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DEFINITION

Psoriasis is a chronic, immune-mediated dermatosis that results from a polygenic predisposition combined with environmental triggers. The natural history is chronic with intermittent remissions.

The characteristic lesion is a sharply demarcated erythematous plaque with scale; the plaques may be localized or widespread in distribution.



2 % Europe

- ✤ 4.6% US and Canada
- 0.7% Africans, African-Americans, Norwegian Lapps, and Asians



Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years.

Type I disease (HLA-Cw6⁺) have an earlier onset, more widespread disease and frequent recurrences, compared to those with **type II psoriasis**.

GENETIC FACTORS

- a positive family history has been reported by 30% of patients with psoriasis
- If one parent has psoriasis, the risk of their child developing psoriasis is 10%
- if both parents has psoriasis, the risk of their child developing psoriasis is 50%
- concordance rates among monozygotic tweens is 70-90%

Psoriasis is associated with HLA-Cw6.

Classic genome-wide linkage analysis has identified at least nine psoriasis susceptibility regions (PSORS1-9) in different chromosomal locations.

IMMUNOPATHOGENESIS

Psoriasis is considered to be a disease with prominent involvement of helper T-cell subsets (Th1 and Th17) and their secreted cytokines: TNF – alfa, interleukin 12, interleukin 23, interleukin 17

Activation and proliferation of keratinocytes.

HISTOPHATOLOGY

- Histologically, hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated vessels, and an inflammatory infiltrate composed primarily of lymphocytes are observed.
- The presence of neutrophils in the epidermis, either in spongiform pustules of Kogoj or in microabscesses of Munro, is a typical histopathologic feature of psoriasis, especially acute or pustular forms.
- Prominent angiogenesis is observed in plaques of psoriasis.

TRIGGERING FACTORS

- External triggering factors: UV radiation, rentgen radiation, surgery, iniections, burns, expositions for toxic substances.
- morbilliform drug eruption, viral exanthem, rosacea, contact dermatitis.

TRIGGERING FACTORS

- Systemic triggering factors: Streptococcal infections, especially pharyngitis; HIV; pregnancy; psychogenic stress; hypocalcemia
- Obesity, increased alcohol consumption, and smoking have all been associated with psoriasis.
- Drugs: lithium, IFNs, β-blockers and antimalarials. Rapid taper of systemic corticosteroids can induce pustular psoriasis as well as flares of plaque psoriasis.

CLINICAL FEATURES

Chronic plaque psoriasis is characterized by sharply demarcated erythematous papulosquamous lesions.

All share the same important hallmarks: erythema, thickening and scale.

The size of a lesion may vary from a pinpoint papule to over 20 cm in diameter.

The outline of the lesion is usually circular, oval or polycyclic (the latter indicating that the lesion is derived from several smaller units).

SPECIFIC PSORIASIS SIGNS

WAX CANDLE SIGN: If the superficial silvery white scales are removed via curettage (grattage method), a characteristic coherence is observed, as if one has scratched on a wax candle ("signe de la tache de bougie").

SPECIFIC PSORIASIS SIGNS

AUSPITZ SIGN: If the latter is removed, then a wet surface is seen with characteristic pinpoint bleeding. This finding, is the clinical reflection of elongated vessels in the dermal papillae together with thinning of the suprapapillary epidermis.

SPECIFIC PSORIASIS SIGNS

KOEBNER PHENOMENON: after skin injury typical psoriatic leasions are seen in affected skin.



The configuration of psoriatic lesions due to the Koebner phenomenon reflects the etiology of the trauma.

During exacerbations, psoriatic lesions often itch.

- Pinpoint papules surrounding existing psoriatic plaques indicate that the patient is in an unstable phase of the disease.
- Expanding psoriatic lesions are characterized by an active edge with a more intense erythema.
- Inflamed lesions may be slightly tender.
- The involution of a lesion usually starts in its center, resulting in annular psoriatic lesions.

CHRONIC PLAQUE PSORIASIS (90%)



The elbows, knees and presacrum are sites of predilection

CHRONIC PLAQUE PSORIASIS

Relatively symmetric distribution of sharply defined, erythematous, scaly plaques.

Plaques may persist for months to years at the same locations. Although the course of this disease is chronic, periods of complete remission do occur and remissions of 5 years have been reported in approximately 15% of patients.



Differential diagnosis: pityriasis lichenoides chronica, lichen planus, tinea, pityriasis Gibert, SCLE- psioriasiform

SUBTYPES OF PSORIASIS

- psoriasis guttata
- psoriatic erythrodermia
- palmoplantar psoriasis.
- pustular psoriasis
- pustulosis of the hand and soles



- inverse psoriasis
- nail psoriasis
- scalp psoriasis

GUTTATE PSORIASIS

- Guttate psoriasis is more commonly seen in children and is frequently preceded by an upper respiratory tract infection- streptococcal infection.
- The small papules appear suddenly
- Scales can be absent.



Erythrodermic Psoriasis (1-2%)

This variant of psoriasis is characterized by generalized erythema (over 90%) and scaling,

Its onset can be gradual or acute.

✤ 25 % of all erythrodermias.

There are many causes of erythroderma; clues to the diagnosis of psoriatic erythroderma include previous plaques in classic locations, characteristic nail changes, and facial sparing.

Other symptoms: fever, limphadenopathy, leukocytosis

DIFFERENTIAL DIAGNOSIS: mycosis fungoides, pityriasis rubra pilaris, atopic dermatitis, seborhoeic dermatitis.

PALMOPLANTAR PSORIASIS



CLINICAL PICTURE: red sharply demarcated psoriatic plaques with thick yellow scales and painful fissures.

DIFFERENTIAL DIAGNOSIS: alergy dermatitis, tinea, palmoplantar keratoderma.

PUSTULOSIS OF THE PALMS AND SOLES

- Is characterized by "sterile" pustules of the palmoplantar surfaces admixed with yellow-brown macules ; scaly erythematous plaques may also be seen.
- A minority of patients have chronic plaque psoriasis elsewhere.
- In contrast to the natural history of generalized pustular psoriasis, the pustules remain localized to the palmoplantar surfaces and the course of this disease is chronic.
- Male: female ratio 3:1

- Focal infections and stress have been reported as triggering factors and smoking may aggravate the condition.
- Pustulosis of the palms and soles is one of the entities most commonly associated with sterile inflammatory bone lesions (SAPHO syndrome: which consists of synovitis, acne, pustulosis, hyperostosis
 - and osteitis).



Generalized pustular psoriasis (von Zumbusch)

Clinical picture: erythema and sterile pustules; Nikolski sign, fever, arthritis

Triggering factors: pregnancy, rapid tapering of systemic corticosteroids (or other systemic therapies), hypocalcemia, infections, and, in the case of the localized pattern, topical irritants.

The infiltration of neutrophils dominates the histologic picture.







GENERALIZED PUSTULAR PSORIASIS

EPIDEMIOLOGY:

Adults F:M 1:1Children F:M 2:3

Mean age in adults patients: 50 years.
Mean age in childrem: 6 week – 10 years.

SCALP PSORIASIS

- The scalp is one of the most common sites for psoriasis. Often it is not possible to distinguish seborrheic dermatitis from psoriasis, and the two disorders may coexist.
- The lesions of psoriasis often advance onto the periphery of the face, the retroauricular areas and the upper neck.





NAIL PSORIASIS (50 %)

- Nail involvement is associated with greater disease activity.
- The fingernails are more often affected than the toenails.
- Patients with nail involvement appear to have an increased incidence of psoriatic arthritis (80%).
Psoriasis affects the nail matrix, nail bed and hyponychium.

MATRIX:

Small parakeratotic foci in the proximal portion of the nail matrix lead to **pits in the nails**. **Leukonychia** and loss of transparency (less common findings) are due to involvement of the mid portion of the matrix. If the whole nail matrix is involved, a whitish, **crumbly**, poorly adherent "nail" is seen.

NAIL BED

Psoriatic changes of the nail bed result in the "<u>oil spot</u>" or "oil drop" phenomenon, which reflects exocytosis of leukocytes beneath the nail plate.

<u>Splinter hemorrhages</u> are the result of increased capillary fragility, and <u>subungual hyperkeratosis</u> and <u>distal onycholysis</u> are due to parakeratosis of the distal nail bed.



DIFFERENTIAL DIAGNOSIS: tinea, onychogryphosis, posttraumatic nail changes.









FLEXURAL PSORIASIS (5%)

- Flexural lesions are characterized by shiny, pink to red, sharply demarcated thin plaques without scales.
- Often a central fissure is seen.
- The most common sites of involvement are the axillae, inguinal crease, intergluteal cleft and skin folds.
- When flexural areas are the only sites of involvement, the term "inverse" psoriasis is sometimes used.
- Localized dermatophyte, candidal or bacterial infections can be a trigger for flexural psoriasis.



PSORIASIS AREA AND SEVERITY INDEX (PASI)

- head, upper extremities, trunk and lower extremities are evaluated separately
- Erythema, induration, scalling (0-4)
- Percentage of body surface area (0-6)

percentage of body surface area (d) < 10% : 1 point 10-29%: 2 points 30-49%: 3 points 50-69%: 4 points 70-89%: 5 points 90-100%: 6 points

PASI:

head = (e+i+s) x d x 0,1 Upper extremities = (e+i+s) x d x 0,2 Trunk= (e+i+s) x d x 0,3 Lower extremities= (e+i+s) x d x 0,4 Sum (max = 72)

PSORIATIC ARTHRITIS

EPIDEMIOLOGY

- Psoriatic arthritis occurs in 30-40%% of patients with cutaneous psoriasis⁻ In a minority of patients (10–15%), the symptoms of psoriatic arthritis appear before involvement of the skin.
- The skin symptomps usually precedes the onset of psoriatic arthritis (10 years)
- Sometimes the skin lessions and arthritis appear one single stage (11-15%).
- In a minority of patients (10–15%), the symptoms of psoriatic arthritis appear before involvement of the skin (10-15 years).

EPIDEMIOLOGY

- Psoriatic arthritis is more prevalent among patients with relatively severe psoriasis.
- Risk factors for a more severe course of the arthritis include: initial presentation at an early age, female gender, polyarticular involvement, genetic predisposition, and radiographic signs of the disease early on.

1. Mono- and asymmetric oligoarthritis. Inflammation of the interphalangeal joints – both distal (DIP) and proximal (PIP) – of the hands and feet is the most common presentation of psoriatic arthritis. Involvement of the PIP or both the DIP and PIP joints of a single digit can result in the classic "sausage" digit.

In contrast to rheumatoid arthritis, the metacarpophalangeal (MCP) joint is an unusual site for psoriatic arthritis. This form may be accompanied by inflammation of larger joints.

2. Arthritis of the distal interphalangeal joints. Exclusive involvement of the DIP joints is a classic but uncommon presentation of psoriatic arthritis. This variant may occur in conjunction with contiguous nail involvement. In some patients, these joints will become fixed in a flexed position.

3. Rheumatoid arthritis-like presentation. The clinical manifestations consist of a symmetric polyarthritis that involves small and medium-sized joints, in particular the PIP, MCP, wrist, ankle and elbow. Patients are usually seronegative, but some have a positive rheumatoid factor. Clinically, this variant is difficult to distinguish from rheumatoid arthritis.

4. Arthritis mutilans. Fortunately, this is the least common variant of psoriatic arthritis. Patients have severe, rapidly progressive joint inflammation that results in destruction of the joints and permanent deformity. The digits become shorter, wider and softer to palpation because of osteolysis and a telescoping phenomenon.

5. **Spondylitis and sacroiliitis (29%)**. The spondylitis resembles that seen in ankylosing spondylitis, with axial arthritis as well as involvement of the knees and sacroiliac joints; many patients also have peripheral joint involvement. Individuals are often HLA-B27-positive and may have associated inflammatory bowel disease and/or uveitis.

The changes are assymetric.



Arthritis mutilans





PSORIATIC ARTHRITIS

- DIP involvement is observed in ~40% of the patients with arthritis
- 5% suffer from arthritis mutilans
- Patients with psoriatic arthritis have involvement of juxta-articular tendons and the sites where they insert into bone (entheses) as well as swelling of the fingers (dactylitis). Enthesitis and dactylitis have been reported in ~20% and 15– 30%



Erosions and bone proliferation are in a single stage together. "pencil in cup"

CASPAR (2005)

Active arthritis and 3 points:

 psoriasis 	 skin lessions are seen in a time of examination (2 pkt) skin lessions are not currently present but was seen before (1 pkt) positive family history(1 pkt)
 nail psoriasis 	1 pkt
 daktylitis 	1pkt
 hiperostosis and entesitis 	1 pkt
 negative RF 	1 pkt

PSORIASIS - ASSOCIATION WITH INTERNAL DISEASES

- Cardiovascular diseases are more common in patients with severe psoriasis. Severe psoriasis is associated with a threefold increased risk for myocardial infarction and a 3.5–4.4-year reduction in life expectancy.
- increased risk of obesity, hypertension and diabetes mellitus (components of the metabolic syndrome).

PSORIASIS - ASSOCIATION WITH INTERNAL DISEASES

- In patients with psoriasis, serum levels of Creactive protein (CRP) have been reported to be elevated.
- It has also been shown that TNF-α and IL-6 can target adipocytes and induce dyslipidemia.
- Non-alcoholic steatohepatitis is more commonly observed in patients with psoriasis.
- Crohn's disease, ulcerative colitis and psoriasis share an association with sacroiliitis and HLA-B27 positivity.

TREATMENT

TOPICAL:

corticosteroids vitamin d₃ analogues retinoids (tazaroten) tar anthralin acetylic acid

SYSTEMIC:

PUVA/UVB311nm Retinoids (acitretin) Metotrexat Cyclosporine A Biologics agents (infliximab, etanercept, adalimumab, ustekinumab, ixekizumab)

VITAMIN D₃ ANALOGUES CALCIPOTRIOL, CALCITRIOL, TACALCITOL

Vitamin D_3 inhibits epidermal proliferation, and induces normal differentiation by enhancing cornified envelope formation and activating transglutaminase; it also inhibits several neutrophil functions.

Due to their therapeutic efficacy and limited toxicity, vitamin D_3 analogues have become a first-line therapy for psoriasis.

VITAMIN D_3 ANALOGUES CALCIPOTRIOL, CALCITRIOL, TACALCITOL

INDICATIONS:

Mild to moderate psoriasis: first-line treatment as monotherapy or in combination.

Severe psoriasis: combination treatment.

CONTRAINDICATIONS:

Abnormality in bone or calcium metabolism Renal insufficiency Pregnancy or lactation

TOPICAL CORTICOSTEROIDS

- They are often first-line therapy in mild to moderate psoriasis and in sites such as the flexures and genitalia, where other topical treatments can induce irritation.
- Once-daily application has been shown to be as effective as twice-daily application, and long-term remissions may be maintained by applications on alternate days

TOPICAL CORTICOSTEROIDS

- Maximal quantities: 50 g/week of a superpotent corticosteroid; 100 g/week of a potent corticosteroid.
- As tachyphylaxis and/or rebound can occur fairly rapidly, i.e. within a few days to weeks, intermittent treatment schedules (e.g. once every 2 or 3 days or on weekends) are advised for more prolonged treatment courses.

TOPICAL CORTICOSTEROIDS- INDICATIONS

- Mild to moderate psoriasis: first-line treatment as monotherapy or in combination
- Severe psoriasis: often in combination with a vitamin
 D₃ analogue, a topical retinoid, anthralin or tar
- Monotherapy for flexural and facial psoriasis (usually mild strength)
- Recalcitrant plaques often require occlusion (plastic, hydrocolloid)

TOPICAL CORTICOSTEROIDS-CONTRAINDICATIONS

- Bacterial, viral and mycotic infections
- Atrophy of the skin
- Allergic contact dermatitis due to corticosteroids
- Pregnancy or lactation

ANTHRALIN

- Anthralin (dithranol, cignolin, 1,8-dihydroxy-9anthrone) has been available since 1916.
- It was more commonly utilized in the past; severe skin irritation is one of the most common adverse event.
- It has marked epidermal effects, including an antihyperproliferative effect. Anthralin also inhibits mitogen-induced T-lymphocyte proliferation and neutrophil chemotaxis.

ANTHRALIN

- In Europe it is used most often in day-care centers and the inpatient setting.
- To minimize irritation, concentration and application time are gradually escalated; neither should be increased more often than once every 3 days, given that peak erythema is seen 3–4 days following application.

TOPICAL RETINOIDS

- Tazarotene has been shown to decrease epidermal proliferation and it inhibits psoriasis-associated differentiation.
- Second-line therapy.
- The maximal area that can be treated with tazarotene is 10–20% of the body surface.
- Side efects: pruritus, burning, irritation and erythema.
- Combination therapy with topical corticosteroids is useful.
TAZAROTENE- CONTRAINDICTATIONS

- Unstable plaque psoriasis in a phase of progression.
- Erythrodermic psoriasis.
- Allergic contact dermatitis to tazarotene
- Pregnancy or lactation

SALICYLIC ACID

- Salicylic acid 5–10% has a substantial keratolytic effect.
- Application of salicylic acid to localized areas can be done daily, but, for more widespread areas, two to three times per week is preferred. This is to prevent systemic intoxication.

TAR

Coal tar has a range of anti-inflammatory actions and is effective as an antipruritic.

In view of its mutagenic potential, tar is contraindicated in pregnant or lactating women. However, guidelines on the use of tar products may differ between countries.

CALCINEURIN INHIBITORS

Calcineurin inhibitors are used to treat facial and flexural psoriasis.

Randomized, placebo-controlled studies have demonstrated efficacy and safety for this indication.

PHOTO(CHEMO)THERAPY

- moderate to severe psoriasis.
- narrowband UVB (311–313 nm)
- **PUVA:** broadband ultraviolet A (UVA) therapy following ingestion of or topical application of a psoralen
- **Re-PUVA**: PUVA teraphy is added after 6 weeks of acitretin treatment.
- The 308 nm excimer laser can be used to treat a limited number of plaques in patients with localized disease.

- High cumulative number of PUVA treatments, i.e. >150–200 individual treatments (PUVA)
- Treatment with cyclosporine (UVB and PUVA)
- Immunosuppressive medication (UVB and PUVA)
- Previous history of skin cancer (UVB and PUVA)
- Atypical melanocytic nevi (UVB and PUVA)
- Seizure disorder (risk of fall/injury; UVB and PUVA)
- Men and women in reproductive years without contraception (PUVA)
- Pregnancy or lactation (PUVA)
- Impaired liver function or hepatotoxic medication (PUVA)
- Cataracts (PUVA)

METHOTREXATE

- MTX is a first-line systemic therapy for psoriasis as it is highly efficacious for severe disease and all clinical variants of psoriasis.
- MTX is administered weekly, usually as a single oral dose (but occasionally intramuscularly or subcutaneously) and less often every 12 hours for three doses per week; the maximum weekly dosage is usually 25 mg.
- The use of folic acid supplementation during MTX administration is controversial due to the concern that folic acid may decrease the efficacy of MTX.

INDICATIONS

- Severe psoriasis
- Chronic plaque psoriasis (>10–15% BSA or interference with employment or social functioning)
- Pustular psoriasis (generalized or localized)
- Erythrodermic psoriasis
- Psoriatic arthritis (moderate to severe)
- Severe nail psoriasis
- Psoriasis not responding to topical treatments, photo(chemo)therapy and/or systemic retinoids

- Severe anemia, leukopenia and/or thrombocytopenia
- Significant liver function abnormalities, hepatitis (active and/or recent), severe fibrosis, cirrhosis, excessive alcohol intake
- Concomitant hepatotoxic medications
- Concomitant medications that increase MTX levels, e.g. trimethoprim—sulfamethoxazole
- Significantly reduced pulmonary function
- Pregnancy or lactation or currently planning to have children (male and female patients)
- Severe infections and Immunodeficiency syndromes
- Peptic ulcer (active)

SIDE EFECTS

Subjective symptoms

Nausea Vomiting Abdominal pain Fatigue Headache **Mucocutaneous Oral erosions** Alopecia **Delayed** phototoxicity Tenderness and/or necrosis

of plaques due to overdose

Hematopoietic

Leukopenia Thrombocytopenia Anemia

Hepatic

Hepatitis Cirrhosis

Pulmonary

Interstitial pneumonitis (acute-onset cough, dyspnea)

CYCLOSPORINE A

- Prevents T-lymphocyte activation from being translated into the release of effector cytokines such as IL-2.
- In view of its nephrotoxic effects (e.g. reduced glomerular filtration rate, tubular atrophy), cyclosporine should be given for several-month courses and alternated with other therapies.
- The recommended starting dose is 3 mg/kg/day in two divided doses.

- Impaired renal function
- Uncontrolled hypertension
- Primary or secondary immunodeficiency
- Concomitant immunosuppressive therapy
- Past or present malignancy
- History of excessive photo(chemo)therapy (>200 PUVA treatments), radiotherapy
- Concurrent photo(chemo)therapy
- Severe infections
- Pregnancy or lactation
- Alcohol and drug abuse

SIDE EFFECTS

- hypertension
- renal impairment
- cyclosporine treatment in psoriatic patients has been reported to increase the frequency of SCCs, especially in those previously treated with PUVA
- gastrointestinal discomfort, hypertrichosis, paresthesias, gingival hyperplasia, headache, vertigo, muscle cramps and tremor
- metabolic side effects include hyperkalemia, hypomagnesemia, hyperuricemia

Systemic retinoids acitretin

- Severe psoriasis that cannot be managed by topical treatments or photo(chemo)therapy.
- Monotherapy is indicated for erythrodermic or pustular psoriasis.
- Combination therapy is indicated for chronic plaque psoriasis.

- Combination treatment with photo(chemo)-therapy and/or vitamin D₃ analogues results in a substantial improvement in clinical response.
- Maximal therapeutic efficacy is reached after 2–3 months.
- Acitretin has been shown to be an effective maintenance therapy.
- As monotherapy, acitretin is highly effective in erythrodermic and pustular psoriasis.
- Its efficacy in nail psoriasis and psoriatic arthritis is only modest.

- Severe liver dysfunction
- Pregnancy or lactation
- Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years following discontinuation of acitretin
- Hyperlipidemia, especially hypertriglyceridemia, that cannot be controlled
- Poorly controlled diabetes mellitus
- History of pancreatitis
- Excessive alcohol intake
- Use of contact lenses

TARGETED IMMUNE MODULATORS ("BIOLOGIC" THERAPIES)

Beginning in 2000, biologic therapies were introduced for the treatment of psoriatic arthritis and moderate to severe psoriasis.

Two major targets are T cells and cytokines, including TNF- α and IL-12/23 and IL-17.

"BIOLOGIC" THERAPIES



Journal of Allergy and Clinical Immunology 2017.

Biologic agent	target	molecule	
Etanercept	TNF-α	Human fusion protein	
Infliximab	TNF-α	Chimeric antibody	
Adalimumab	TNF-α	Human antibody	
Ustekinumab	p40 subunit of IL- 12/23	Human antibody	
Secukinumab Ixekinumab Brodalumab	IL-17	Human antibody	

Biologic therapies are indicated for patients with moderate to severe psoriasis and/or psoriatic arthritis.

Several guidelines restrict their use to "highneed patients" in whom all other existing treatments are contraindicated or have led to insufficient improvement.