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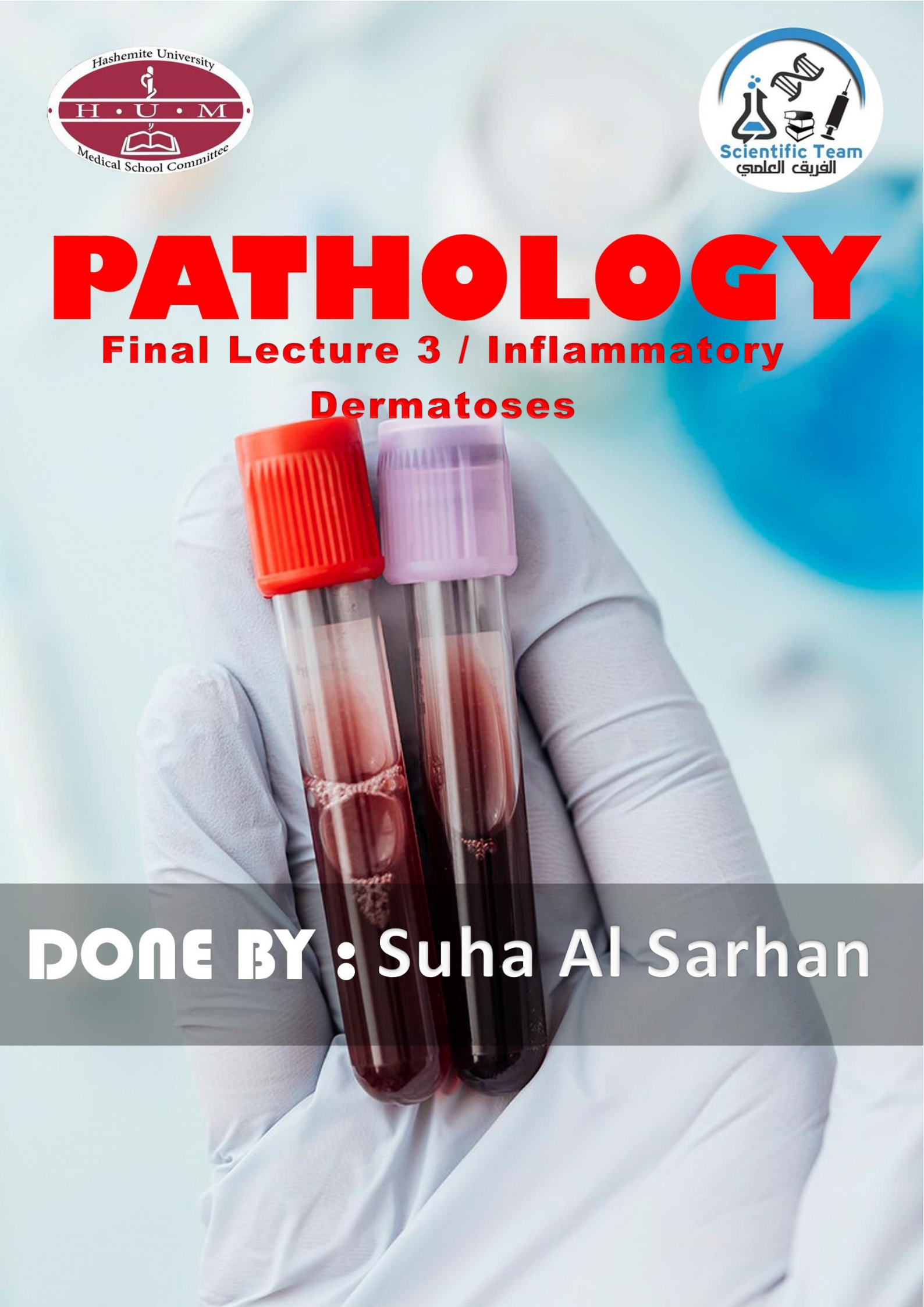
PATHOLOGY

Final Lecture 3 / Inflammatory Dermatoses



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Skin

- Cutaneous disorders are extremely common & range from irritating acne to life-threatening melanoma.
- Many are intrinsic to the skin, but some are manifestations of systemic disease, e.g. Kaposi sarcoma of AIDS, SLE, neurofibromatosis genetic syndromes. Thus, skin provides a uniquely window for the recognition of numerous & varied disorders.

- Skin, the largest organ of the body, is a complex organ, with regulated cellular & molecular events that govern interactions with the external environment.
- Skin is constantly bathed with microbial & non microbial antigens that are processed by bone-marrow-derived dendritic Langerhans cells, which in turn communicate with the immune system by migrating to regional LNs.
- The squamous cells (keratinocytes) help maintain skin homeostasis by secreting many cytokines that not only regulate interactions among the epidermal cells but also diffuse into & influence the dermal microenvironment.
- The dermis contains → both CD4+ helper & CD8+ cytotoxic T lymphocytes; some of these T cells home selectively to the skin by virtue of homing receptors called the cutaneous lymphocyte antigen (CLA).
- The epidermis contains → intraepithelial lymphocytes, including γ/δ T cells. All these cells are rich sources of cytokines.

- The local tissue response, involving these T cells & cytokines, accounts for the microscopic patterns & clinical expressions of cutaneous inflammatory & infectious disease. These patterns can be recognized & interpreted through the microscope by the experienced pathologist.

- The practice of dermatopathology is unique in its close interaction with dermatologists. Clinical assessment of skin diseases involves: Clinical presentation + history + gross skin examination, + correlated (sometimes) with Histopathological Ex to make a Diagnosis.

- **Glossary (Dermatologic terms) Gross terms** :

Macule	Flat circumscribed (limited) colored area of any size
Papule	Elevated solid area <5mm in Diameter=Ø)
Nodule	Elevated solid area >5mmØ
Plaque	Elevated flat-topped area >5mmØ
Vesicle	Fluid-filled raised area <5mm Ø
Bulla	Fluid-filled raised area, >5mmØ
Blister:	Common term used for both vesicle or bulla.
Pustule	Pus-filled raised discrete (isolated) area
Scale	Dry, horny, platelike excrescence (growth); usually the result of imperfect cornification
Lichenification	Thickened rough skin characterized by prominent skin markings; usually the result of repeated rubbing in susceptible persons (see "Lichen Simplex Chronicus")
Excoriation	A traumatic lesion characterized by breakage of the epidermis, causing a raw linear area usually due to scratching.

Excoriation : التقشر
تمزق الطبقة السطحية من الجلد نتيجة الحكة الشديدة

- **Microscopic Terms**

Spongiosis	Intercellular edema of the epidermis
Acanthosis	hyperplasia of the stratum spinosum
Acantholysis	Loss of intercellular connections, resulting in lack of cohesion between keratinocytes.
Hyperkeratosis	Hyperplasia with thickening of the keratin layer.
Parakeratosis	keratinization characterized by retention of the nuclei in the keratin layer on mucosal membranes, parakeratosis is normal واي مكان تاني غيره بتكون غير طبيعية
Dyskeratosis	Abnormal premature keratinization occurring in individual cells or groups of cells, below the stratum granulosum
Papillomatosis	hyperplasia of papillary dermis, with elongation or widening of the dermal papillae.
Litigious	linear melanocyte proliferation within the epidermal basal cell layer; can occur as a reactive change or as part of a tumor of melanocytes.

الجدولين مهمين و 100% في سؤال عليهم بالامتحان

ACUTE INFLAMMATORY DERMATOSES

- Are acute lesions, with limited course, lasting from days to weeks, characterized by inflammation (unlike other tissues, these are often marked by mononuclear cells rather than neutrophils infilteration) edema, & sometimes epidermal vascular, or subcutaneous injury.
- Many are self-limited & never progress; but some acute lesions may persist, resulting in transition to a chronic phase.

1. Urticaria

- is a common disorder, mediated by localized mast cell deregulation, resulting in dermal vascular hyperpermeability, This gives rise to erythematous, edematous, & pruritic (itchy) plaques termed wheals

- Pathogenesis:

In most cases, urticaria (typical example of Type I Hypersensitivity Reaction),
A, results from exposure to a number of antigens {Ag}, including pollens, foods, drugs, & insect venom.
B,The Ag-react with specific IgE Abs on the surface of mast cell, induce their sensitization, degranulation & release of their vasoactive mediators. مهم
C, Ag-independent urticaria may result from substances that directly incite mast cell degranulation, such as opiates & certain antibiotics.

In the vast majority of cases, no clinical cause is discovered despite extensive searching.

Hereditary angioneurotic edema:
results from inherited deficiency of C1 esterase inhibitor, yielding uncontrolled activation of the early components of the complement system.
The resulting urticaria affects the lips, throat, eyelids, genitals, & distal extremities. When the larynx is affected, it can result in dangerous airway obstruction especially in infant قد تؤدي للوفاة نتيجة الاختناق

- H, features of urticaria:

(1) Superficial dermal edema;
(2) very sparse(mild,simple) superficial perivenular infiltrate of mononuclear cells & scattered eosinophils,
(3) Degranulation of mast cells اهم نقطة that normally reside around superficial dermal venules (these cells are often not prominent in routine H & E stains, but can be highlighted using special Giemsa stain).

- Clinically :

1. Occurs between the ages of 20 & 40 years.
2. Lesions develop & fade within hours (usually <24 hours), but episodes may persist for days or even months.
3. Lesions vary from small pruritic papules to large red edematous plaques resulting from superficial vascular dilation & ↑ vascular permeability, leading to dermal edema.
4. Sites include any area exposed to pressure, such as the trunk, distal extremities, & ears.
5. Urticaria is more irritating & embarrassing than life- threatening
6. is managed with antihistamines, or steroids in more severe cases.

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2. Acute Eczematous Dermatitis

☼ **Eczema** → is a clinical term that embraces a number of conditions with different underlying etiologies.

☼ **All are characterized by :** ينضح سائل

Red, papulovesicular, oozing, & crusted lesions at an early stage. The degree of these changes varies with clinical subtype.
With persistence, these lesions develop into raised, scaling plaques.

☼ **Clinical differences permit classification of eczematous dermatitis into:**
(1) allergic contact dermatitis
(2) atopic
(3) drug- related eczematous
(4) photoeczematous
(5) primary irritant forms.

☼ Most of these forms resolve completely when the offending stimulus is removed or exposure to it is limited , thus stressing the importance of investigating the underlying cause.

☼ Only the most common form, **contact dermatitis**, will be discussed here.

☼ **Pathogenesis of contact dermatitis:**

- After initial exposure to an environmental contact sensitizing agent, e.g., poison ivy,
- self-proteins modified by the agent are processed by epidermal Langerhans cells that then migrate to draining LNs & present the Ag to naive T cells.
- This sensitization event leads to acquisition of immunologic memory; on re-exposure to the Ag, the now-educated CD4+ T lymphocytes migrate to the affected skin sites, where they release cytokines that recruit additional inflammatory cells & also mediate the epidermal damage as in any (DHR).

- Spongiosis characterizes all forms of acute eczematous dermatitis.

(Spongiosis is intercellular edema of the epidermis with accumulation of edema fluid within it)
(hence the synonym "spongiotic dermatitis“).
Edema seeps into the intercellular spaces, separating the keratinocytes. Intercellular bridges are stretched & become more prominent visually, giving a "spongy" appearance

- This is accompanied by a superficial perivascular lymphocytic infiltrate, papillary dermal edema, & mast cell degranulation. Eosinophils may be present & especially prominent in spongiotic eruptions provoked by drugs, but, In general, there are no specific features for differentiating the various causes of eczema & therefore, careful clinical correlation is needed.

☼ **Clinically** :

- acute eczematous dermatitis lesions are pruritic (itchy), edematous, oozing plaques, with vesicles & bullae.
- With persistent Ag stimulation, lesions become progressively scaly (hyperkeratotic) & acanthotic & can become chronic.
- Some of these changes also result from scratching or rubbing of the lesion (see "Lichen Simplex Chronicus").

☼ The **clinical causes** of eczema :
are sometimes divided into "inside" & "outside" jobs-disease resulting from external application of antigen (such as poison ivy) or reaction to an internal circulating antigen (such as ingested food or drug).

Susceptibility to atopic dermatitis is often inherited & this form can be more chronic, although it sometimes improves with age. Atopic individuals often suffer from asthma.

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3. **Erythema Multiforme** احمرار متعدد الأشكال

☼ is an uncommon, self-limited hypersensitivity response to certain **infections & drugs**.

*Among antecedent **infections** → are those caused by herpes simplex, mycoplasmas, & fungi such as Histoplasma Capsulatum, & Coccidiodes imitis.
*The implicated **drugs** → include sulfonamides, penicillin, salicylates, hydantoins, & antimalarials.

☼ Patients present with an array of "multiform" lesions, including macules, papules, vesicles, & bullae, as well as the characteristic targetoid lesion consisting of a red macule or papule with a pale vesicular or eroded center.

F14-9: Erythema multiforme, macular type. Result of toxic hypersensitivity response to drugs, which includes sulfonamides, penicillin, salicylates, hydantoins antiepileptic, & antimalarials, so-called drug rash.
هاي الصورة مهمة جدا انتبهولها باللاب

☼ **Pathogenesis:**

- The lesions of erythema multiforme result from the action of cutaneous lymphocyte antigen (CLA) positive, skin-homing cytotoxic T cells that are concentrated in the central portion of the lesions, while CD4+ helper & Langerhan cells are more prominent in the raised, erythematous periphery.

- The cytotoxic cells directed against an inciting drug or microbe presumably respond to cross-reactive antigens of the basal cell layer of skin & mucosae, damaging these tissues (Cytotoxic, or Type II Hypersensitivity Reaction).

☼ **H:**
Early lesions show a

1. superficial perivascular, lymphocytic infiltrate associated with dermal edema
2. margination of lymphocytes along the dermoepidermal junction in intimate association with degenerating keratinocytes (interface dermatitis).
3. With time, discrete, confluent zones of basal epidermal necrosis occur, with concomitant blister formation.
4. In the more rare & severe form of this disease, toxic epidermal bullosal necrosis, the necrosis extends through the full thickness of the epidermis.

☼ **Clinical Features**: مهممم

- Range of severity:
  Erythema multiforme forms associated with infection, most often herpesvirus, are sometimes termed **erythema multiforme minor** because of their **less severe clinical presentation**.

  More severe forms of erythema multiforme are termed **erythema multiforme major**, Stevens-Johnson syndrome, toxic epidermal necrolysis. These can be life-threatening because they can cause sloughing of large portions of the epidermis & loss of moisture & infectious barriers. They are most often seen as idiopathic reactions to drugs such as antibiotics or NSAID

CHRONIC INFLAMMATORY DERMATOSES

- These are persistent inflammatory dermatoses that exhibit their most characteristic features over many months to years, although they may begin with an acute stage. The skin surface in some chronic inflammatory dermatoses is roughened as a result of excessive or abnormal scale formation & shedding (desquamation).

1. Psoriasis

☼ is a common chronic inflammatory dermatosis affecting 1% to 2% of US people (6 Millions).
Rarely, it is associated with arthritis, myopathy, enteropathy, & spondylitic heart disease.

☼ **Pathogenesis**

- Psoriasis is an immunologic disease with contributions from genetic susceptibility & environmental factors.
  It is not known if the inciting antigens are self or environmental.

- Sensitized populations of T cells enter the skin, including dermal CD4+ TH1 cells & CD8+ T cells that accumulate in the epidermis. T cells homing to the skin secrete cytokines & GFs that induce **acanthosis**, resulting in the characteristic lesions.

- Psoriatic lesions can be induced in susceptible individuals by local trauma, a process known as the Koebner phenomenon. The trauma may induce a local inflammatory response that promotes lesion development.

- While reserved for use in severe psoriatic arthritis, recent therapeutics exploits advances in our understanding of T-cell biology.

☼ **Various clinically useful agents block:**
(1) T-cell activation & proliferation
(2) T cell trafficking & keratinocyte interaction with T cells
(3) binding of TNF to its receptor thus inhibiting T cell functions.

☼ **H:**

- There is acanthosis, with regular downward elongation of the rete ridges, likened to "test tubes in a rack"
- Extensive parakeratosis, due to the ↑ epidermal cell turnover & lack of maturation resulting in loss of the stratum granulosum with extensive overlying parakeratotic scale.
- There is thinning of the suprapapillary plates, i.e., epidermal cell layer overlying the tips of dermal papillae & the blood vessels within the papillae are dilated & tortuous.
- These vessels bleed readily when the scale is removed, giving rise to multiple punctate bleeding points (Auspitz sign).

- Neutrophils form small aggregates within both the spongiotic superficial epidermis (pustules of Kogoj) & the parakeratotic stratum corneum (Munro microabscesses).
- Similar changes can be seen in superficial fungal infections, & it is important to exclude this possibility with special stains in newly diagnosed psoriasis. مهم

☼ **Clinically:**

- Psoriasis most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal cleft, & glans penis.
- Typical lesion is a well-demarcated, pink to salmon- colored plaque covered by loosely adherent silver-white scale مهم
- Nail changes occur in 30% of cases of psoriasis & consist of yellow-brown discoloration, pitting, thickening, crumbling & separation of the nail plate from the underlying bed (onycholysis).
- In most cases, psoriasis is limited in distribution, but it can be widespread & severe on occasion.

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2. Lichen Planus

☼ Skin & mucosal "6p's" lesions " pruritic + purple + polygonal + planar + papules + plaques"

☼ is self-limited & usually resolves spontaneously 1 to 2 years after onset. Oral lesions may persist for years.

☼ The pathogenesis is not known.
Expression of altered Ags (which could be due to viral infection or drug treatment) at the level of the basal cell layer & the dermoepidermal junction may elicit a CD8+ T cell-mediated cytotoxic immune response.

☼ **H:**
Lichen planus characterized by :

➔ interface dermatitis; i.e., a dense, continuous inflammatory infiltrate of lymphocytes along the dermoepidermal junction, resulting in basal cell keratinocytes degeneration & necrosis, causes the dermoepidermal interface to assume an angulated, zigzag contour ("sawtoothing").

➔ Non-nucleate, necrotic basal cells are seen in the inflamed papillary dermis & are referred to as colloid bodies or Civatte bodies.

☼ **Clinical Features:**

- Cutaneous lesions consist of pruritic, violaceous, flat- topped papules, which may coalesce focally to form plaques
- Hyperpigmentation may result from melanin loss into the dermis from the damaged basal cell layer.

- Multiple lesions are symmetrically distributed, particularly on the extremities, often about the wrists & elbows, & on the glans penis. In 70% of cases, oral lesions are present as white, reticulated, or netlike areas involving the mucosa.

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3. Lichen Simplex Chronicus

☼ Lichen simplex chronicus presents as roughening of the skin that takes on an appearance reminiscent of lichen on a tree.
☼ It is a response to local repetitive trauma such as continual rubbing or scratching. When this condition is localized to nodules, it is termed prurigo nodularis.

☼ **Pathogenesis**:-
it is probable that repetitive trauma induces epithelial hyperplasia with eventual dermal scarring.

☼ **H:**

- lesions are characterized by **acanthosis** (with elongation of the rete ridges) + hypergranulosis + hyperkeratosis + fibrosis of the papillary dermis with a chronic inflammatory infiltrate
- Interestingly, these lesions are similar to normal volar (palms & soles) skin, an area conditioned by constant "trauma," but at these sites the changes appear to represent an adaptive response to such stimuli.

☼ **Clinically**:

- the lesions are often raised & erythematous, with ↑ scale & can be mistaken for keratinocytic neoplasms.
- Often lichen simplex chronicus is superimposed upon, & masks another (often pruritic) dermatomes; & it is therefore important to rule out an underlying cause, But, keep in mind that the lesion can be entirely self-inflicted!

SUMMARY: Inflammatory Dermatoses.

❖ There are many specific inflammatory dermatoses; which may be mediated by
IgE antibodies (urticaria),
Antigen-specific T cells (eczema, erythema multiforme, & psoriasis)
Trauma (lichen simplex chronicus).

❖ The histologic features can be grouped into patterns of
Inflammation, such as interface dermatitis (e.g. lichen planus & erythema multiforme),
superficial perivascular dermatitis, & panniculitis (inflammation in subcutaneous fat) that provide insight into the mechanism & the ability to organize the diseases into pathogenic categories.

❖ Careful **clinical correlation is needed to diagnose specific skin diseases, since the features overlap within histologic pattern groups**. مهم