoms subside during the summer and aggravate during the winter
- **RX:** are symptomatic. Moisturizer, urea ointments, salicylic acid petrolatum, and vitamin D3 ointments are applied.
- **Prognosis:** The symptoms subside after adolescence (improve with age)

X-Linked Recessive Icthyosis

- Its uncommon type
- **Etiology:** It is caused by loss or marked reduction of steroid sulfatase enzyme resulting in delayed exfoliation of the horny cell layer.
- **Inheritance:** It is X-linked recessively inherited affects male children in the family only.
- **Pathogenesis:** the lack of steroid sulfatase causes accumulation of cholesterol sulfate, leading to delayed exfoliation of horny cells and hyperkeratosis.
- **H/P:** Thickening of the horny cell layer. Normal or mildly thickened granular and suprabasal cell layers.
- **C/F:** ichthyosis manifests shortly after birth and does not improve with age.
  - The symptoms are severer than those of ichthyosis vulgaris, the scales are large and dark brown.
  - The scalp is scaly.
  - Eruptions also appear on the flexures of joints.
  - The whole body of newborns may be encased in a translucent covering (collodion baby).
- **Complication:** Corneal opacification may occur.
- **D.DX:** ichthyosis vulgaris is differentiated from X-linked ichthyosis by the decrease of steroid sulfatase in the case of the latter.
- **RX:** The treatments are symptomatic and the same as those for ichthyosis vulgaris. The retinoids drugs may give good improvements, but the side effects limit their use in infants and young children and may be reserved for severe reluctant cases in older age groups.

LAMELLAR ICTHYOSIS & Nonbullous congenital ichthyosiform erythroderma (NBCIE)

- **Etiology:** Defect in Transglutaminase–1 enzyme in some cases that is necessary for the formation of cornified cell envelopes in keratinocytes.
- Rare conditions.
- Both may inherited as an autosomal recessive trait (AR).
- In both of them the skin changes begins usually at birth and those of collodion baby.
• Later the two conditions can be distinguished by:
  o Quadrilaterally shaped large dark brown scales, free at the edges and adherent in the center and plate-like or lamellar in LAMELLAR ICTHYOSIS while finer scaling and diffuse flushing in NBCIE
  o Both last for life.
• The areas involved in mild cases are the antecubital, popliteal and the neck.
  o The palms and soles may present with mild hyperkeratosis (PPK).
  o Ectropion of eyelids may also occur.
• Dermatopathology: Hyperkeratosis; granular layer present; acanthosis.
• RX: Oral retinoid (a vitamin A derivative) is effective.

Epidermolytic Hyperkeratosis, Bullous congenital Ichthyosiform Erythoderma (BCIE)

• It is rare autosomal dominantly inherited. (AD)
• Sometimes born as collodion babies
• Presents at or shortly after birth with blistering.
• With time skin becomes keratotic, verrucous.
• Shedding of hyperkeratotic masses results in circumscribed islands of normal-appearing skin.
• Involvement of flexural areas.
• Palmar and plantar involvement.
• May have erythroderma
• Frequent skin infections; characteristic odor.
• Pathogenesis: The cytoskeleton (intermediate filament) of suprabasal cells composed of keratin 1 and keratin 10.
• Because of this defect, abnormal keratin fiber formation, cytoskeleton distortion, and epidermal blistering occur, leading to secondary thickening of the horny cell layer.
• H/P: The horny and suprabasal cell layers thicken. Degeneration of the granular cell layer.
• D.DX: Blistering is marked particularly in newborns. It is necessary to differentiate BCIE from epidermolysis bullosa, incontinentia pigmenti and impetigo contagiosa by the pathological findings.
• RX: The treatments are oral retinoid and application of moisturizer
• Prognosis: is good

Harlequin Ichthyosis

• i.e: HARLEQUIN fetus. Very rare condition.
• It is autosomal recessively inherited.
• The patient is covered with an extremely thick stratum corneum at birth causing thick, horny, armor-like plates that cover the entire skin surface.
• Cracks in the skin, ectropion of eyelids, protrusion of lips, and difficulty of opening the mouth are so severe that most patients die within 2 weeks after birth.
• There is abnormality of the lamellar granules in harlequin ichthyosis.
• DNA-based prenatal diagnosis is clinically applied.
Acquired Icthyosis

- Acquired ichthyosis has the same skin manifestations as the other types of ichthyosis but it is caused by different diseases.
- Different diseases may have icthysiform manifestations besides the other manifestations are:
  - SLE (Systemic lupus erythematosus)
  - Hodgkin’s disease.
  - Malignant diseases
  - Nutritional deficiencies
  - Drug reaction as a reaction to medications used for lowering cholesterol.
- The diagnosis of an itchy icthysiform skin lesion in infancy or early childhood should exclude the possibility of Hodgkin's lymphoma

Keratosis Pilaris

- It is a common disorder. Inherited as an autosomal dominant in childhood and reaches its peak incidence in adolescence.
- Keratinous plugs in the follicular orifices with varying degrees of perifollicular erythema.
- **Clinical Picture:**
  - The lesions appear as small gray to white plugs of keratin that obstruct the mouths of the follicles entrapping the hair.
  - Sites of predilection: extensor surfaces of the upper arms, thighs and buttocks or any body part except glabrous skin (like the palms or soles of feet)
- **Treatments:** may consist of moisturizing or keratolytic treatments including: urea, lactic acid, salicylic acid, or topical retinoids.
Keratosis Follicularis or Darier Disease

- Rare, Autosomal dominant trait (AD)
- Late-onset genetic disorder of keratinization, Usually in the first or second decade
- Males and females equally affected
- Caused by mutations in the ATP2A2 gene
- Precipitating Factors: Frequently worse in summer with heat and humidity as major factors; can be exacerbated by UVB, mechanical trauma, bacterial infections
- Clinical features: consist of warty papules and plaques in seborrheic areas and face, back ears, nasolabial folds, forehead, scalp; neck, axilla & groin.
  - Palms and Soles Multiple, flat, cobblestone like papules, specific nail changes, Nails thin, splitting distally and showing characteristic V-shaped scalloping
  - Mucous Membranes: White, centrally depressed papules on mucosa of cheeks, hard and soft palate, and gums, “cobblestone” lesions
  - Histologic examination of skin lesions shows suprabasal acantholysis in the epidermis with dyskeratotic cells
- Course and prognosis: Persisting throughout life, not associated with cutaneous malignancies
- Management: Sunscreens, antibiotic therapy (systemic and topical) systemic retinoids (isotretinoin or acitretin). Systemic therapy can be modified according to seasonal variation of the disease.

Callosities & Corns

- Callosities represent variants of abnormal keratinization which are more common in adults
- Both are responses to pressure.
- A callosity is more diffuse type of thickening of the keratin layer which seems to be a protective response to widely applied repeated friction or pressure.
- Calluses (keratotic plaques), are often occupational, e.g. they are seen on the hands of manual workers.
- Corns (keratotic papules), on the other hand, have a central core of hair keratin which can hurt if forced inwards. They appear where there is high local pressure, often between bony prominence and shoes.
- Favorite areas include the backs of the toe joints, and the soles under prominent metatarsals ‘soft corns’ arise in the 3rd or 4th toe clefts the toes are squeezed together by tight shoes, such corns are often macerated
- Treatment
  - Mild callosities respond to local application of salicylic acid (20%) and lactic acid (20%) in collodion base for few days.
  - Before each application the dead tissues can be removed by shaving.
  - Extensive cases can be resurfaced by CO2 laser lesion may be mistaken as skin wart.

Palmoplantar Keratodermas

- Its chronic thickening of palms and soles.
- Keratoderma may be inherited (hereditary) or, more commonly, acquired.
  - Hereditary keratoderma: the condition runs in families, its Ad or AR
  - Acquired keratoderma: occurs as a result of a change in the health or the environment of the affected person or associated with skin disorders.
- Clinically, three distinct pattern:
  1. Diffuse type: the whole palm and sole,
  2. Docal type: are restricted to more limited areas(mainly affect pressure areas)
  3. Punctate type: are bead-like tiny lesions
Complications include severe pain, difficulty in walking, and secondary infection.

The genetic basis of many keratodermas particularly involves mutations in genes encoding keratins, connexins, and desmosomal components.

Treatments: the target is removal of hyperkeratotic material by keratolytics and systemic retinoids; appropriate footwear is helpful.

Keratodermas due to other Dermatoses

Different skin diseases may give rise to palmoplanter hyperkeratosis.

These include:

- **Psoriasis**: Hyperkeratosis of the palms and soles are associated with the characteristic psoriatic lesions with the silvery scales.
- **Reiter’s disease**: The lesions are compact, heaped up and resemble the heads of nails (keratoderma blenorrhagica).
- **Pityriasis rubra pilaris**
- **Eczema**
- **Lichen planus**
- **Viral warts** in immuno-compromised patients may be confluent on the palms or soles.
- **Hyperkeratosis due to dermatophytes (fungal skin infections)**.
- **Syphilis**: Syphilis may involve the palms and soles leading to hyperkeratosis. Hyperkeratotic lesions of late syphilis may be very warty or focal.
- **Arsenic ingestion**: causes multiple, irregular warty keratoses.