Dermatology Lecture: 3

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Psoriasis:
is a chronic, non infectious, inflammatory disorder with a genetic predisposition for the illness.

Pathophysiology:
The characteristic psoriatic plaque occur as a result of polymorphnuclear leukocyte recruitment to the dermis and epidermis. especially, there is a large infiltrate of T-lymphocytes to the affected areas with the release of pro inflammatory mediators as (IL 17/23).

- Elevated levels of (TNF-α) specially that are found to correlate with flares of psoriasis.
- Key findings in the affected skin with psoriasis include superficial blood vessels dilation and tortuosity.

Common characteristics of psoriasis (pathophysiology):

1. Parakeratosis in stratum cornium: high proliferation of the skin cells in the epidermis so high no. of nucleated cells appear at the top of the skin forming (plaque).
2. Superfacial blood vessels dilation and tortuosity and increase of their no.
3. Large infiltration of T-lymphocytes to the affected areas in the dermis.
4. Epidermal thickening as a result of hyperproliferation and hyperplasia of the epidermal cells.
5. Infiltration of polymorphnuclear leucocytes (neutrophils) in the epidermis.
6. Elevated levels of (TNF-α) specially that are found to correlate with flares of psoriasis.

Clinical picture:
Psoriasis has the tendency to wax and wane with flares related to systemic or environmental factors, including stress events and infection.

Note:
- Psoriasis is not a malignant disease and it is never ever turn malignant, it is only described as hyperproliferation of skin cells.
- Psoriasis not characterized by hypermitosis, hyperchromatesia, abnormal mitotic figures or abnormal DNA which all are characteristics of cancer cells.
Types of psoriasis

**Plaque Psoriasis**
- Most common type appear as raised erythematous lesion covered with silvery white scales.
- More commonly occur in the elbow and knee with mild irritation and itching.
- Plaque psoriasis = psoriasis vulgaris = common psoriasis

**Flexural Psoriasis**
- Occur in the axillae, groin, and skin folds في ثنايات الجلد

**Pustular Psoriasis**
- Present as sterile pustules (as it is not invaded by bacteria so psoriasis is not infectious disease).
- Appear in the palms and soles or diffusively over the body.
- When it is extensively diffused it requires hospitalization.
- Collection of neutrophils over the skin to a degree that appears macroscopic while on other types of psoriasis it is macroscopic.

**Erythrodermic Psoriasis**
- Present as generalized erythema and scaling affecting >90% of the body (الرجل الأحمر)
- Extensive loss of proteins in scales, hypoalbuminemia.
- Excessive vasodilation with inability for heat regulation, hypothermia and heart failure. (As normally cold weather lead to v.c to maintain body temp. while psoriatic patient cant do so due to V.D)
- Require hospitalization

**Scalp Psoriasis**
- With erythema, scaling and itching in the scalp only

**Psoriatic Arthritis**
- Affect (10-30%) of the cases
- The arthritis is usually in hands and feet and occasionally, the large joints.
- When the patient present to the dermatologist having both skin psoriasis and arthritis together at the same time in this case the differential diagnosis is: psoriatic arthritis not psoriasis and rhematoid arthritis.
- As the inflammatory response of psoriasis when causes attack on the joints lead to rhematoid arthritis
- Arthropathic psoriasis = psoratic arthritis.
Psoriasis is not completely a curable disease but upon treatment patient experience periods of remission while relapse and flaring may occur again after these periods of remission.

Psoriasis is not infectious disease (not transmitted from one person to another by skin contact).

The subtypes of psoriasis that are associated with fatal potential and require hospitalization (severe extensive pustular psoriasis and erythrodermic psoriasis).

General role in dermatology:

- Any dermatologic disease affecting a small part of our skin requires: **topical therapy**.
- Any dermatologic disease affecting large part of our skin requires: **topical therapy + systemic therapy**.

**Treatment**

1- **topical**
   - salicylic acid oint. (5%)
   - anthralin (0.1-1%)
   - coal tar
   - topical corticosteroids.
   - vitamine D3 analogues.

2- **systemic**
   - methotrexate
   - acitretin
   - cyclosporin
   - TNF-α inhibitor (etanercept, infliximab, adalimumab)
   - ustekinumab

3- **phototherapy**
   - narrow band UV-B phototherapy
   - PUVA + 8-methoxypsoralen
A- Topical therapy

1-Keratolytic agents as Salicylic acid ointment (5%):
• Used to remove scales and to treat hyperkeratosis, which allows better penetration of other topical agents.

2-Anthralin (0.1-1%):
• Reduces the rate of cell proliferation by reducing epidermal mitosis. (decrease epidermal hyperproliferation and hyperplasia)
• Side effects: 1- irritation of surrounding normal skin and
• 2- staining of the skin and clothes by yellowish orange color.

3-Coal tar
• Coal tar: Antipruritic and inhibits unregulated epidermal proliferation and dermal infiltration.
• Limitation of use: It is a messy application, with staining of skin and clothes, except for shampoos. It also has offensive odor.
• Now coal tar used as shampo in scalp psoriasis only but it still has offensive odor on hair.

3-Topical corticosteroids (TCs):
• Topical corticosteroids (TCs): Used to 1- reduce plaque formation (decrease epidermal hyperproliferation)
• 2- decrease inflammation by suppressing migration of polymorphonuclear leukocytes (as it is immunosuppressant)
• 3- reverse capillary permeability by causing V.C.
• Low-midstrength-potency TCs are preferred for large areas, and could be covered by an occlusive polyethylene film while the application of potent topical C.S on large areas of skin for prolonged time lead to severer form of psoriasis upon stopping therapy that may progress to erythrodermic psoriasis.
• Corticosteroid potency table

4- vitamin D3 analogues
• Vitamin D3 analogues:
• (Calcipotriene and calcipotriol) is a synthetic vitamin D-3 analogue that regulates skin cell production and development. It inhibits epidermal proliferation, promotes keratinocyte differentiation, and has immunosuppressive effects on lymphoid cells.
• This treatment does not cause long-term skin thinning or systemic effects, but it degrades in sunlight.
• It is used in combination with topical corticosteroids (calcipotriol and betamethasone dipropionate) to provide greater response rates, fewer side effects and is steroid sparing.
• Steroid sparing effect?
• No data available for use in women who are pregnant or breast feeding.
• Daivonex or daivobet or calcipoheal (only vit.D3 preparation) not used any more as it has a weak effect to administered alone or as alternative to steroids.
• Now available preparations are combination of both VitD3 and steroids as (VELGAROL and Xamiol).
• Oitments are used for skin while gels are used for scalp.
Systemic corticosteroids are contraindicated in psoriasis as it may lead to flaring of symptoms and progression to severer forms of erythrodermic or pustular psoriasis.

### Potency Table

<table>
<thead>
<tr>
<th>Potency</th>
<th>Type</th>
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<tbody>
<tr>
<td>Very potent</td>
<td>Clobetasol propionate</td>
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<tr>
<td></td>
<td>Betamethasone</td>
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<tr>
<td></td>
<td>Betamethasone-gentamycin</td>
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<td>Fluticasone</td>
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<td>Mometasone</td>
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<td></td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>Potent</td>
<td>Clobetasone</td>
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<tr>
<td>Mild</td>
<td>Hydrocortisone</td>
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**A- Systemic Therapy**

**1- Methotrexate:**

- Methotrexate is only indicated in sever case as erythrodermic, pustular or arthritic psoriasis and also it can be used in severe extended plaque psoriasis when affecting > 30% of the body.
- MTX is a folic acid antagonist and antimetabolite.
- Dihydrofolates must be reduced to tetrahydrofolates by the enzyme dihydrofolic acid reductase before they can be utilized as carriers of one-carbon groups in the synthesis of nucleotides and thymidylate of DNA. **Inhibiting this enzyme by methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues (as in psoriasis) are in general more sensitive to this effect of methotrexate.**
- **Dose:** 7.5mg for 3 doses 12 hrs apart as a single dose/week orally or 25 mg/week IM.
- Once optimal clinical response is reached. dosage reduced to lowest effective dose.
  - **Side effects:** Liver toxicity, oral ulcerations and anemia, neutropenia and thrombocytopenia (as it mainly affect highly proliferating cells as B.M).

**2- Acitretin: isotretinoin**

- It is a Vitamin A derivative.
- Oral treatment with this retinoid ethyl ester is effective in controlling psoriasis especially in pustular type.
- Decrease the hyperproliferation of keratinocytes and to less extend anti-inflammatory.
- The dose used is 0.5-1 mg/kg /day.
- **Side effects:** include 1- **teratogenicity** (pregnancy should be avoided during and for two years of the treatment course);
  - 2- increase cholesterol and triglyceride levels;
  - 3- affecting liver function,
  - 4- phototoxicity and dryness of skin and mucous membranes. (very irritant if taken topically)
3- cyclosporine

- Cyclosporine is a natural product of fungi.
- It is a specific modulator of cell function and an agent that depresses cell-mediated immune responses by inhibiting helper T-cell function, with minimal activity against B-lymphocytes.
- It binds to intracellular protein, which in turn, prevents formation of IL-2 and the subsequent recruitment of activated T cells.
- Used in extensive disease refractory to other treatments.
- **Dose:** 2.5 mg/kg/d orally; to be increased by 0.5 mg/kg/d every 2 weeks if response insufficient. Once adequate response is achieved, dose tapered to lowest effective dose for maintenance.
- Treatment for 3-4 months at a time (not longer to prevent immunosuppressant).
- Remission is rapid with this therapy; however, skin lesions tend to recur within days to weeks after treatment is stopped.
- **Side effects include:**
  - 1- elevating blood pressure,
  - 2- affecting renal functions,
  - 3- inducing sometimes hypertrichosis and gum hyperplasia.
  - 4- immunosuppressant if used in a high dose for prolonged time
  - 5- high recurrence of psoriasis (short periods of remission)
- Monitoring of treatment is done by performing regular check-ups of patient’s blood pressure, renal functions and serum cholesterol levels.

4- Tumor necrosis factor inhibitors

- These agents neutralize the effects of TNF-alpha.
  - **i- Etanercept (Enbrel):** A recombinant human TNF-alpha receptor protein fused with Fc portion of IgG1 that binds to soluble and membrane bound TNF-alpha, thereby neutralizing the effects of TNF-alpha.
  - It is indicated for moderate-to-severe psoriasis and moderate-to-severe psoriatic arthritis. It provides good balance between safety and efficacy. Precautions: Patients should be screened for **** TB (tuberculin test) and hepatitisB and chest x-ray before treatment.
  - as reactivation of both illnesses (TB + HBV) associated with TNF-alpha inhibitors.
  - **Dose:** 50 mg SC 2 times/wk for 3 months followed by 50 mg once/wk.
  - **ii- Infliximab (Remicade):** A chimeric antibody that binds both the soluble and transmembrane TNF-alpha molecules, thereby neutralizing the effects of TNF-alpha.
  - Acts more rapidly than other available agents with better responses, but serious side effects occur (infections + increase rate of malignancy).
  - **Dose:** 4-6mg/kg/dose given at day 0, week 2, week 6, and every 4-8 weeks later on.
  - **iii- Adalimumab (Humira):** Full human anti-TNF-alpha monoclonal antibody binds specifically to soluble and membrane bound TNF-alpha.
  - side effects: 1- fatal blood disorders 2- serious infection including (TB, virusis, bacteria and fungi)
5- Ustekinumab (Stelara)

- **Ustekinumab (Stelara)** is a human monoclonal antibody that antagonizes interleukin-12 (IL-12) and IL-23.
- Administered subcutaneously
- **Side effects:**
  - 1. Serious infection (bacterial, fungal, viral)
  - 2. Increase risk of malignancies
  - 3. Serious allergic reaction (angioedema, rash, urticaria)

**c- photo (chemo) therapy**

- **Narrow band UV-B phototherapy (311 nm):**
  - Narrow-band UV-B phototherapy uses fluorescent tubes with an emission spectrum of 310-315 nm.
  - Sub-erythemogenic doses are effective in inducing plaque thinning, decreased erythema and scaling.
  - **Treatment frequency is 2-3 times weekly**, with improvement appearing after 2-3 months.
  - Short-term adverse effects include pruritus and xerosis.
  - The advantages of narrow-band UV-B over PUVA include no adverse gastrointestinal effects (eg, nausea), and no need for subsequent photoprotection for the whole day.

- **PUVA photochemotherapy = psoralen + UVA (320-400 nm):**
  - Treatment with 8-methoxypsoralen, followed by exposure to artificial UVA light 2hrs apart.
  - Inhibits mitosis by covalently binding to pyrimidine bases in DNA when photoactivated by UV-A. Thus decreasing hyperproliferation seen in psoriasis.
  - Dose: 0.5-0.7 mg/kg orally with food (1.5-2 hrs) before UV-A exposure.
  - **It is not recommended for children under 12 years.**
  - 8-methoxypsoralen cause liver toxicity so liver function test should be performed.

**Algorithm for ttt of psoriasis**

- **Psoriasis +/- psoriatic arthritis**
  - **Anti-TNF-α +/- MTX**
    - Yes
    - **Limited disease**
      - Topicals / targeted phototherapy
      - **Lack of effect**
    - **Extensive disease**
      - UVB/PUVA
      - Systemic
      - Biological = (TNF-α inhibitors or ustekinumab)