Cutaneous lymphomas

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Lymphoma Definition

- malignant transformation of the immune cells
- characterized by an abnormal clonal proliferation of lymphocytes
- most lymphomas begin in the lymph nodes, but primary cutaneous types starts in the skin

Classification of Lymphomas

- **Hodgkin's Lymphomas**
  - lymph nodes
  - skin changes in 30% of patients
  - pruritus is a subjective symptom
  - marker CD30 typical for malignant cells (Reed-Stemberg cells)

- **non-Hodgkin's Lymphomas**
  - T cell lymphomas of the skin mycosis fungoides, Sezary syndrome, pagetoid reticulosis
  - B cell lymphomas

Classification of Lymphomas

- Hodgkin's Lymphomas
- non-Hodgkin's Lymphomas

75-80%

- T cell lymphomas of the skin mycosis fungoides, Sezary syndrome, pagetoid reticulosis

20-25%

- B cell lymphomas

Primary cutaneous lymphomas

Table 1 WHO classification of cutaneous lymphomas (Blue book 2008).

Cutaneous T-cell and NK cell lymphomas	Cutaneous B-cell lymphomas
Mycosis fungoides (MF)	▸ Primary cutaneous follicular B-cell lymphoma (PCFCL) ▸ Primary cutaneous marginal zone B-cell lymphoma (PCMCL) ▸ Primary cutaneous diffuse large B-cell lymphoma – leg type (PCBLT) ▸ Primary cutaneous diffuse large cell B-cell lymphoma, other types ▸ Primary cutaneous intravascular large B-cell lymphoma
Mycosis fungoides variants and sub-types ▸ Folliculotropic MF ▸ Pagetoid reticulosis ▸ Granulomatous slack skin	
Sézary syndrome (SS)	
Adult T-cell leukemia/lymphoma	
Primary cutaneous CD30+ lymphoproliferative diseases ▸ Primary cutaneous anaplastic large-cell lymphoma (PCALCL) ▸ Lymphomatoid papulosis (LyP)	**Hematological precursor neoplasms** CD4+, CD56+ hematodermic neoplasm (plasmacytoid dendritic cell neoplasm)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	
Extranodal NK/T-cell lymphoma, nasal type	
Primary cutaneous γ/δ T-cell lymphoma ▸ Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional) ▸ Primary cutaneous small/moderate-sized pleomorphic T-cell lymphoma (provisional)	
Peripheral T-cell lymphoma, not specified	

2022 WHO classification of haematolymphoid / skin tumours, 5th edition	2022 international consensus classification of mature lymphoid neoplasms
MF	MF
MF subtypes	MF variants
FMF (clinical early/advanced)	FMF
Pagetoid reticulosis	Pagetoid reticulosis
GSS	
SS	SS
	CD30 LPD
CD30 LPD: pc ALCL	pc ALCL
CD30 LPD: LyP	LyP
SPTCL	SPTCL
Severe mosquito bite allergy Hydroa vacciniforme LPD	Severe mosquito bite allergy Hydroa vacciniforme LPD
pc gamma/delta T-cell lymphoma	pc gamma/delta T-cell lymphoma
CD8+ AECTCL	CD8+ AECTCL
pc CD4+ SMT LPD	pc CD4+ SMT LPD
pc acral CD8+ LPD	pc acral CD8+ LPD
pc PTCL, NOS	

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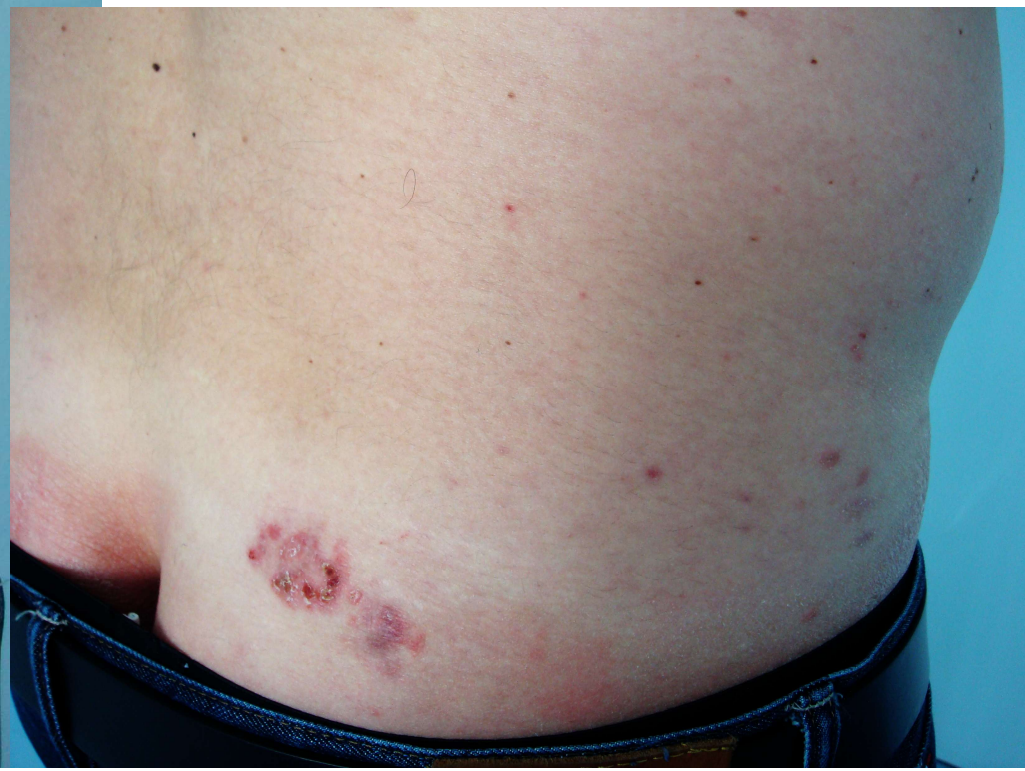
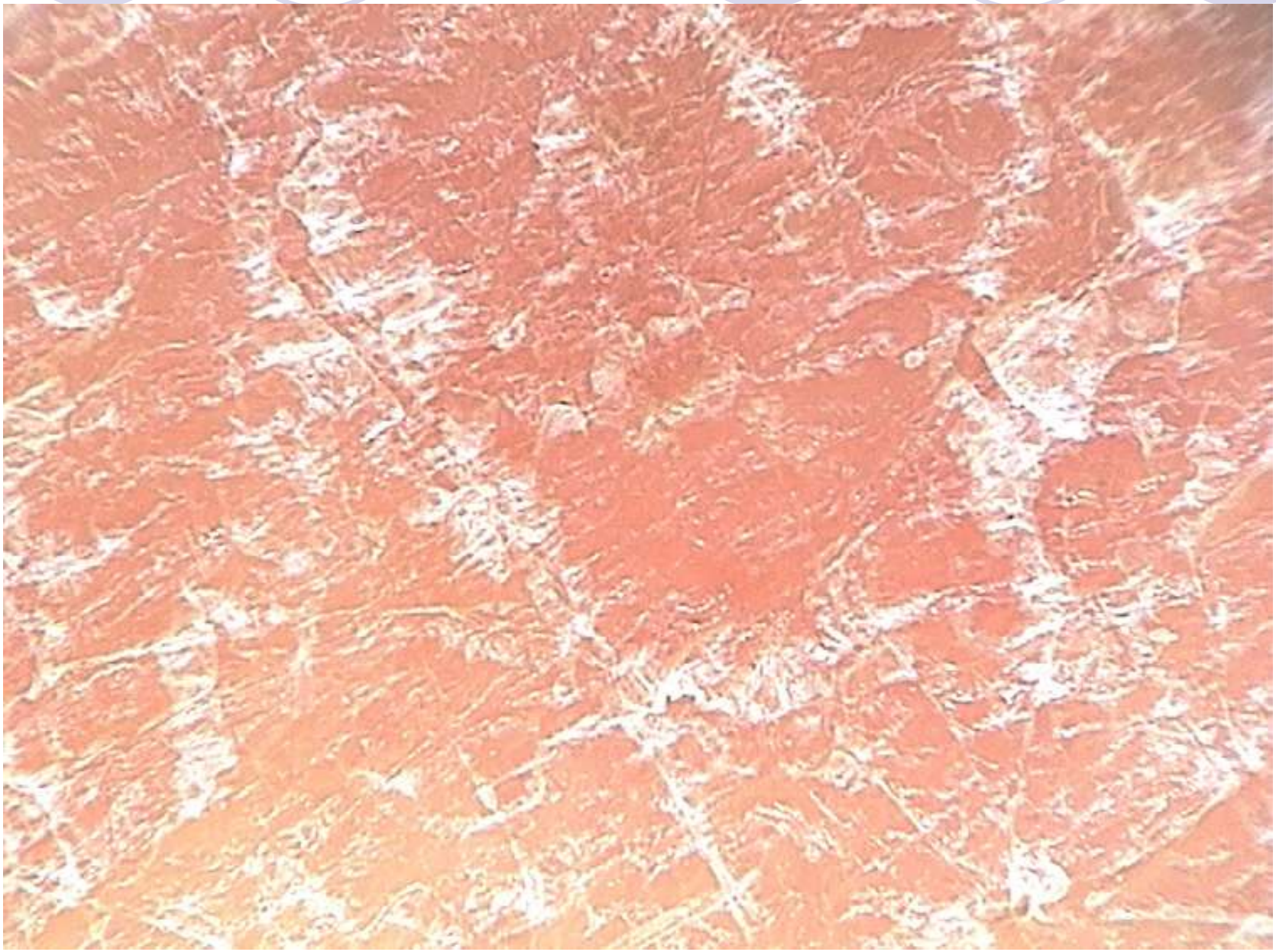
Case 1

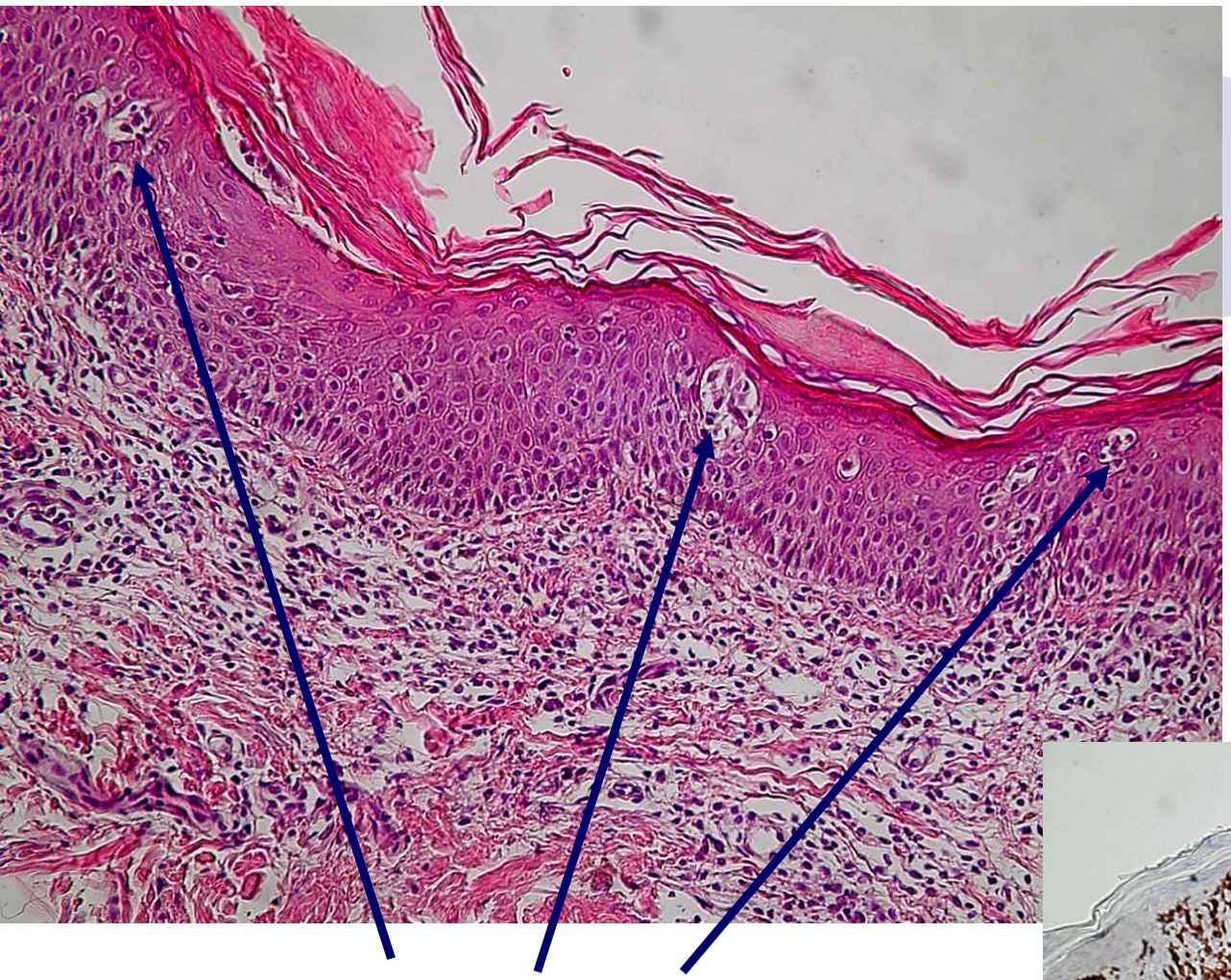
- 38-yo man with scaly erythematous patches present for the recent 3 years
- itchy and worsening in fall and winter
- located in covered parts of his body
- persistent and expanding
- get better in a summer

Eczema? What kind?



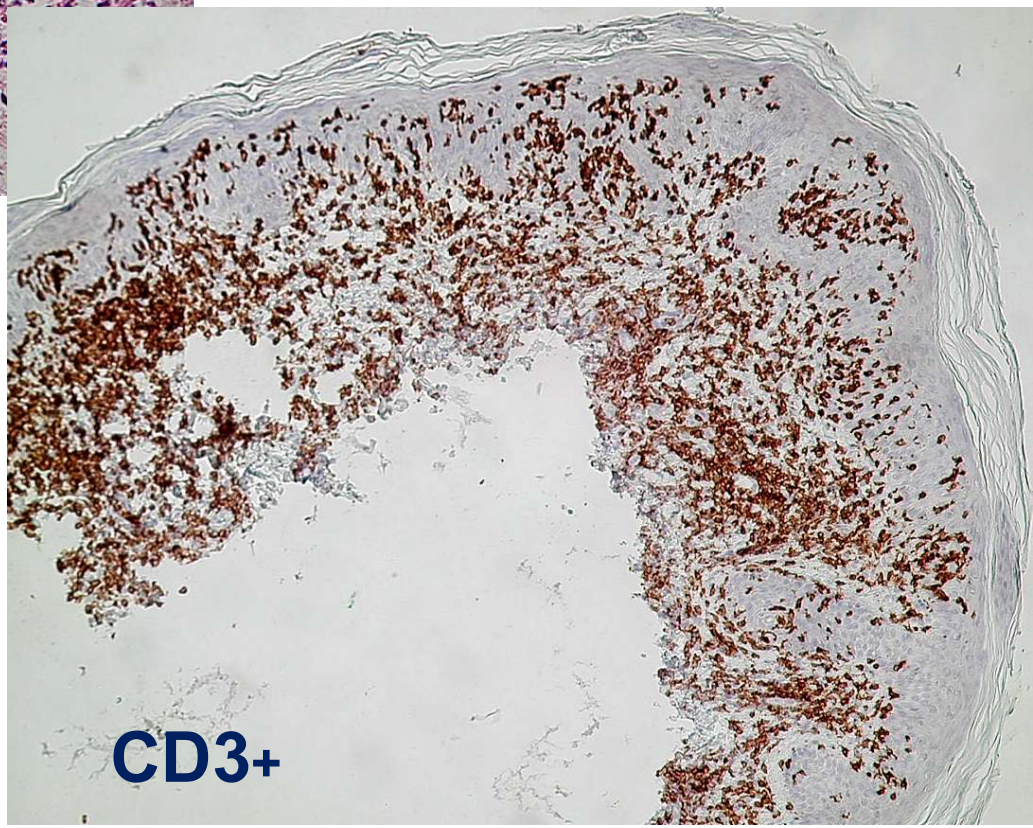
Dermoscopy examination revealed pityriasiform scale on the salmon pink base

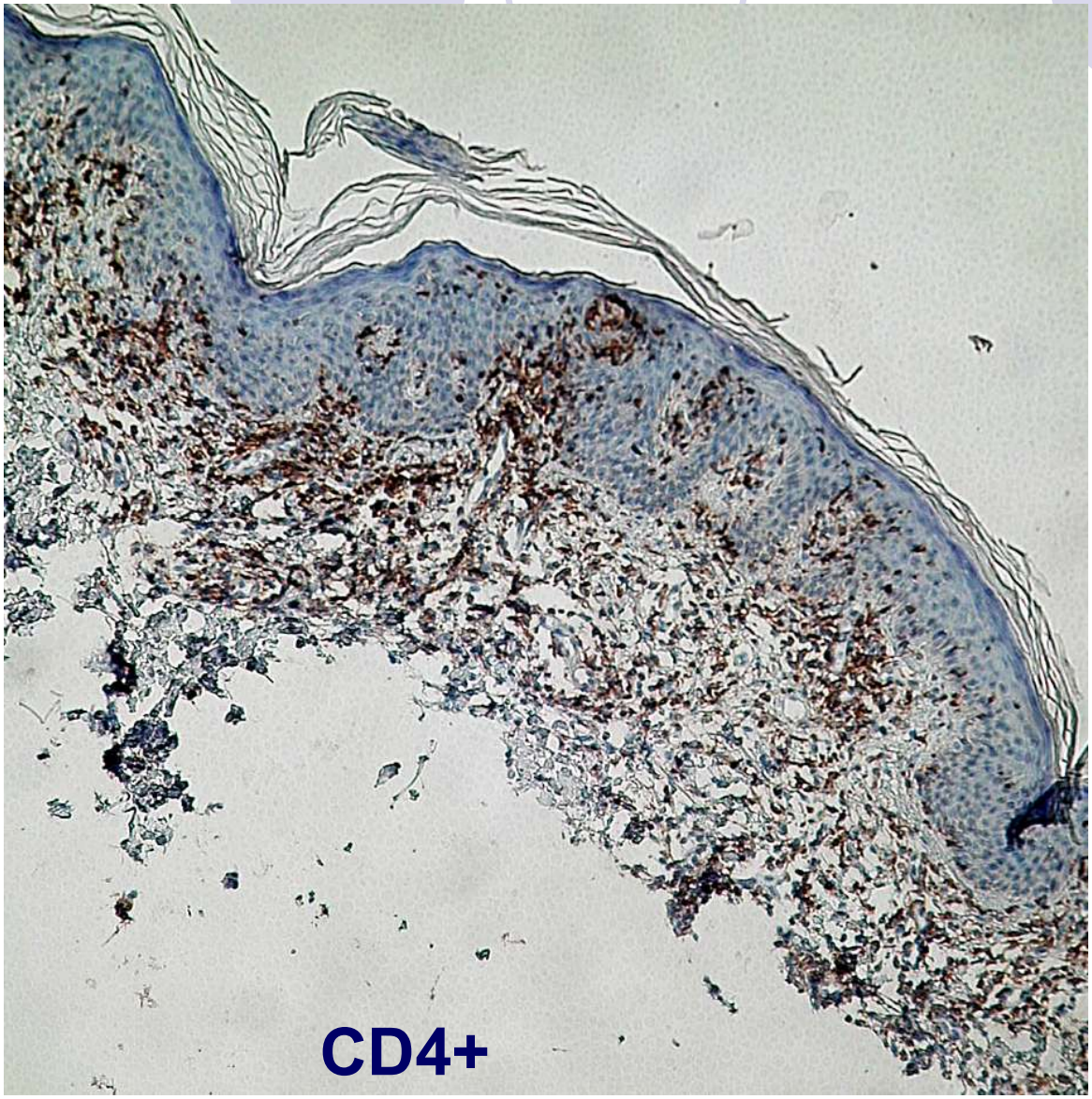


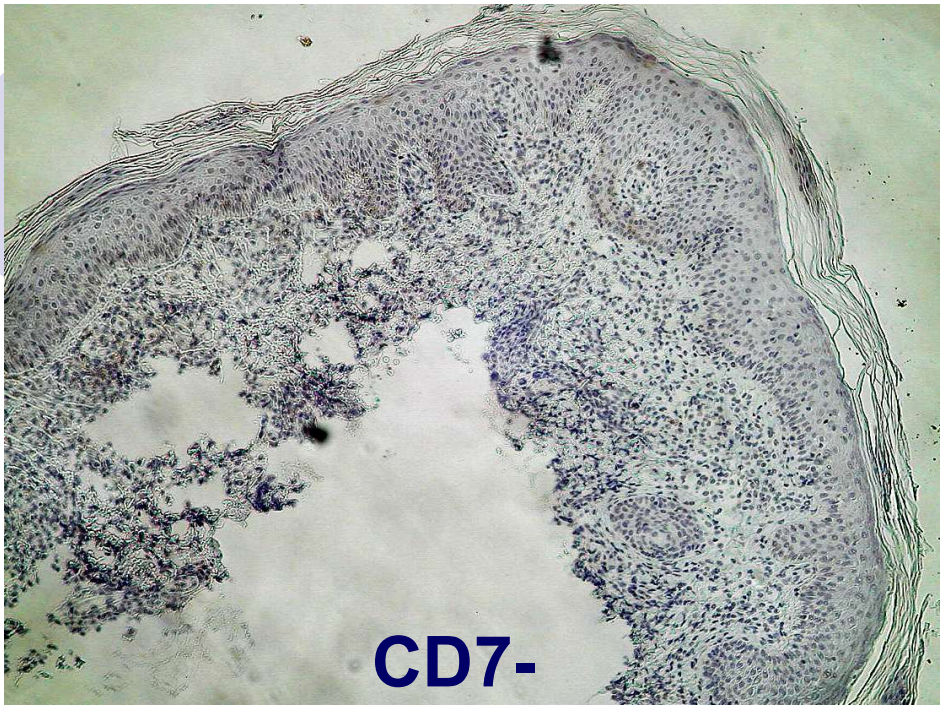


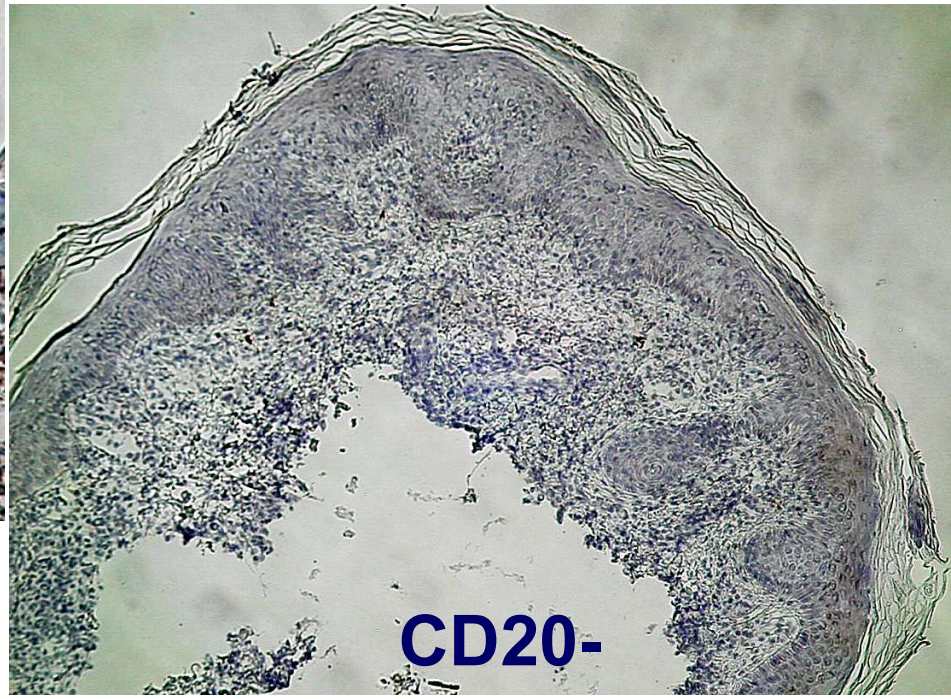
Epidermotropism

(presence of single or grouped lymphocytes in the epidermis without spongiosis)




CD4+


CD7-


CD20-

Diagnosis of mycosis fungoides

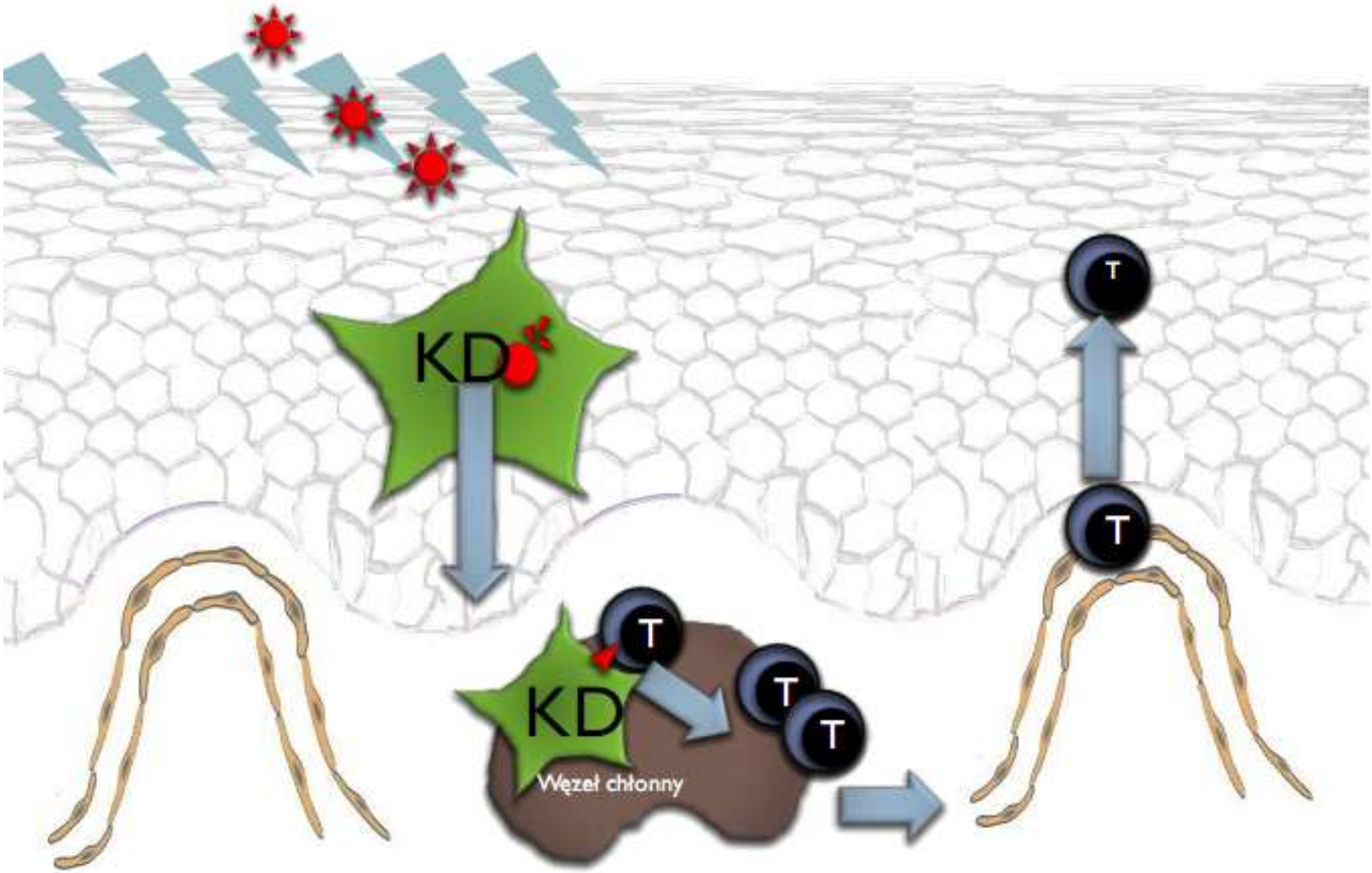
- Cutaneous T cell lymphoma (mycosis fungoides, MF)
- patch stage – initial stage of mycosis fungoides
- scaly erythematous patches predominate
- they mimic eczema but location on the trunk and on the double covered parts of the body is characteristic for MF
- correct diagnosis determinates treatment and prognosis

Mycosis fungoides

- T cell lymphoma which begins in the skin (primary cutaneous)
- remains localized in the skin for many years
- is a low-grade T cell lymphoma
- this is primarily CD4-positive helper T cell type
- it accounts for 50% of cutaneous lymphomas
- predilection for men (2:1)
- the age of incidence is over 40
- occurs more frequently in a population chronically exposed to chemical compounds, infections, occupational factors inducing genetic mutations

Chronic inflammation in the skin

Skin and lymph nodes



T cell lymphoma – clonal cell transformation and proliferation
One of theory – persitent hypersensitivity reaction

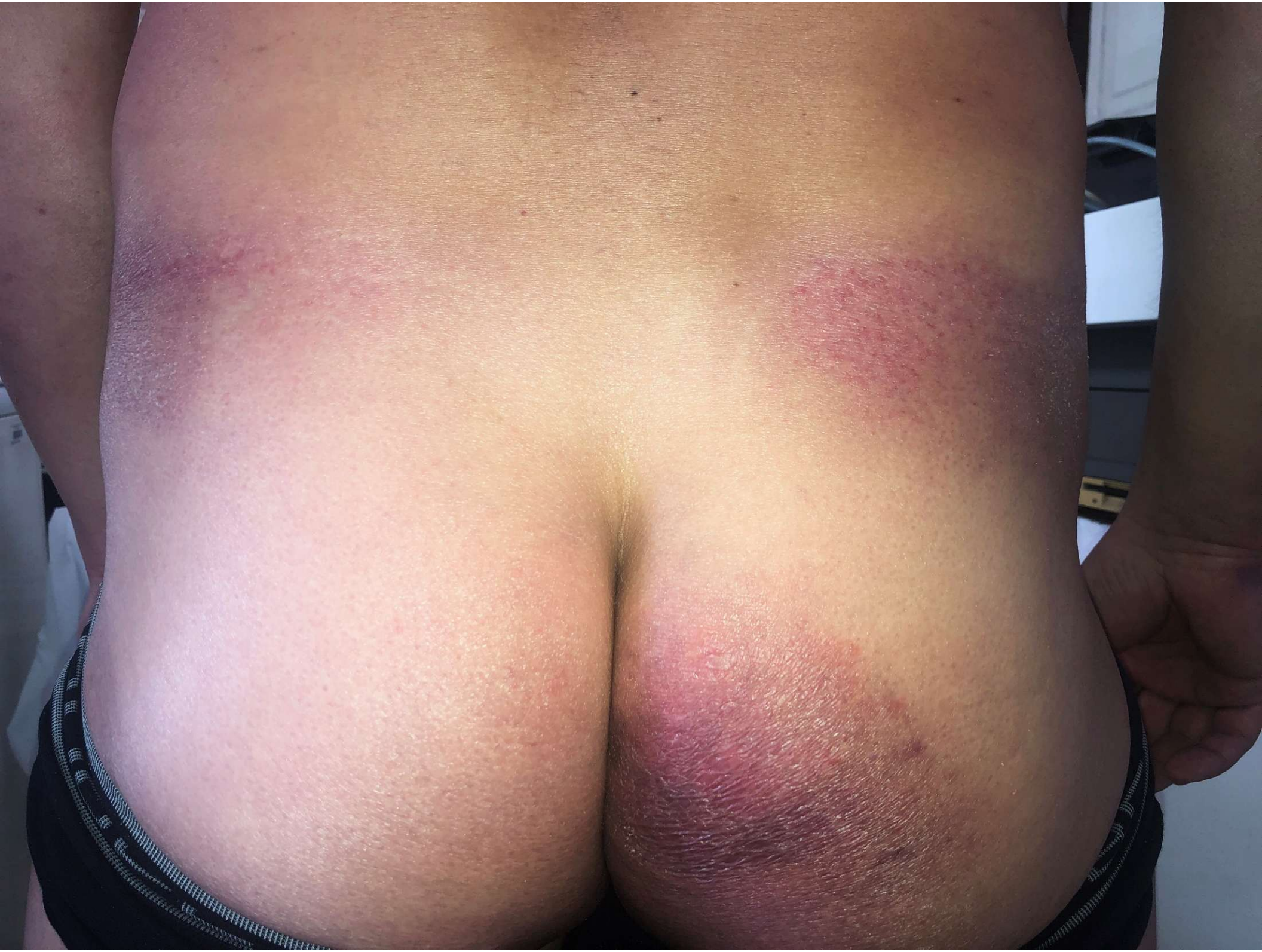
Clinical stages of mycosis fungoides

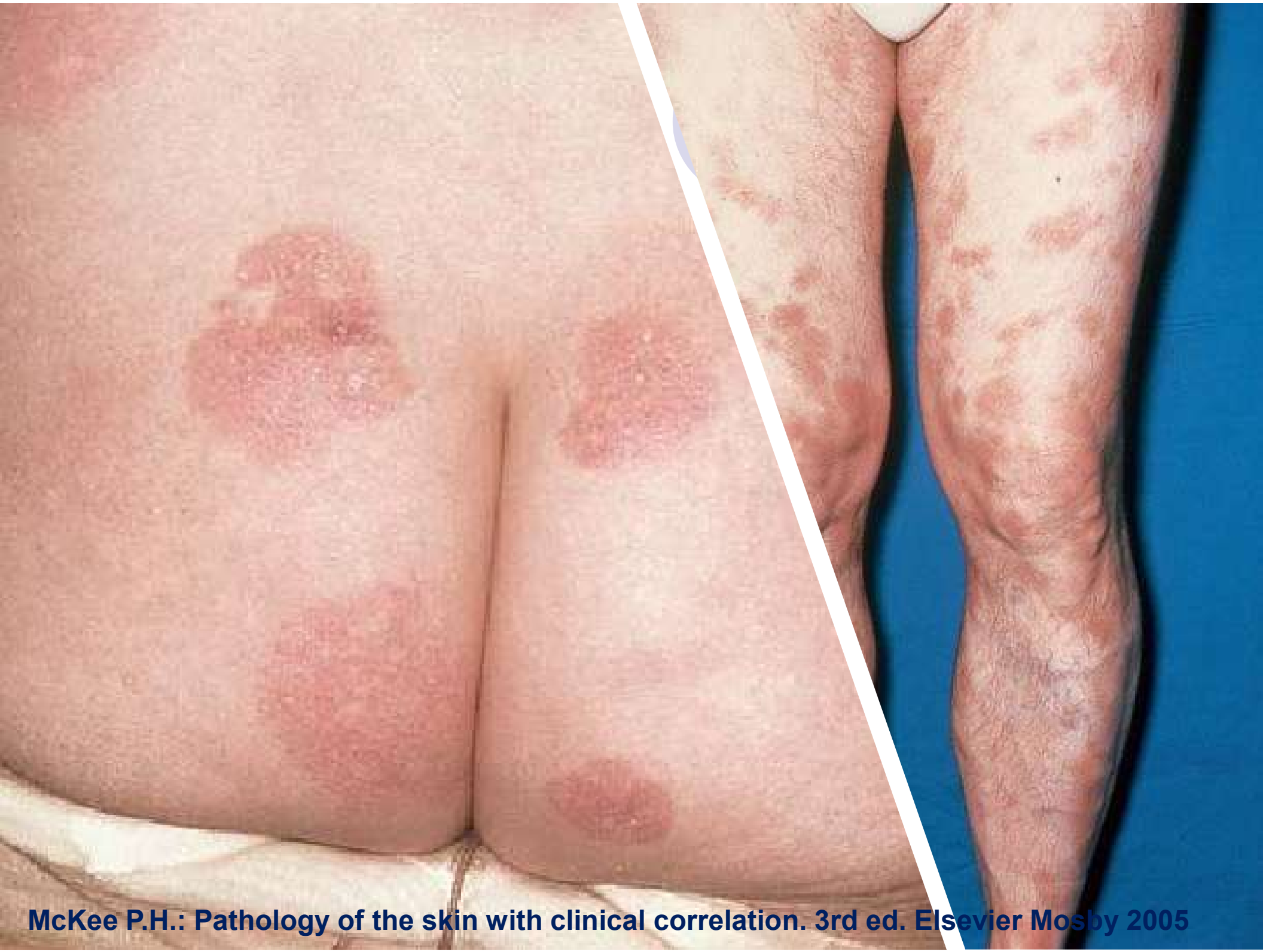
I phase	II phase	III phase
Time course 10-14 years	4-5 years	1-2 years
Patch stage Persistent scaly patches	Plaque stage Infiltrative elevated lesions	Tumor stage nodules

- Bazin 1876

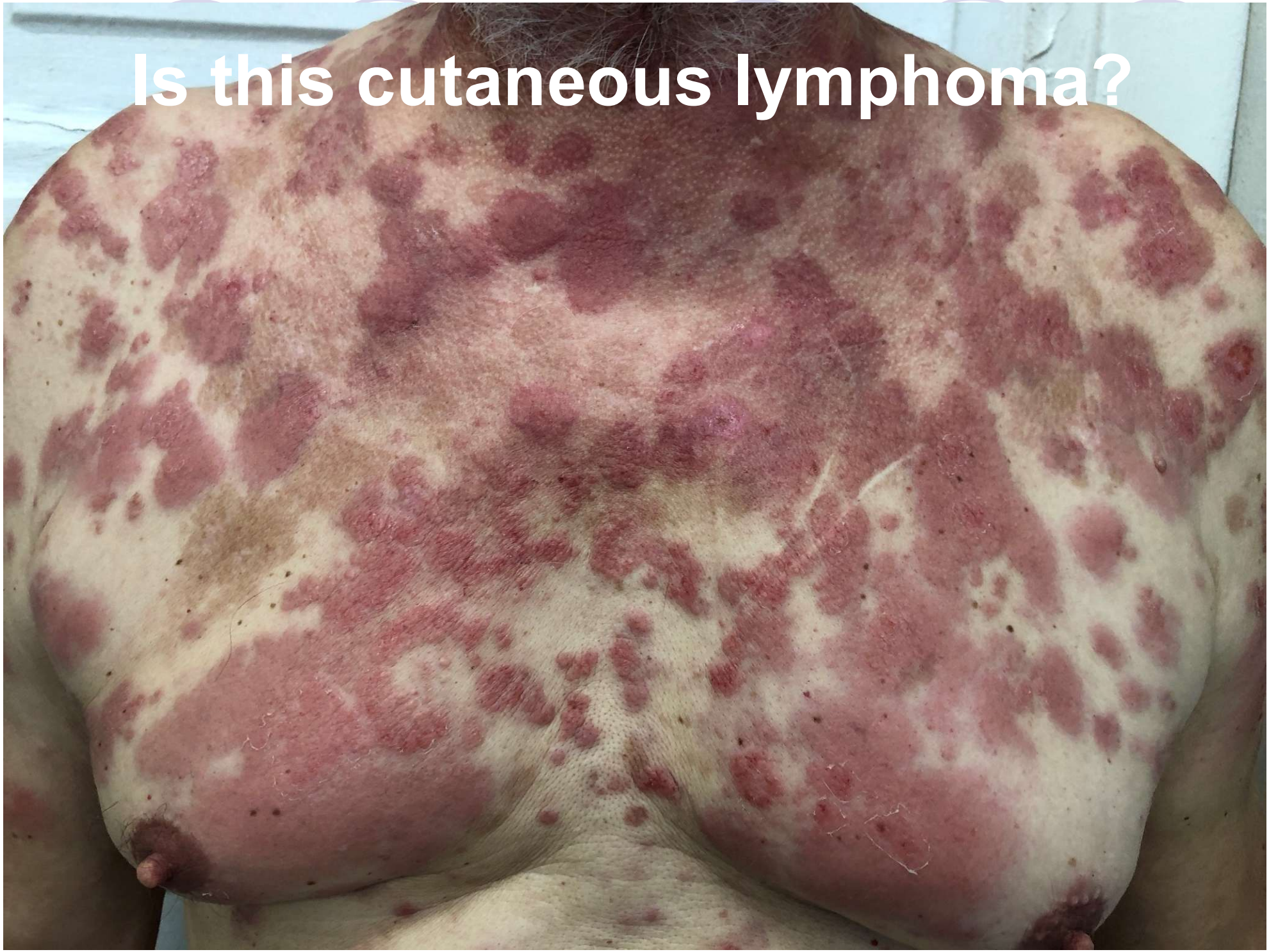
MF – patch stage

- the longest phase – 10 years of duration
- persistent scaly patches
- poor response to topical therapy with emollients and topical steroids
- pruritus -/+
- improvement after sun exposure
- in early stages, skin biopsy of MF is difficult to diagnose
- the average time from the onset of skin lesions to diagnosis is 4 years (7 years in the past)
- trunk and proximal extremities are affected (buttocks, breast, truncal flanks)
- oval and round asymmetric, scaly, erythematous patches with telangiectasias

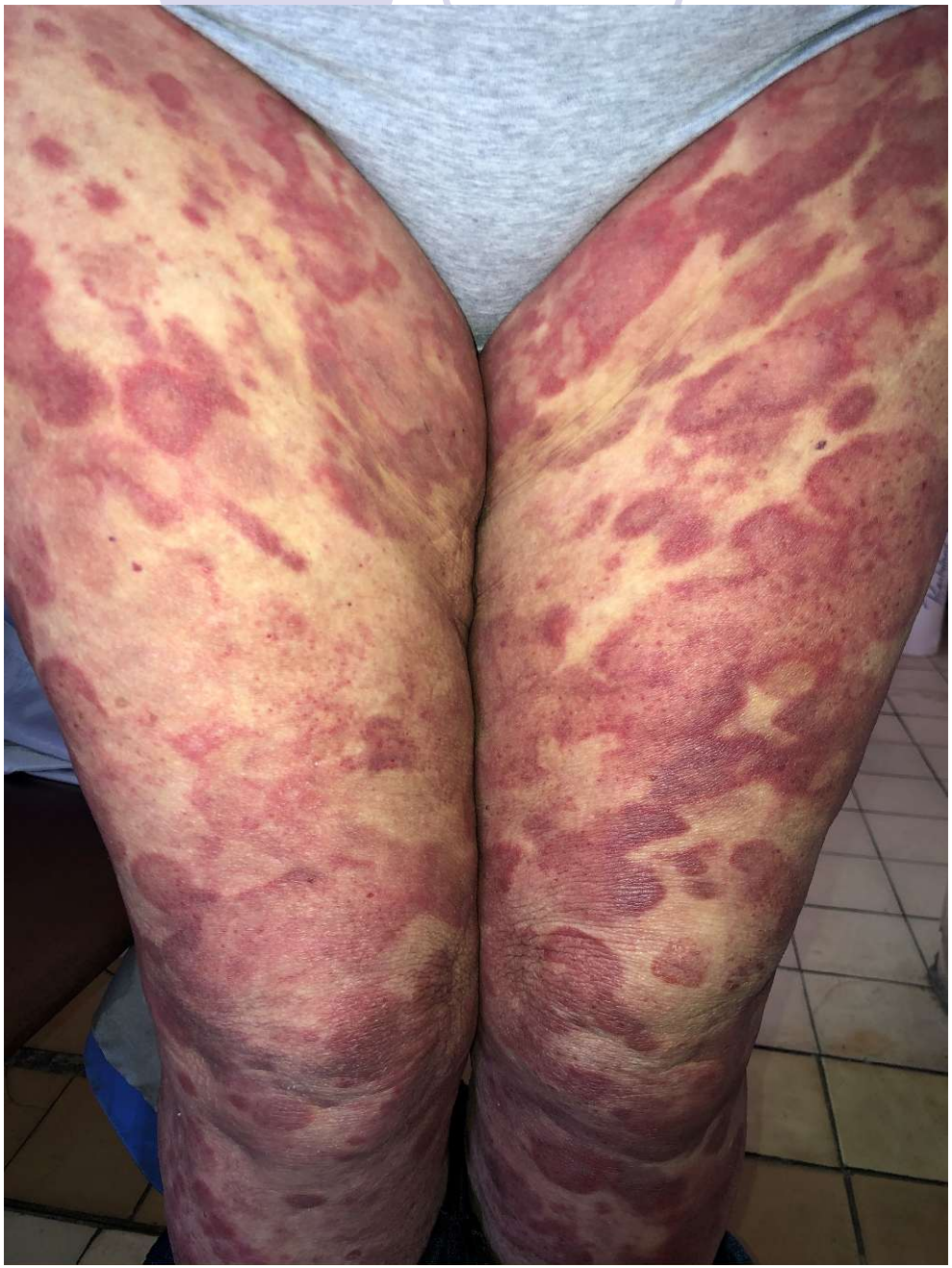


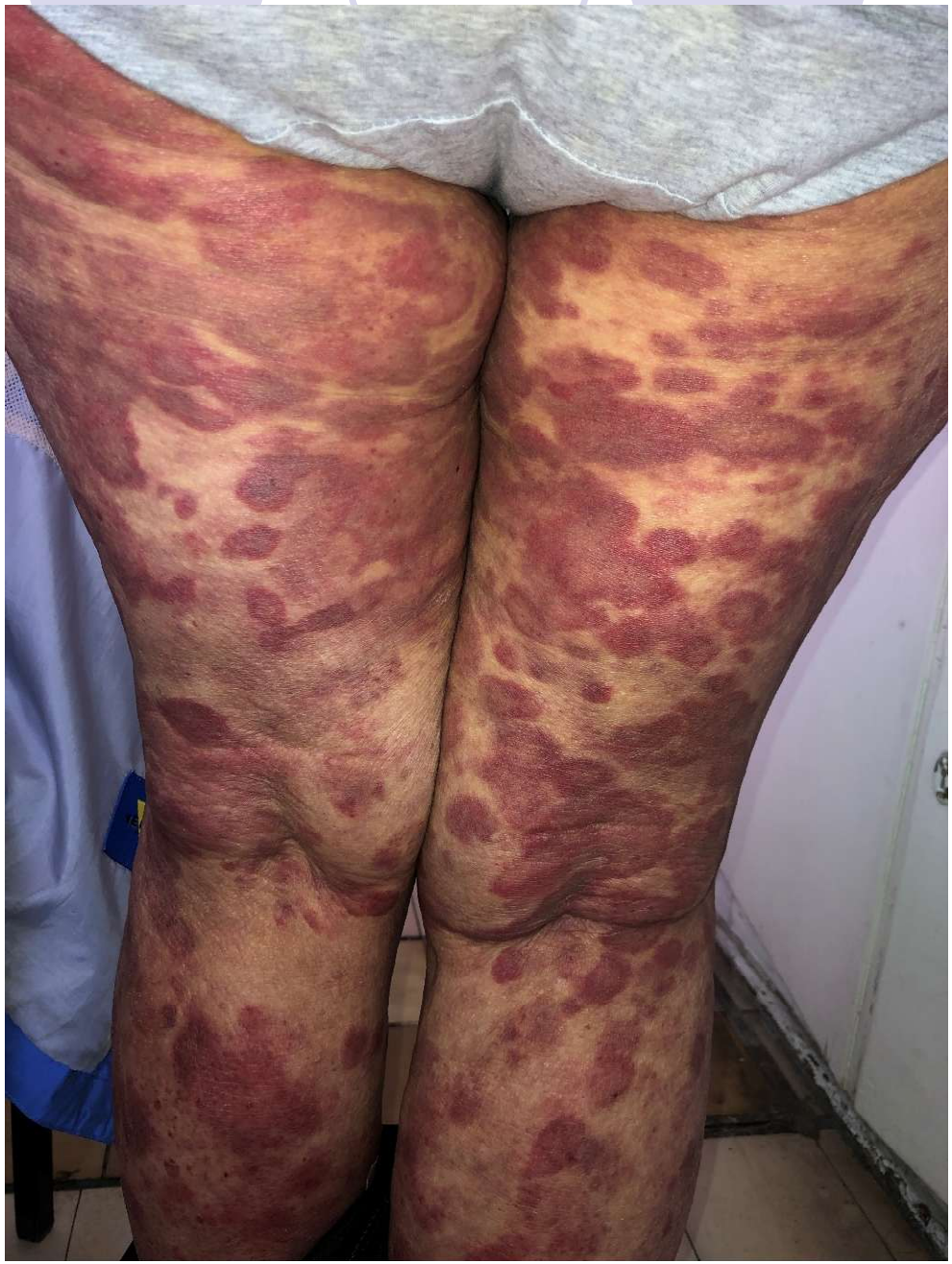


McKee P.H.: Pathology of the skin with clinical correlation. 3rd ed. Elsevier Mosby 2005


Is this cutaneous lymphoma?

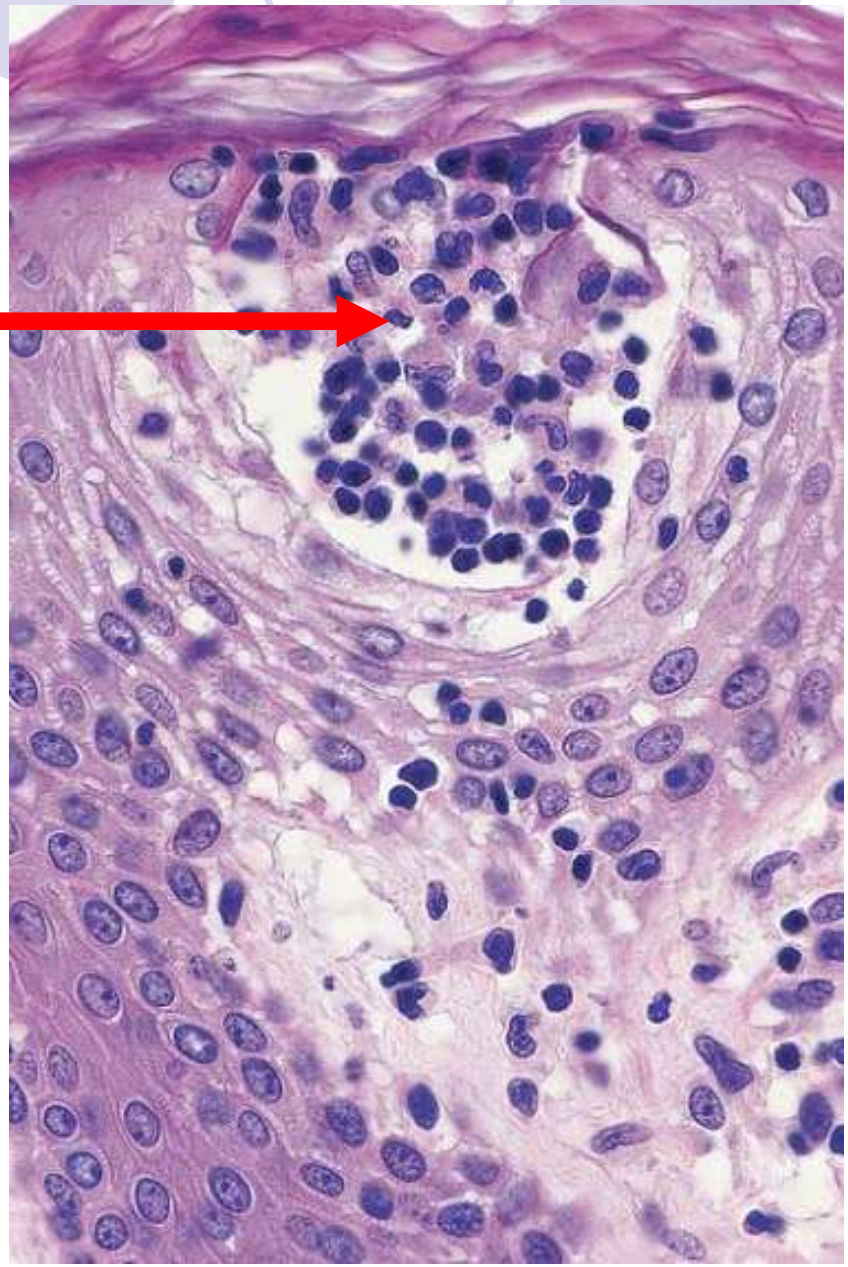
Is this cutaneous lymphoma?





Histopathology of mycosis fungoides

- epidermotropism
- collections of lymphocytes in the epidermis (Darier microabscess) 25% „+”
- atypical lymphocytes 10%+
- subepidermal band-like lymphocytic infiltrate
- linear arrangement of single atypical lymphocytes at dermal-epidermal junction
- markers CD3+, CD4+, CD7-, CD5-
- monoclonal TCR
- cerebriform nuclear shape (ME)



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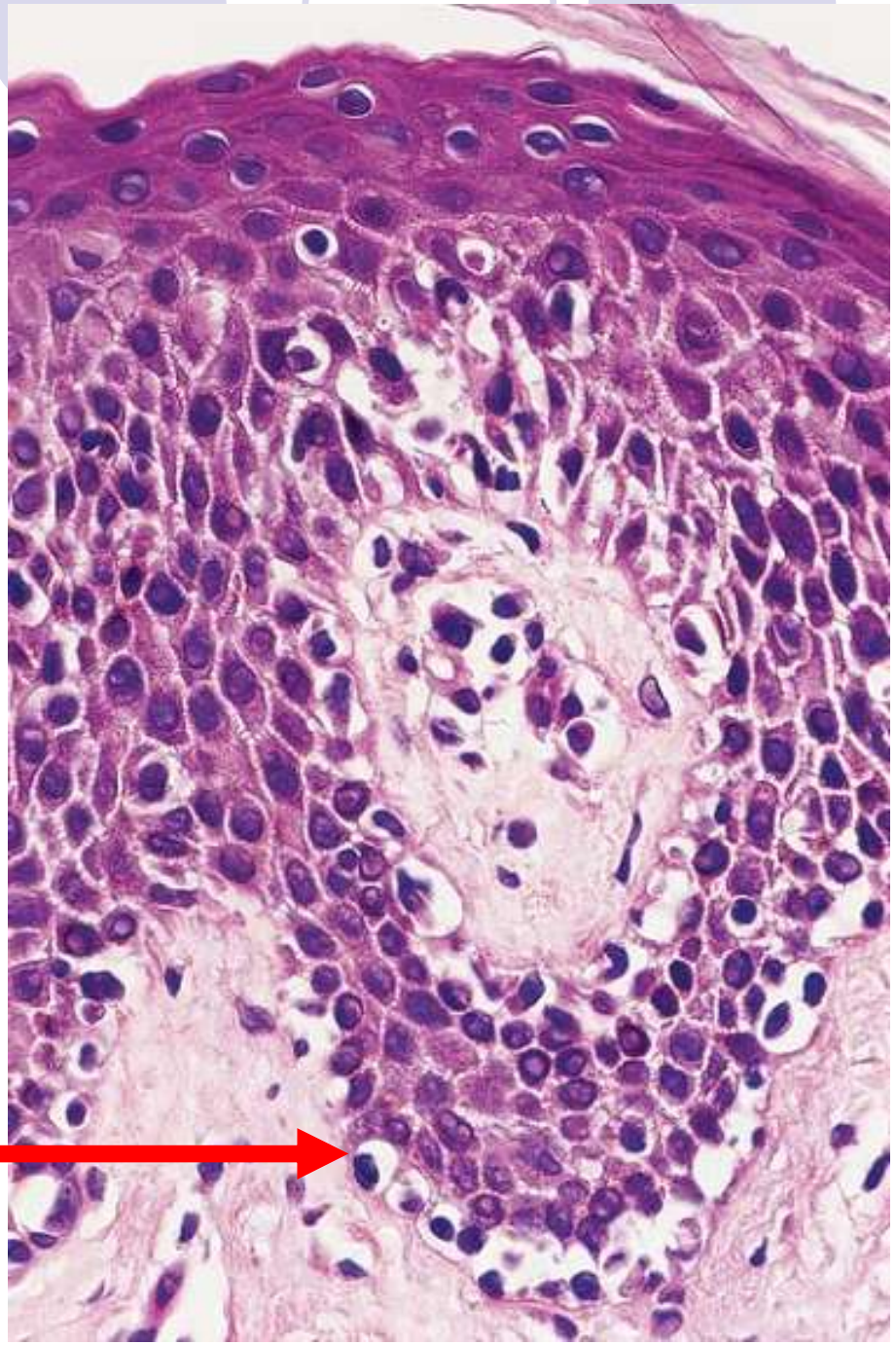
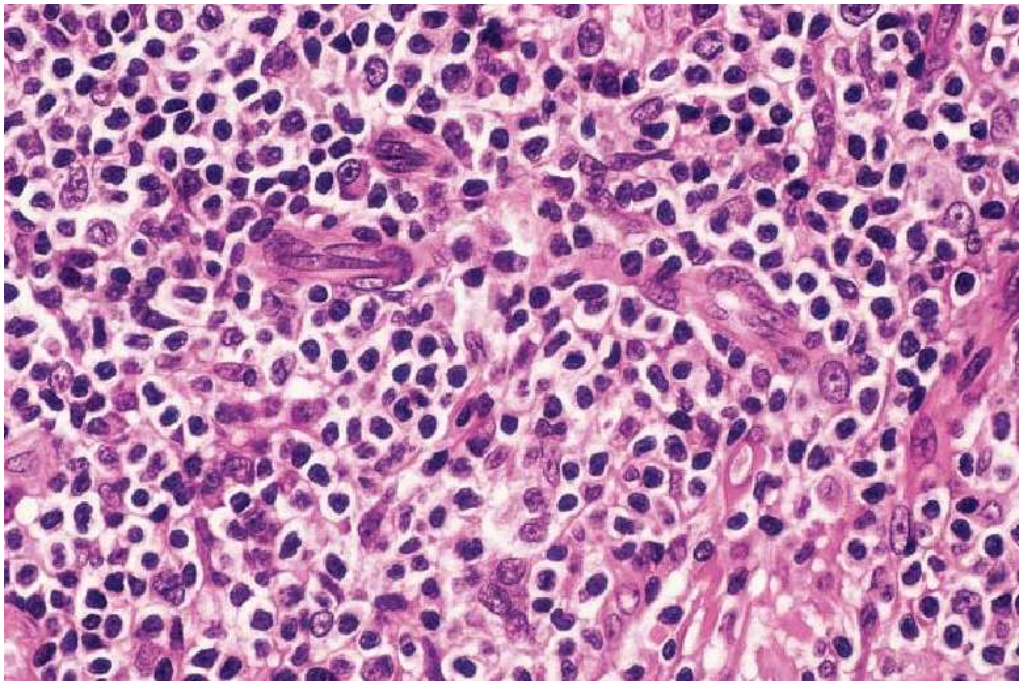
Mycosis fungoides

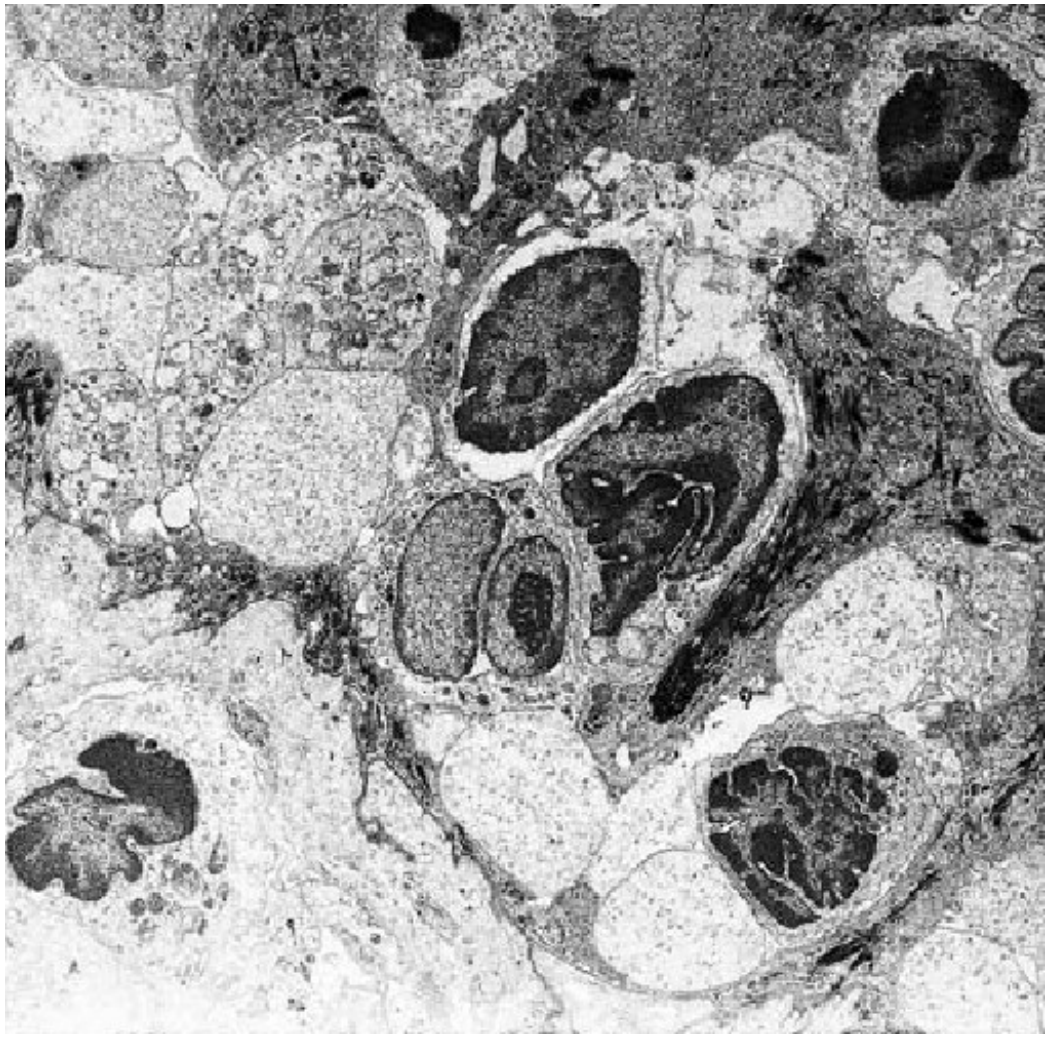


- Atypical lymphocytes „tagging” the DEJ

Atypical lymphocytes



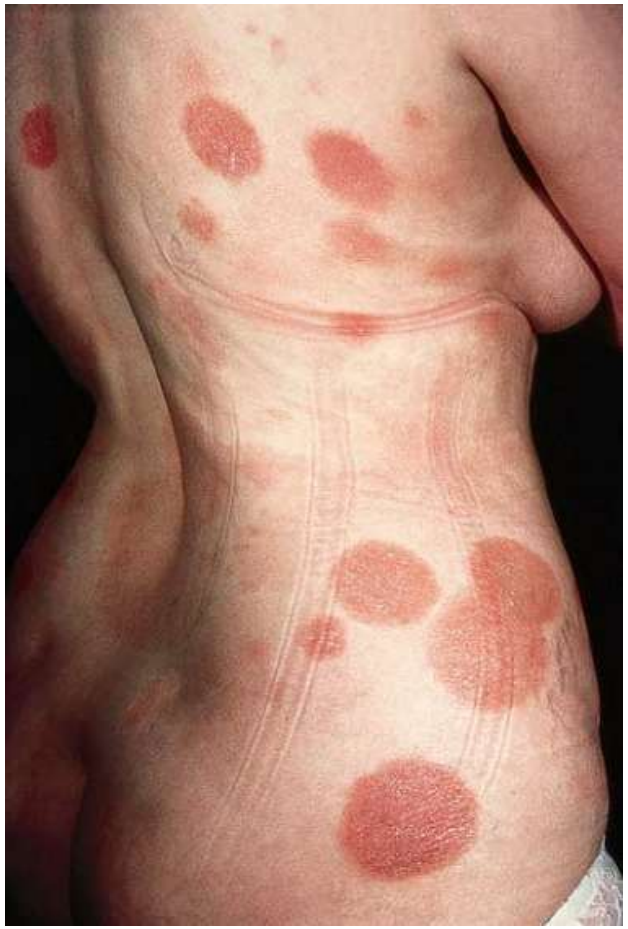
Hyperchromatic and highly irregular nuclei with pericellular „halo”



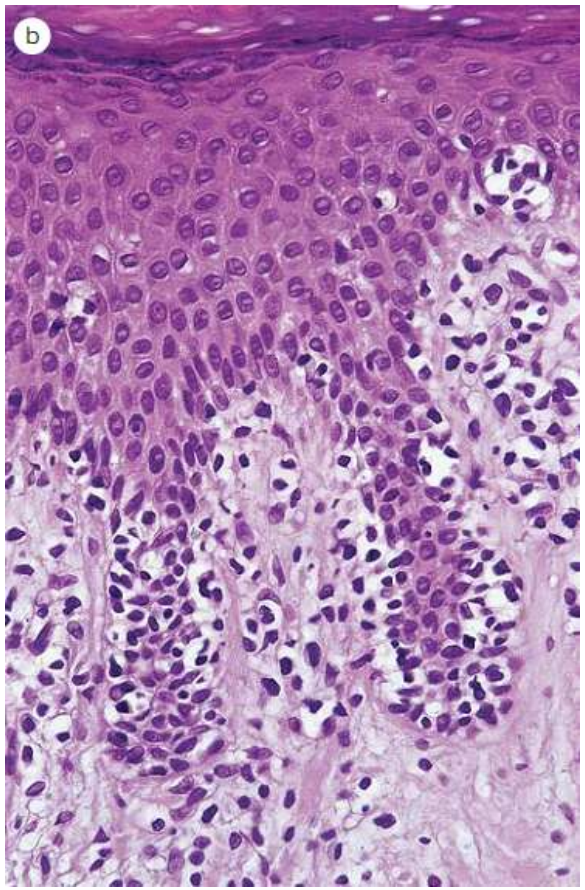
Highly convoluted (cerebriform) nuclei

MF diagnosis

- Clinical lesions – suspected of MF



- Histopathology estimated in the context of clinical suspicion
- parapsoriasis/mycosis fungoides



MF diagnosis = clinical skin changes + histopathology

Clonality of T-cells is reported in

- MF (mycosis fungoides)
- PLEVA (*pityriasis lichenoides et varioliformis acuta*)
- lichen planus, lichen striatus
- lichen sclerosus
- atopic dermatitis
- lichenoid eczema, syphilis
- chronic actinic dermatitis
- pseudolymphoma (insect bite reaction, HSV infection, prolonged scabies, molluscum contagiosum, drug reactions)

Clinical-pathological correlation is needed to diagnose MF

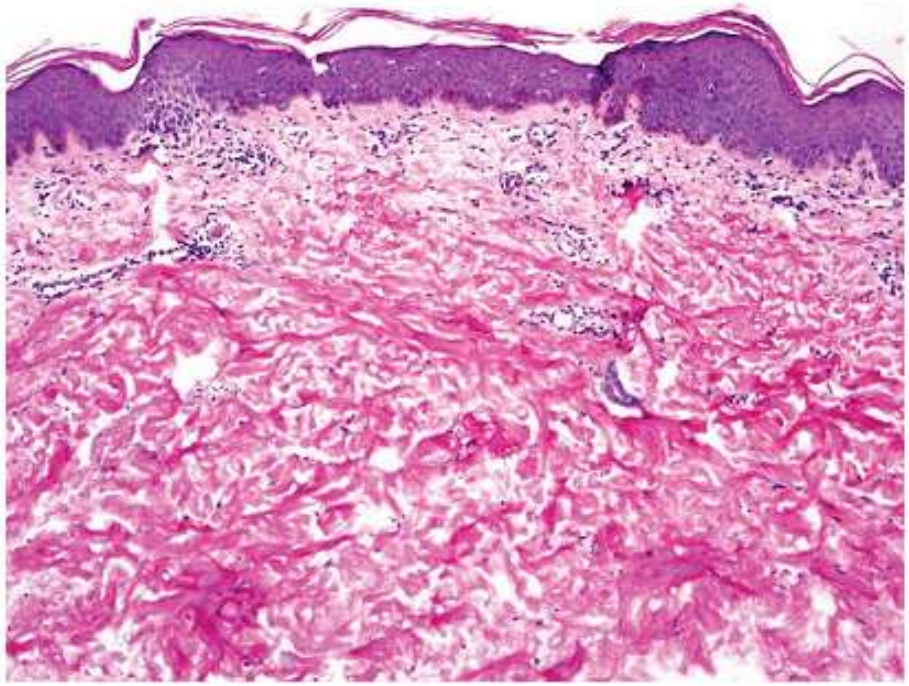
Mycosis Fungoides: An Updated Review of Clinicopathologic Variants

Christine S. Ahn, MD, Ahmed ALSayyah, MD,† and Omar P. Sangüeza, MD‡*

TABLE 1. Algorithm for the Diagnosis of Early MF. Adapted From Pimpinelli et al[6]

Criteria	Score
Clinical	
Basic	2 points for basic criteria and 2 additional criteria
Persistent and/or progressive patches/thin plaques	
Additional	2 points for basic criteria and 2 additional criteria
Non–sun-exposed location	
Size/shape variation	
Poikiloderma	
Histopathologic	
Basic	2 points for basic criteria and 2 additional criteria
Superficial lymphoid infiltrate	
Additional	
Epidermotropism without spongiosis	1 point for basic criteria and 1 additional criterion
Lymphoid atypia defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours	
Molecular biological	
Clonal TCR gene rearrangement	1 point for clonality
Immunopathologic	
Less than 50% $CD2^+$, $CD3^+$, and/or $CD5^+$ T cells	1 point for one or more criteria
Less than 10% $CD7^+$ T cells	
Epidermal/dermal discordance of CD2, CD3, CD5, or CD7	

TCR, T-cell receptor.



perform several biopsies if early mycosis fungoides is suspected to establish the proper diagnosis

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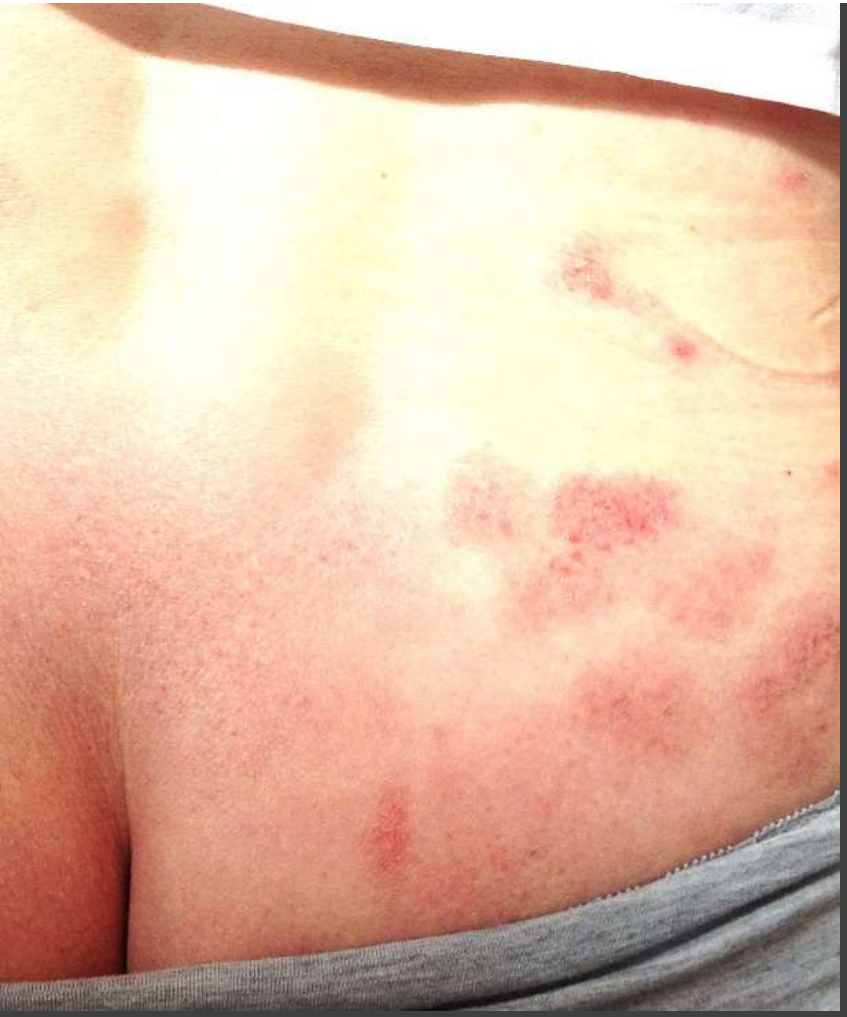
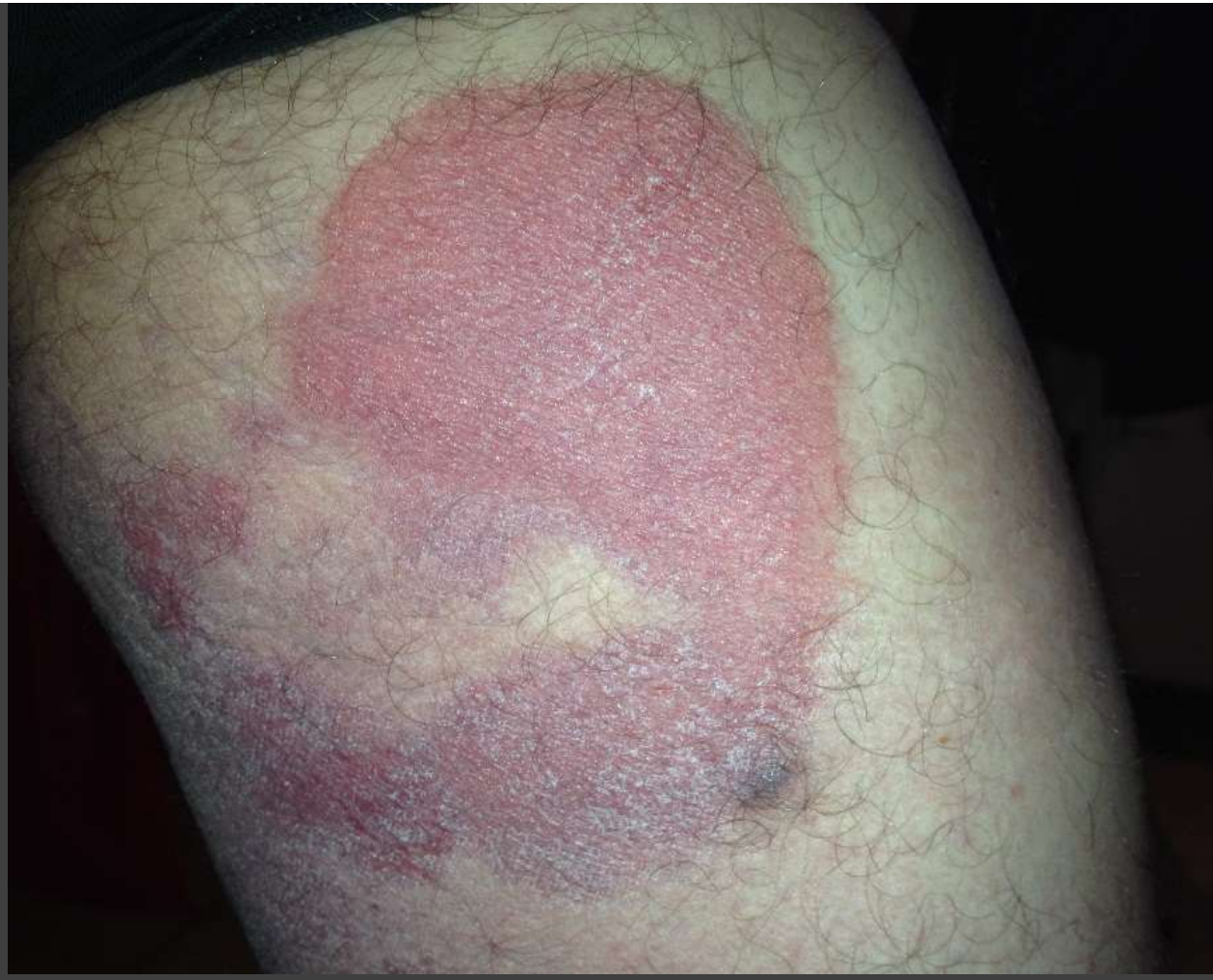
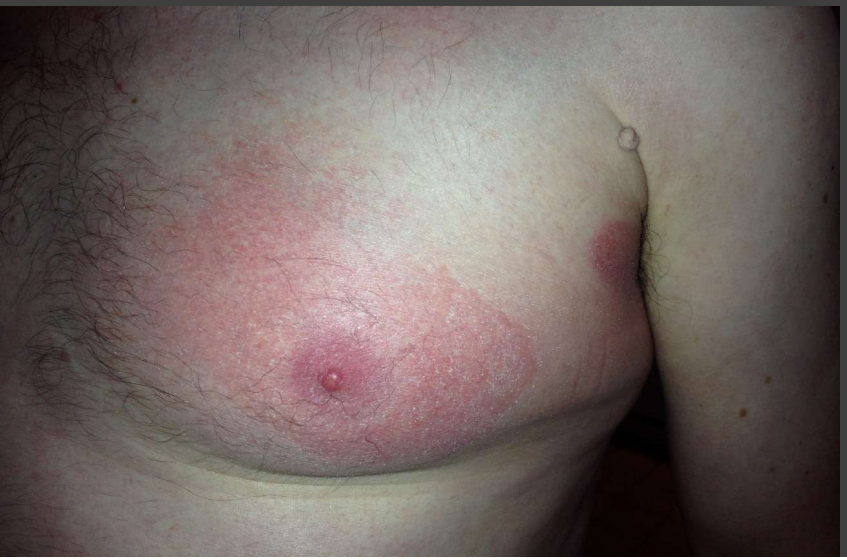
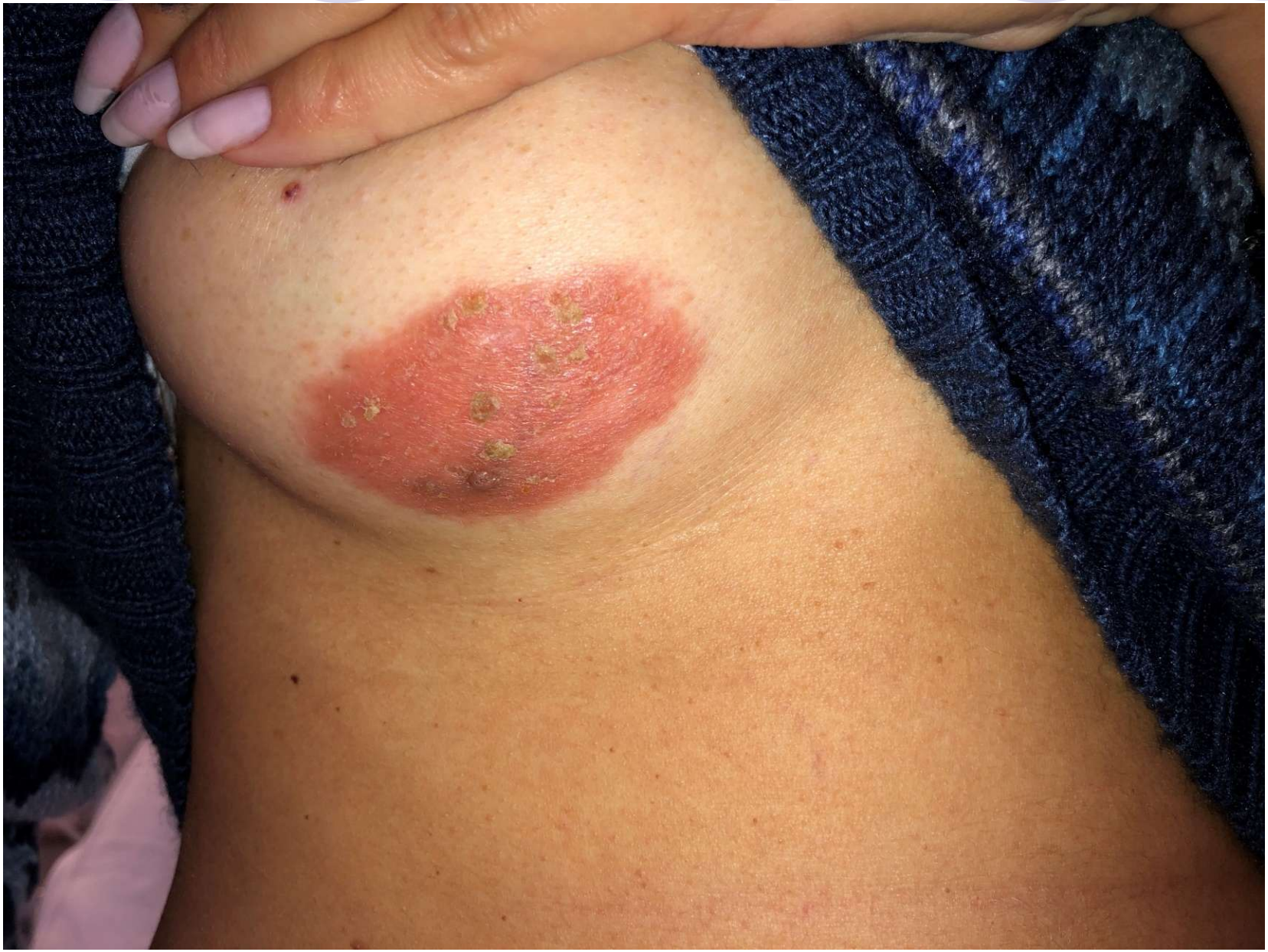




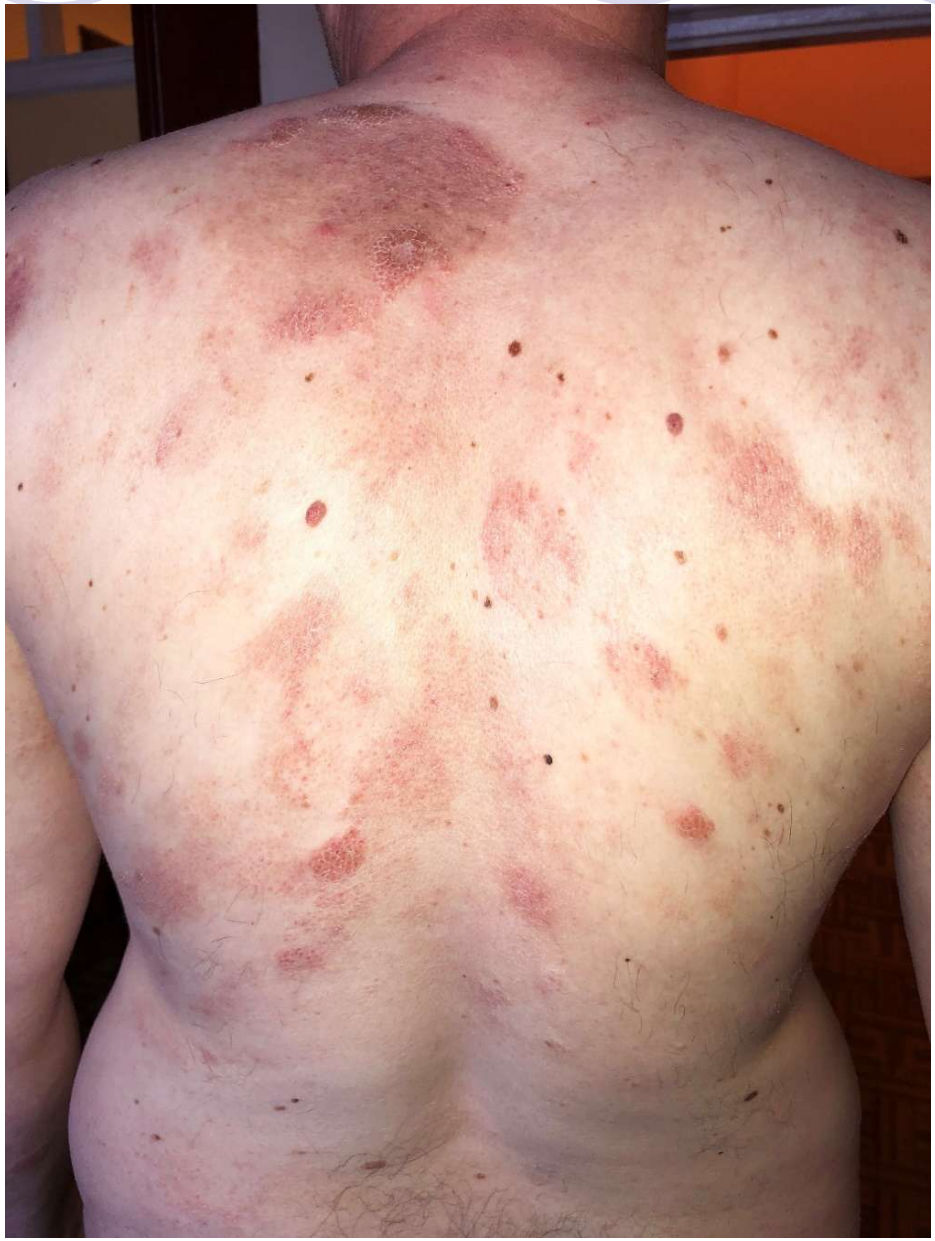


Oval, round or kidney-shaped erythematous scaly skin lesions in sun protected or double covered locations

Mycosis fungoides with only one location, duration over 3 years, persistent plaque



Mycosis fungoides in a patient with contact dermatitis – difficult for histopathological evaluation due to overlapping eczema with MF



Clinical stages of MF and Sezary Syndrome in TNMB

TNMB CLASSIFICATION OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME	
T (SKIN)	
T_1	Limited patch/plaque (involving <10% of total skin surface)
T_2	Generalized patch/plaque (involving ≥10% of total skin surface)
T_3	Tumor(s)
T_4	Erythroderma
N (LYMPH NODE)	
N_0	No enlarged lymph nodes
N_1	Enlarged lymph nodes, histologically uninvolved
N_2	Enlarged lymph nodes, histologically involved (nodal architecture uneffaced)
N_3	Enlarged lymph nodes, histologically involved (nodal architecture [partially] effaced)
M (VISCERA)	
M_0	No visceral involvement
M_1	Visceral involvement
B (BLOOD)	
B_0	No circulating atypical (Sézary) cells (or <5% of lymphocytes)
B_1	Low blood tumor burden (≥5% of lymphocytes are Sézary cells, but not B_2)
B_2	High blood tumor burden (≥1000/µl Sézary cells + positive clone)

lungs
GI tract
liver
spleen

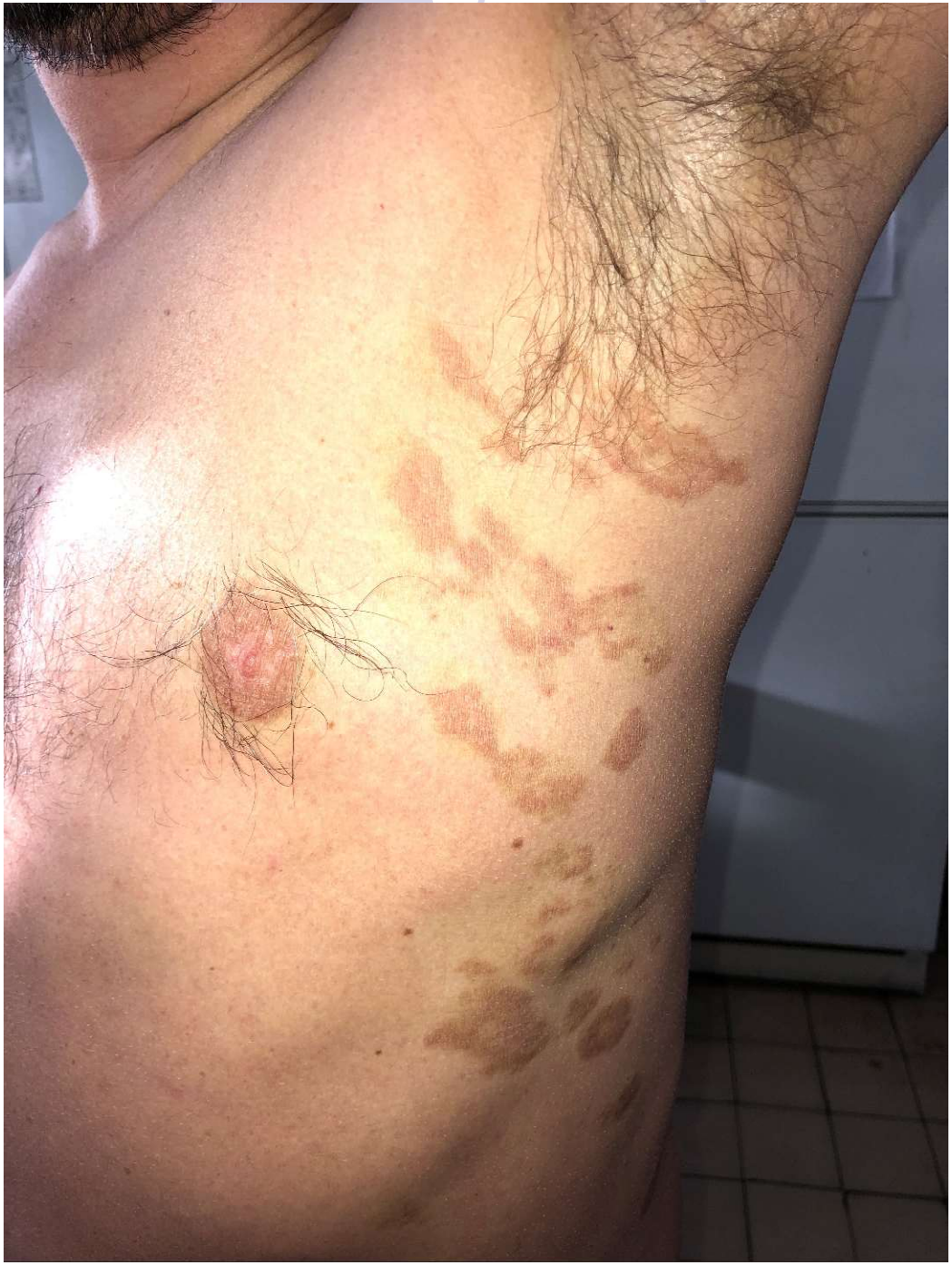
MF treatment is dermatological for years

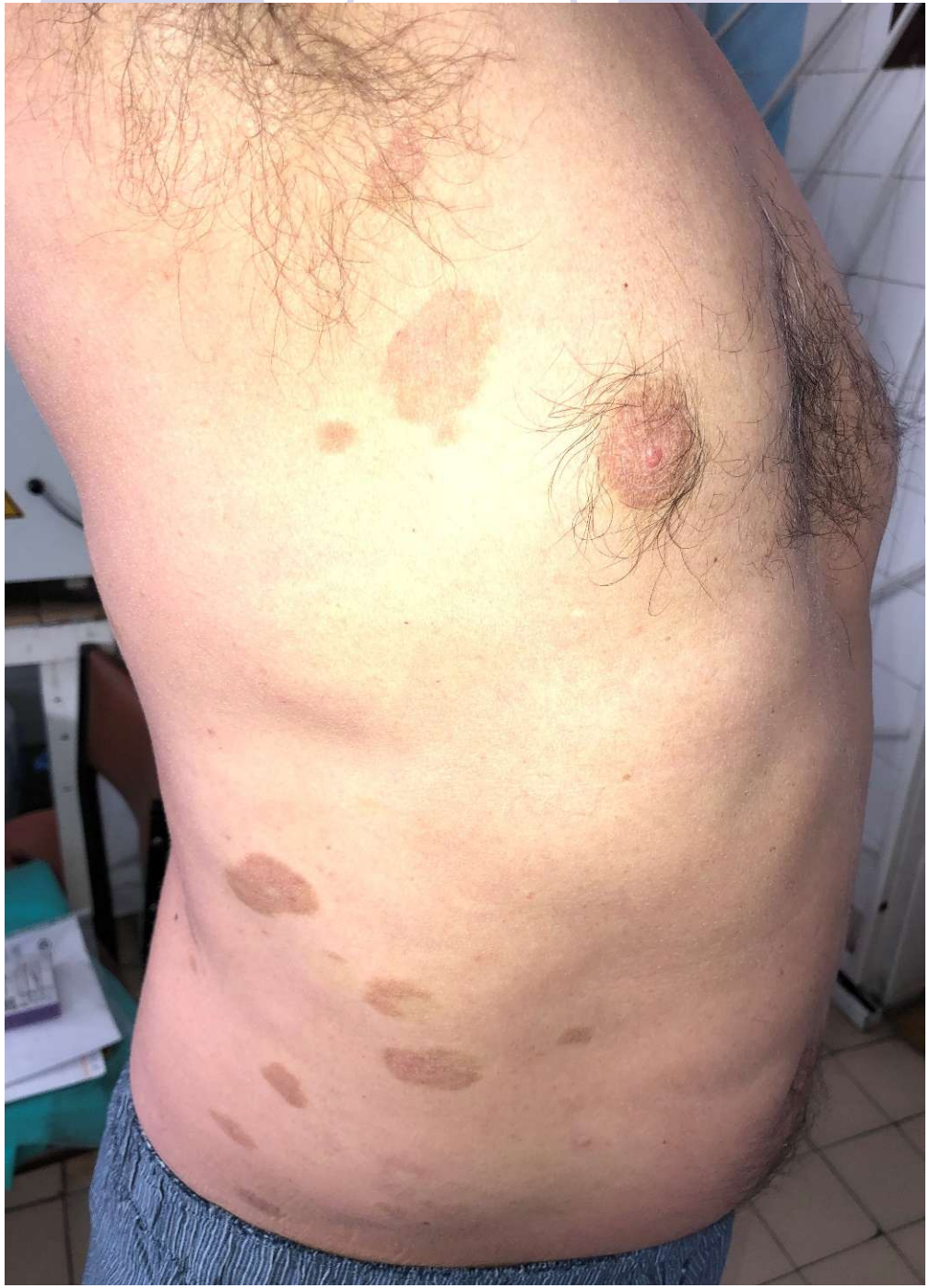
According to the stage of MF

- Topical: moderate to potent corticosteroids, carmustine, chlormethine
- Phototherapy: PUVA, Re-PUVA, NB-UVB (311nm)
- Oral retinoids (bexaroten, acitretin)
- Methotrexate p.o., s.c.
- extracorporeal photopheresis (FDA-approved)
- electron-beam therapy
- INF-alfa
- chemotherapy
- radiotherapy

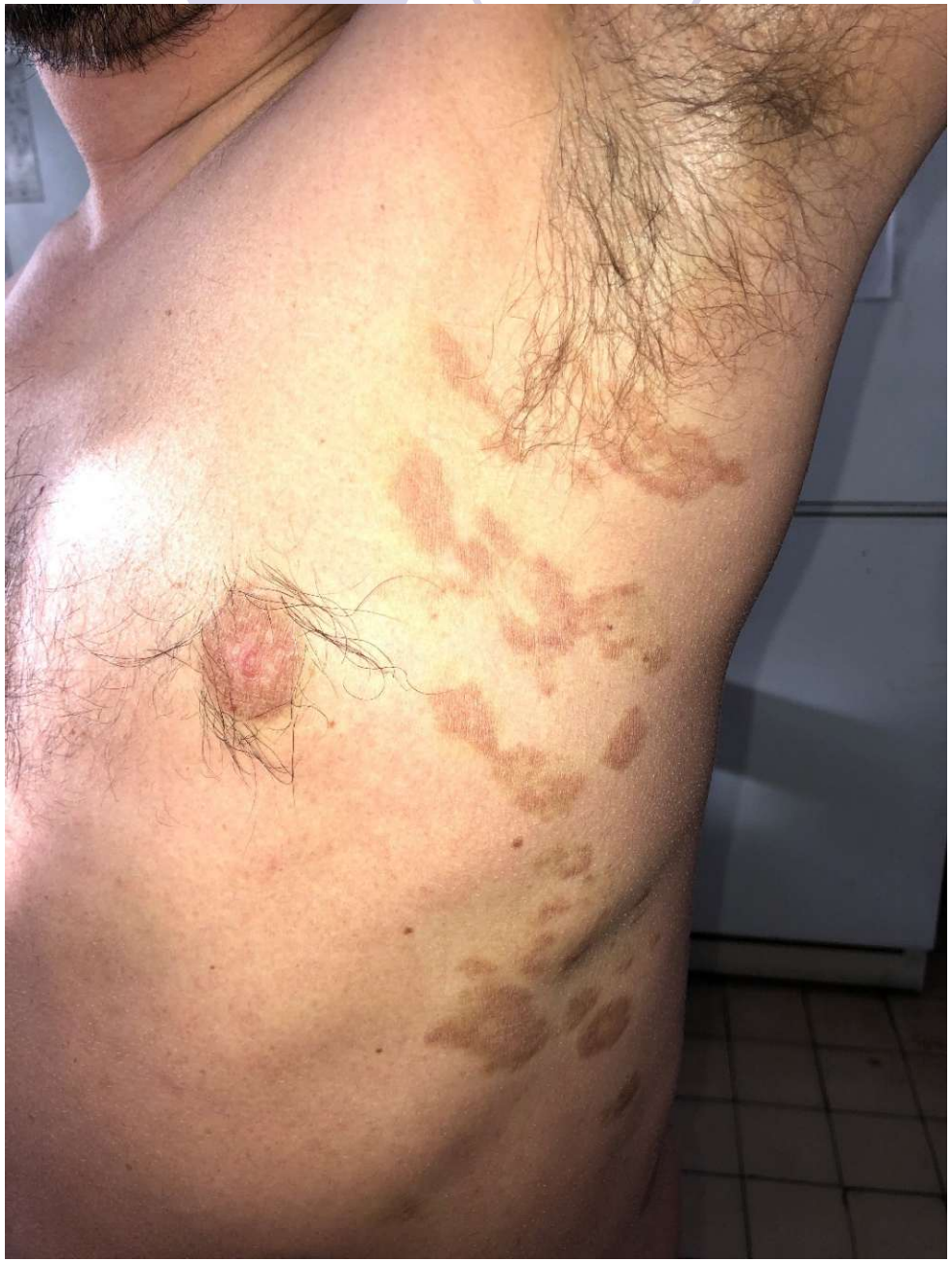
Complete remissions are common, especially in the early-stage of the disease!

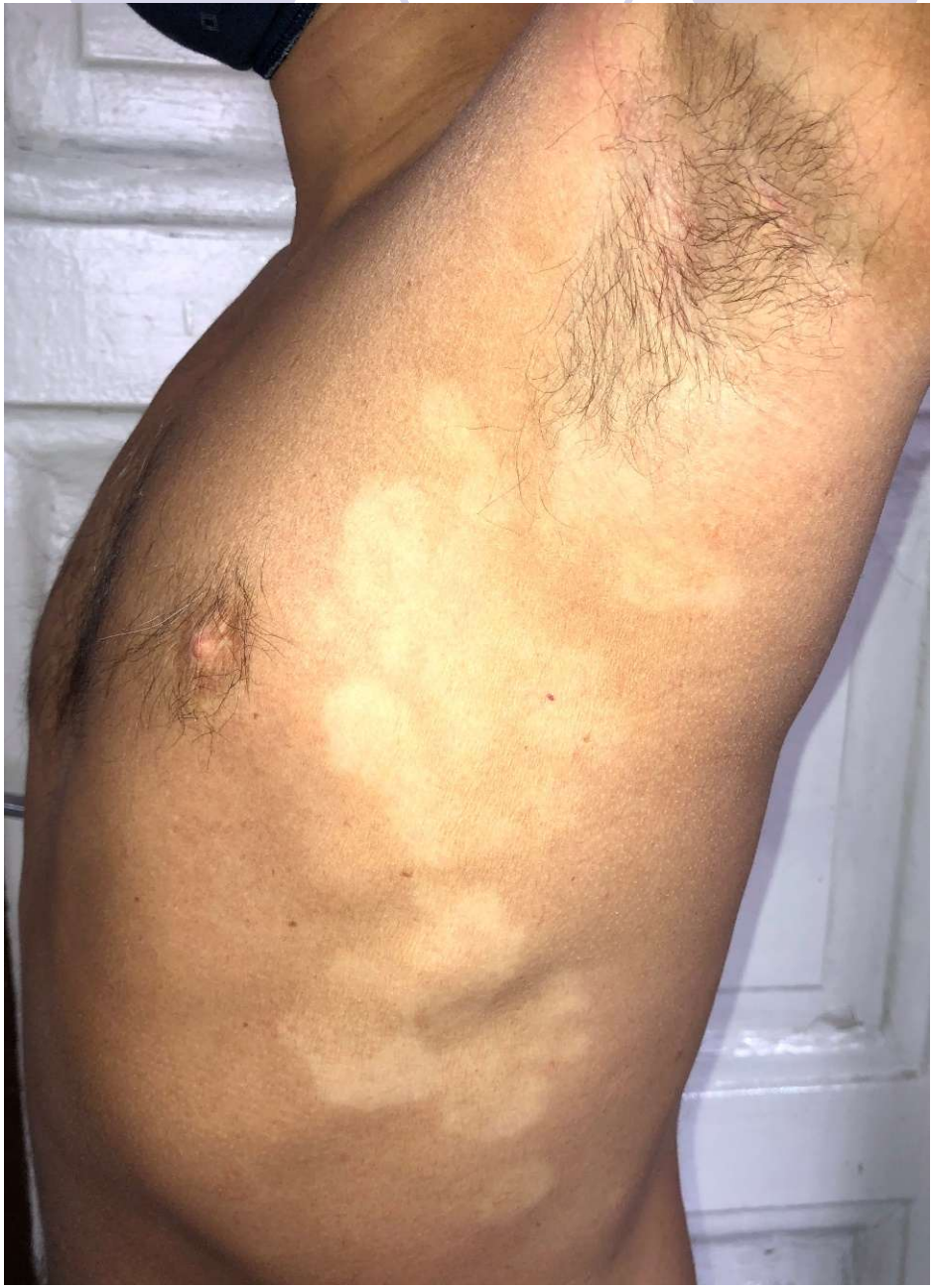
Mycosis fungoides before Re-PUVA therapy





Remission of mycosis fungoides after Re-PUVA – postinflammatory hypopigmentation

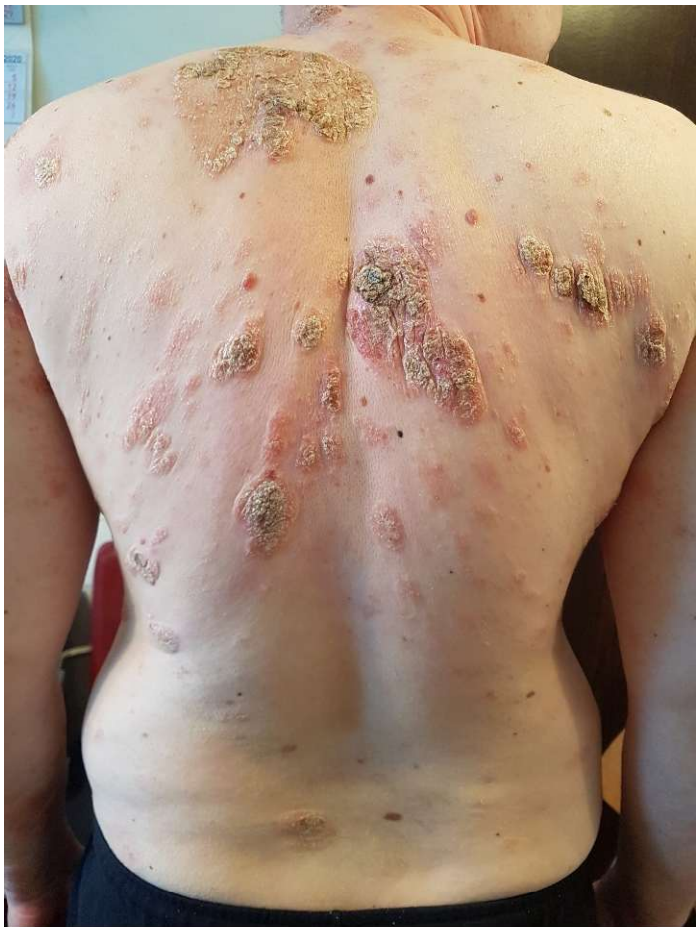




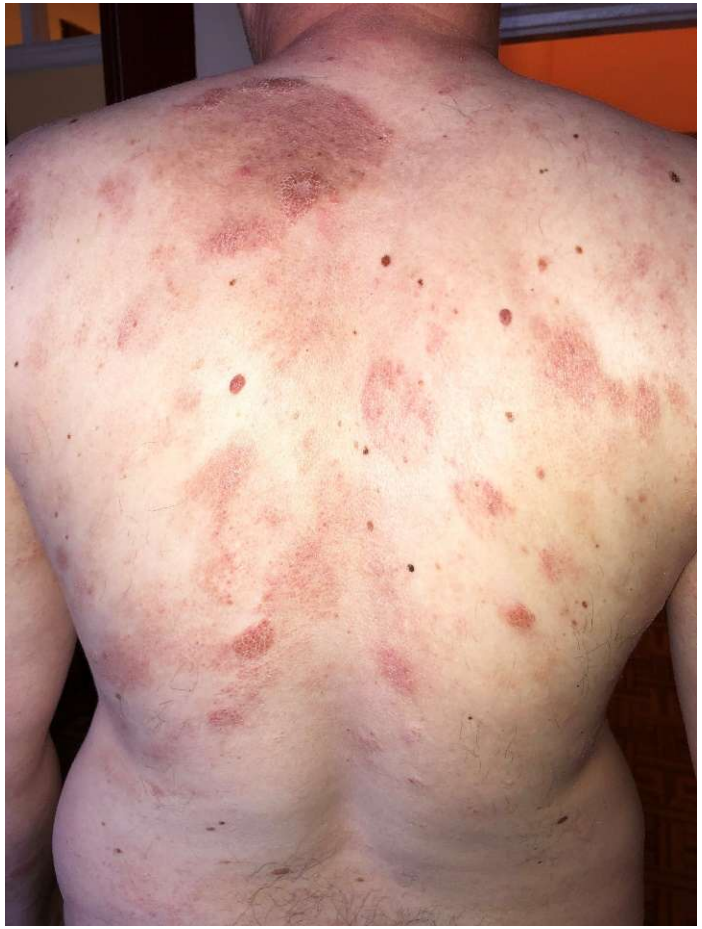
Bexarotene (Targretin)

- synthetic retinoid
- selectively activates retinoid X receptors - rexinoid
- oral form at the recommended dose of 300 mg/m^2
- teratogenic drug
- topical form in the gel is also available (Targretin gel) but not in Poland

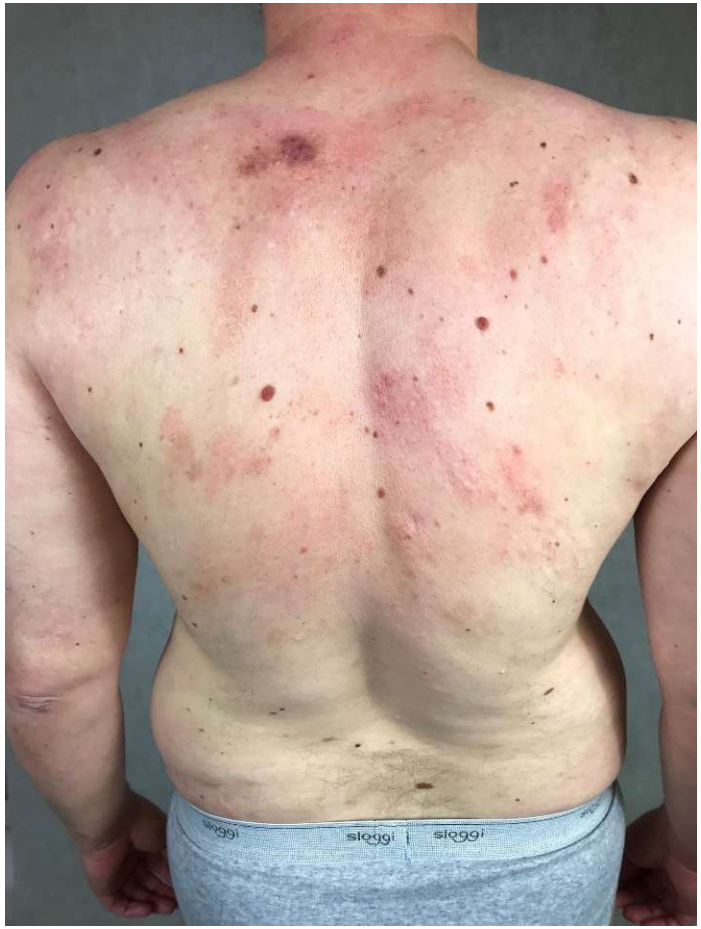
Bexarotene effect on MF



Diagnosis of MF



Methotrexate effect



During bexarotene treatment

Other methods of treating mycosis fungoides

- **Methotrexate as the first-line drug in both early (patch and infiltrative) and advanced** forms of mycosis fungoides, at doses of 7.5-25 mg/week (up to 75 mg/week)

- **Vorinostat and romidepsin - histone deacetylase inhibitors (HDACi)** are recommended as second-line and subsequent-line drugs in the treatment of chronic and recurrent mycosis fungoides

- **Denileukin diftitox (ONTAK)** is a fusion protein consisting of recombinant interleukin-2 and diphtheria toxin. It is a second-line treatment, used after unsuccessful treatment with bexarotene or HDACi. The drug's initiation requires expression of the CD25 antigen on tumor cells

- **Chemotherapy** with gemcitabine and liposomal doxorubicin is used as monotherapy or in polychemotherapy according to doxorubicin-based regimens, including **CHOP** (cyclophosphamide, doxorubicin, vincristine, prednisolone)

Other methods of treating mycosis fungoides

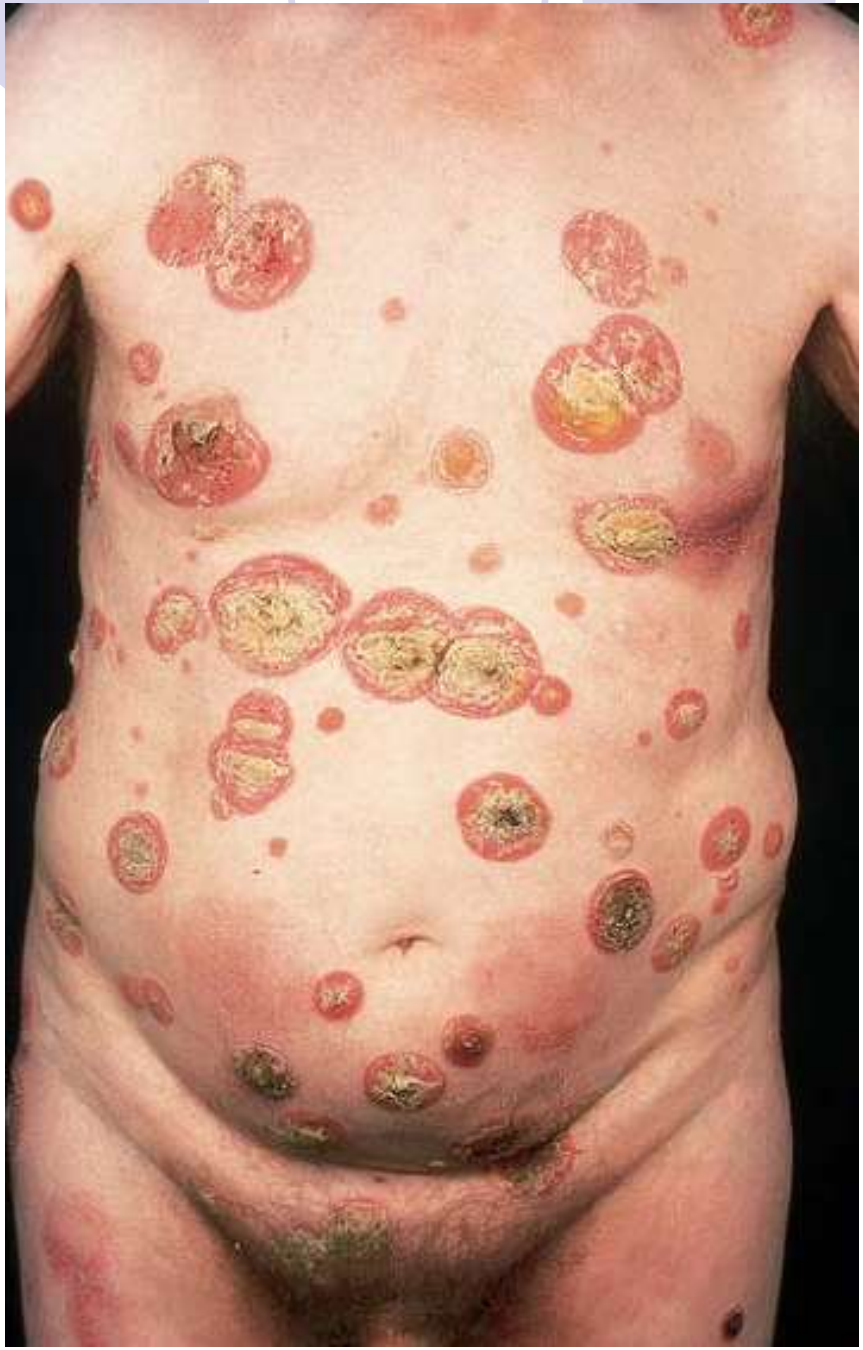
- **Mogamulizumab (Poteligeo)** humanized Ab against CCR4

- **Brentuximab vedotin** – anti-CD30 Ab combined with auristatin E acting on the mitotic spindle

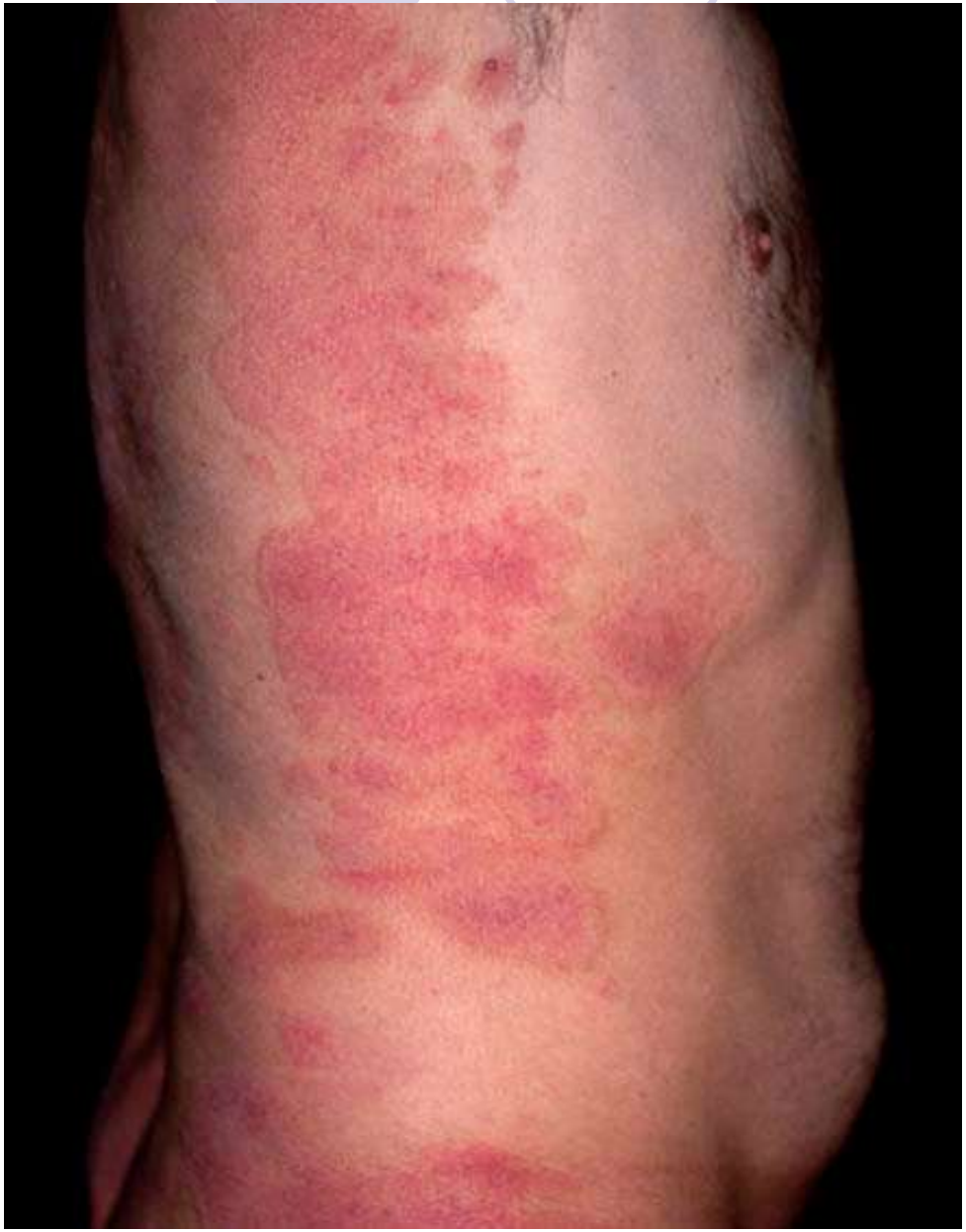
- **Allogeneic stem cell transplantation** (allo-HSCT) for the advanced stages of mycosis fungoides

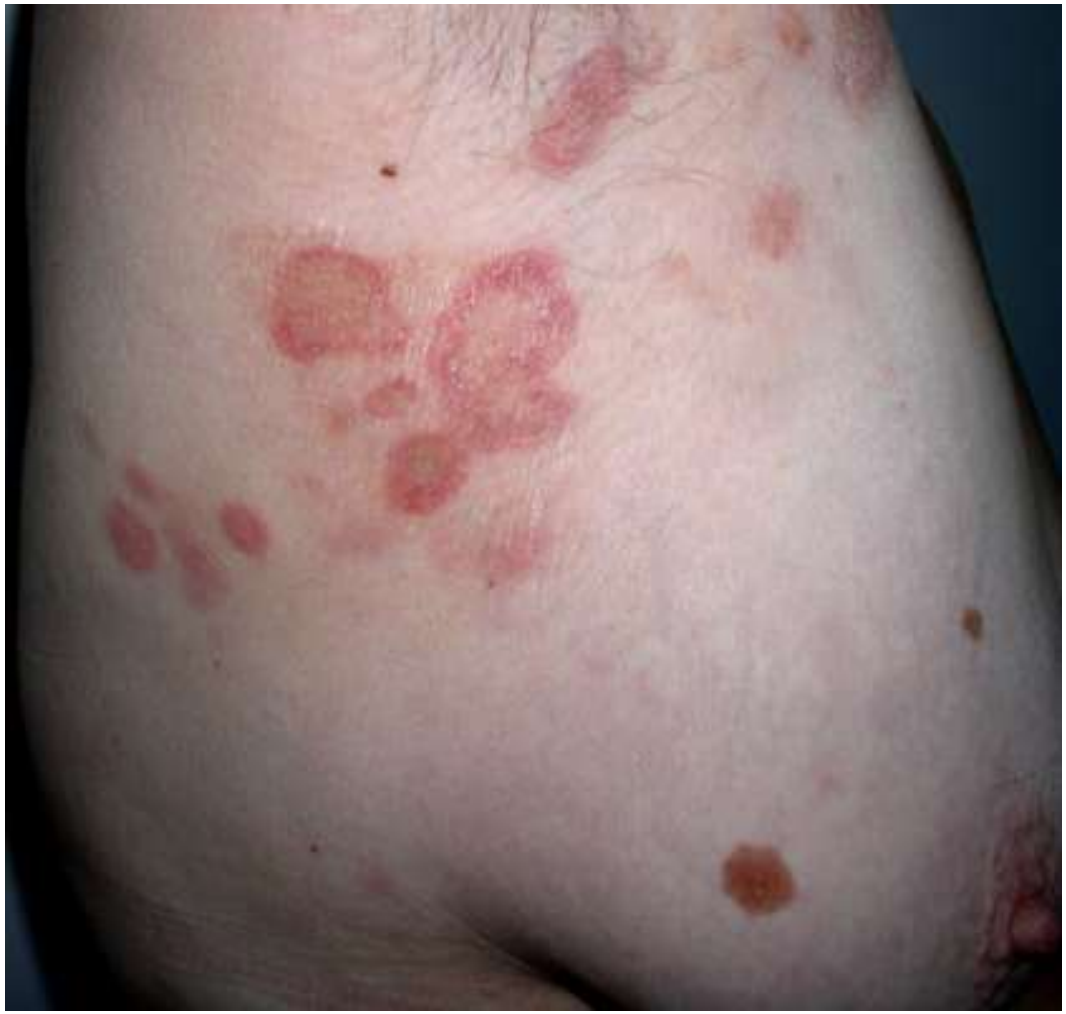
Clinical differentation of MF

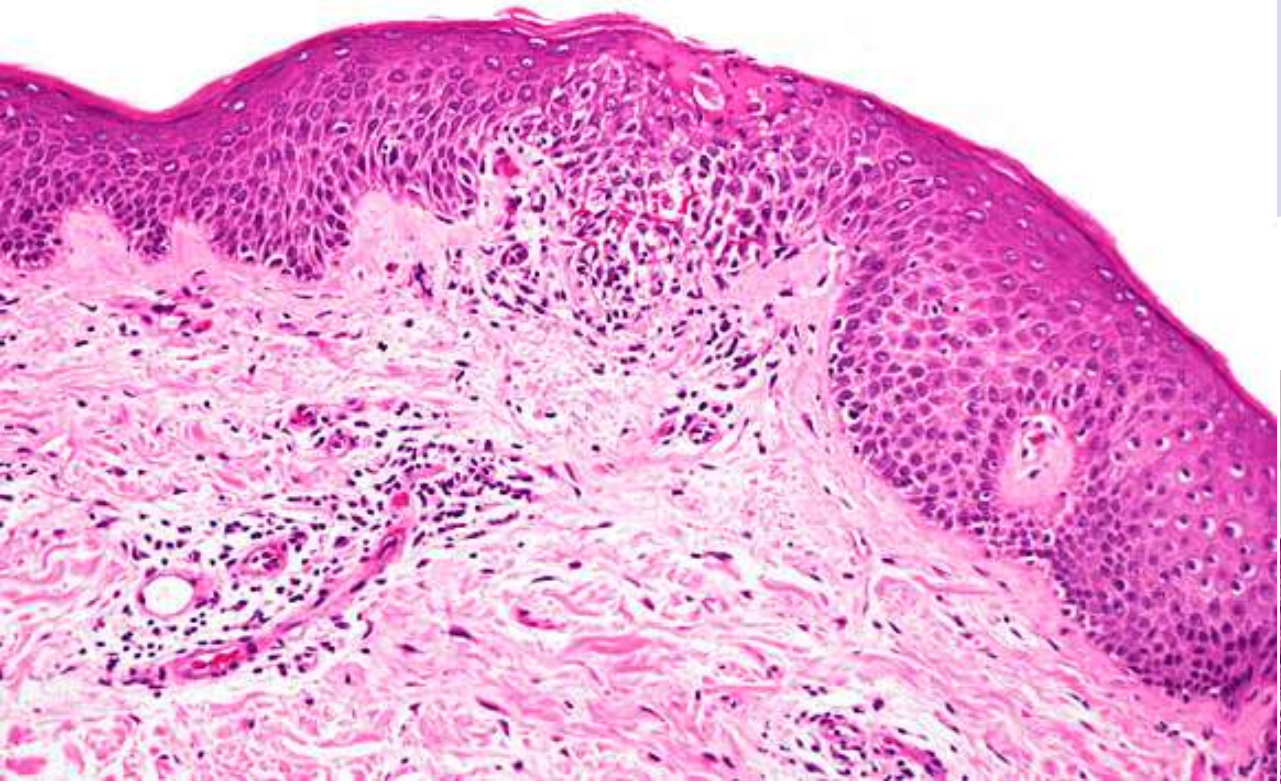
1. Atopic dermatitis
2. Allergic contact dermatitis
3. Irritated dermatitis
4. Psoriasis
5. Dermatophytosis
6. Chronic superficial lichenoid dermatitis
7. Morphea
8. Drug reactions (anticonvulsants: phenytoin, barbiturates, carbamazepine), atenolol, ACE inhibitors, allopurinol



Eczema vs mycosis fungoides

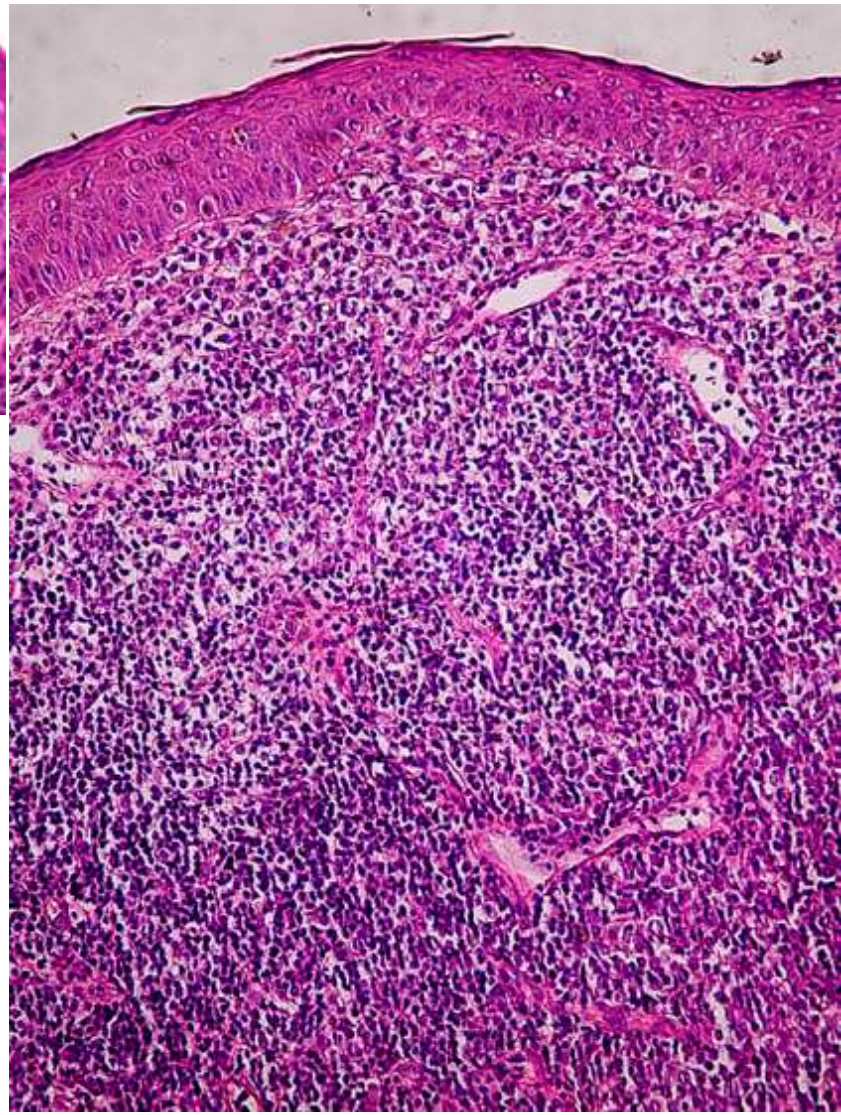




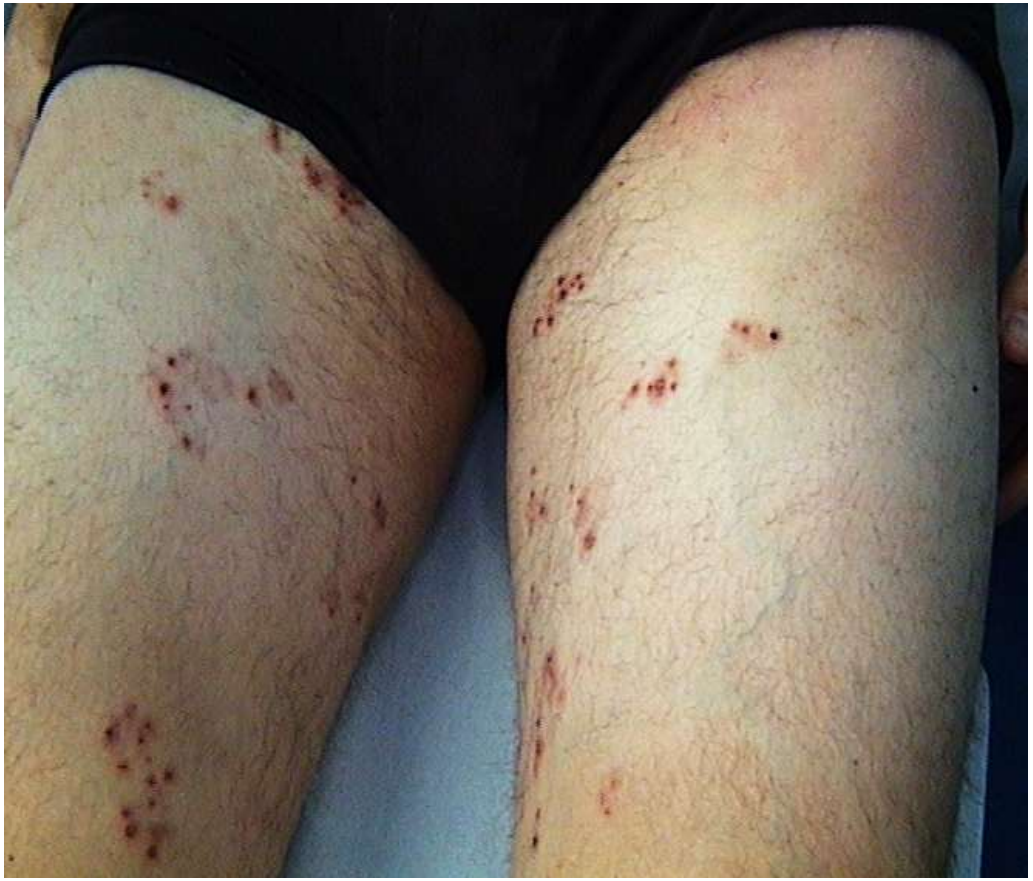


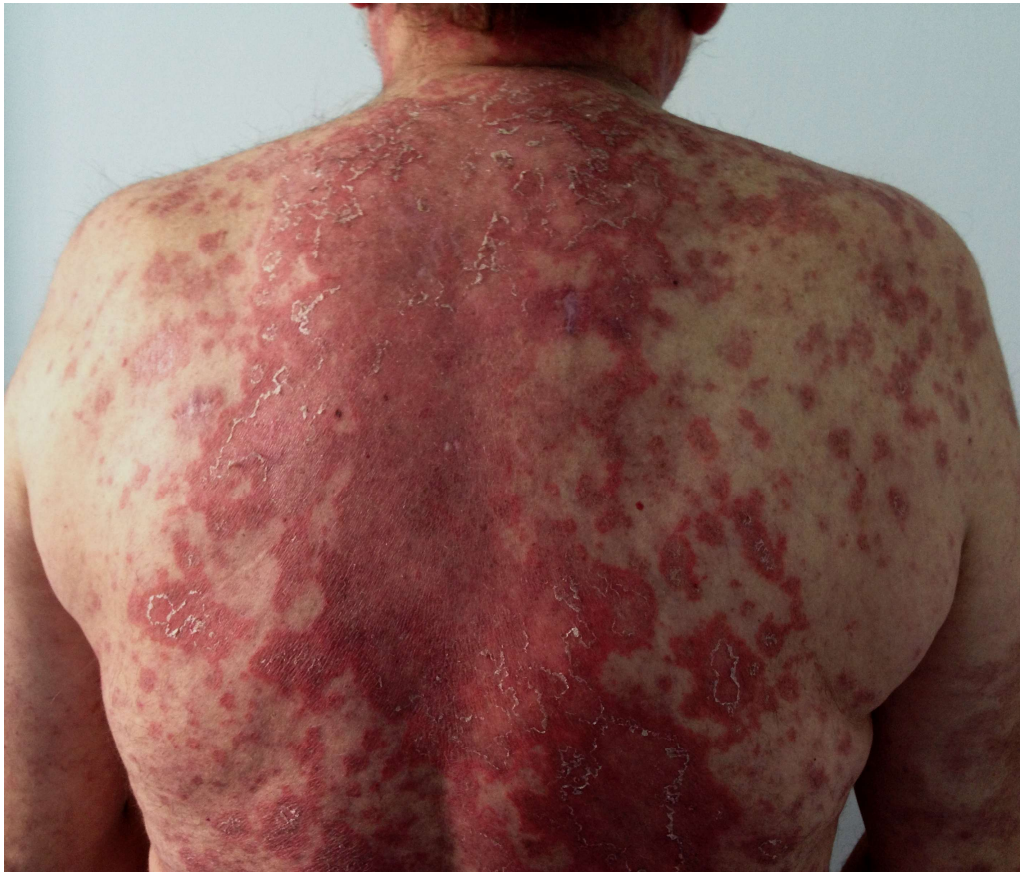
Allergic contact dermatitis

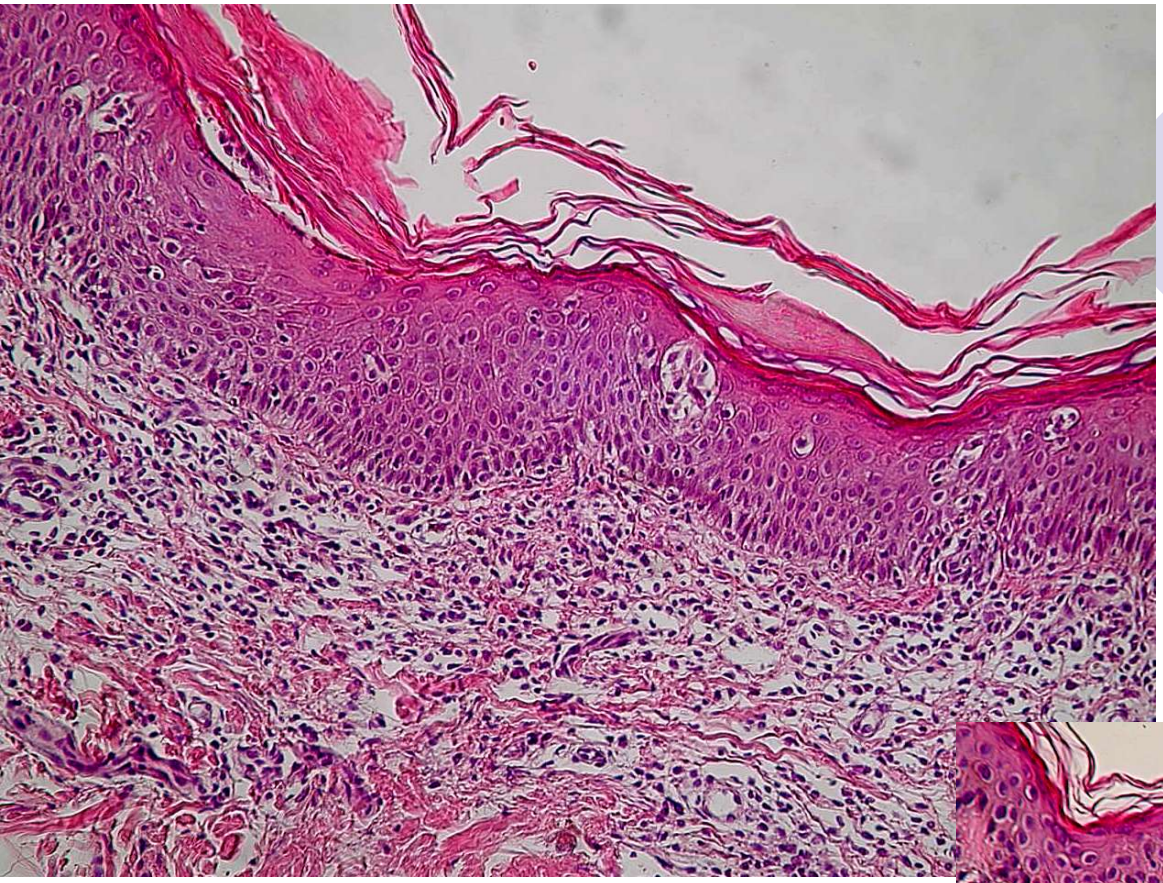
Mycosis fungoides



Mycosis fungoides vs subacute cutaneous lupus erythematosus

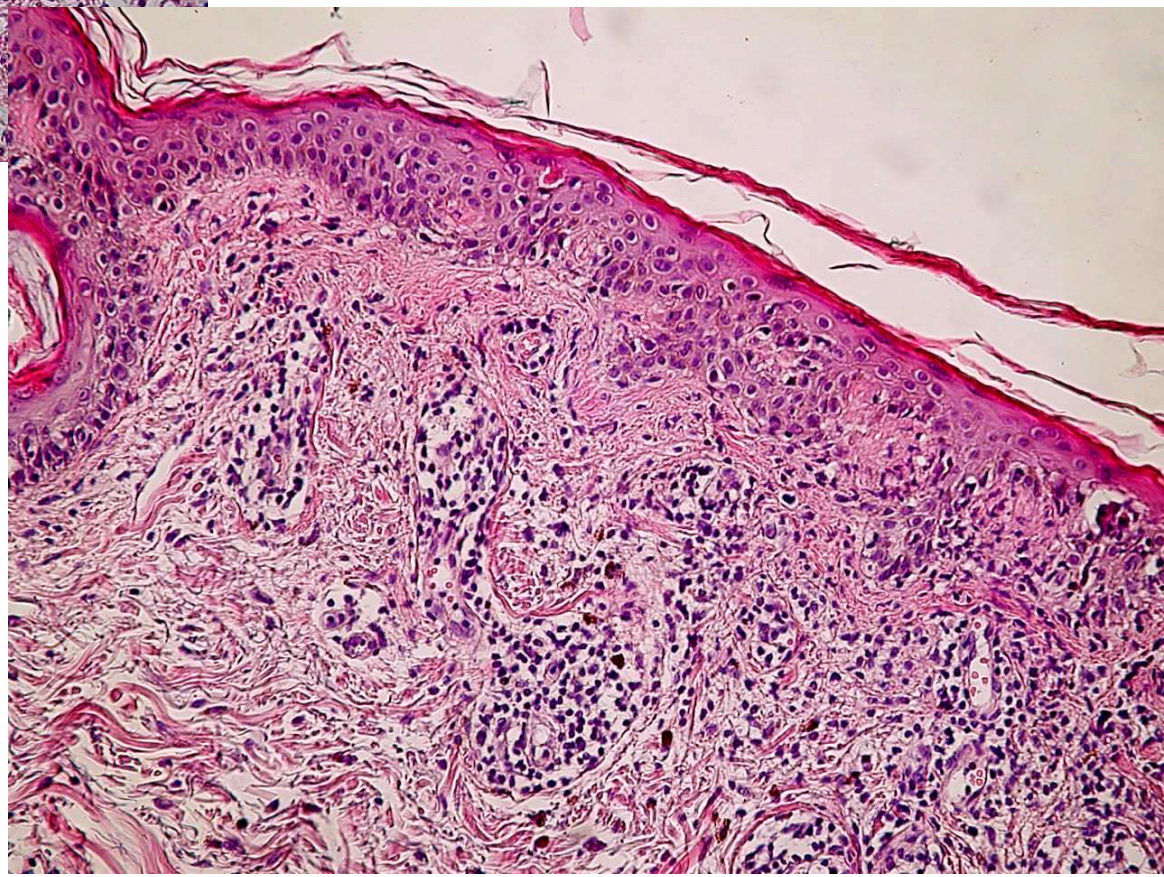




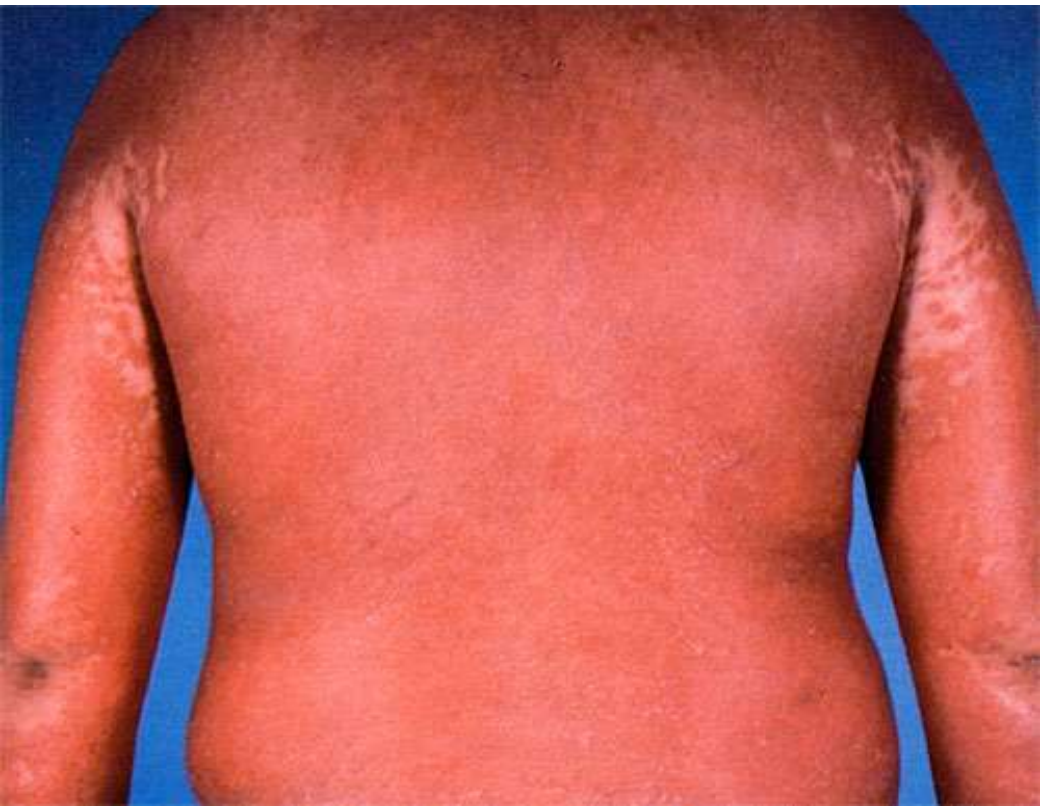


Subacute cutaneous lupus erythematosus

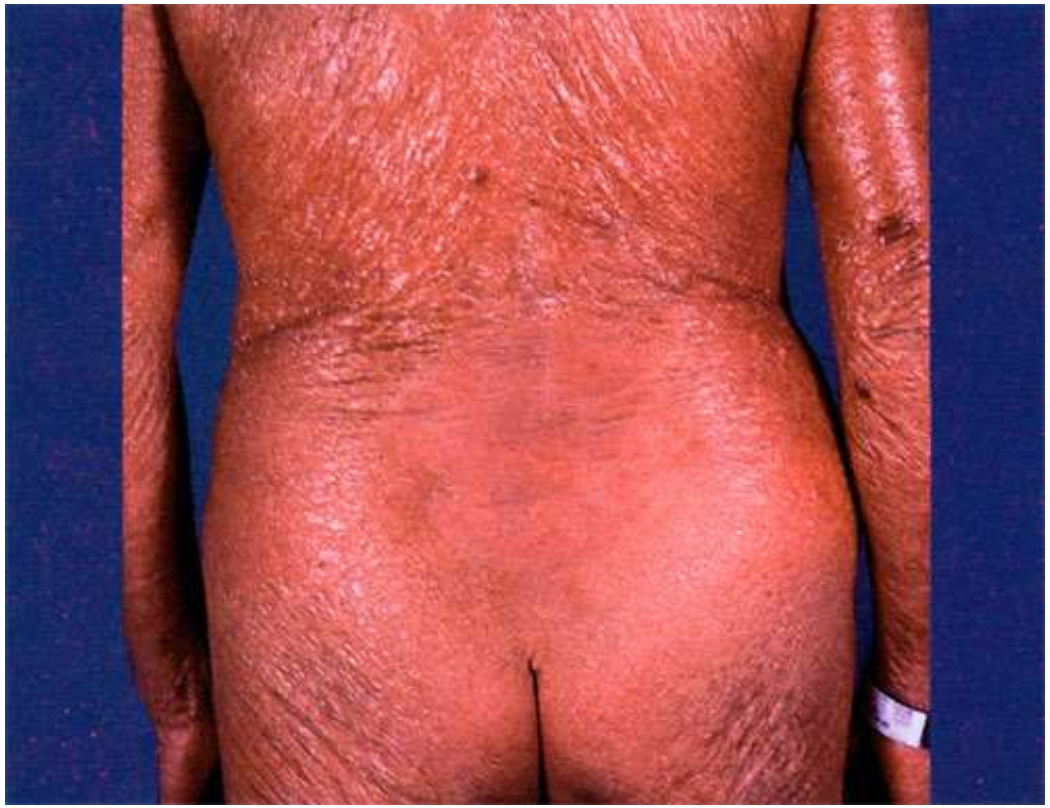
Mycosis fungoides



Erythroderma



Psoriasis

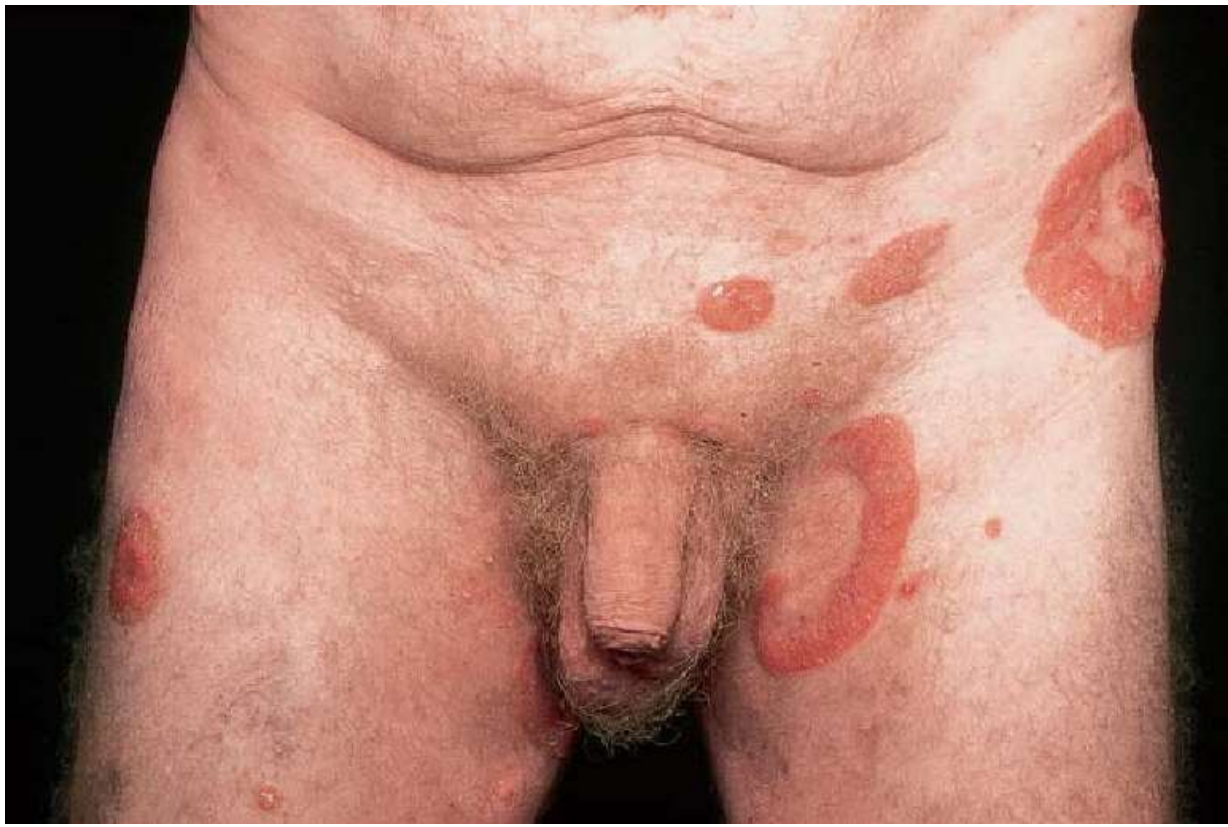


Mycosis fungoides
(Cutaneous T cell lymphoma)

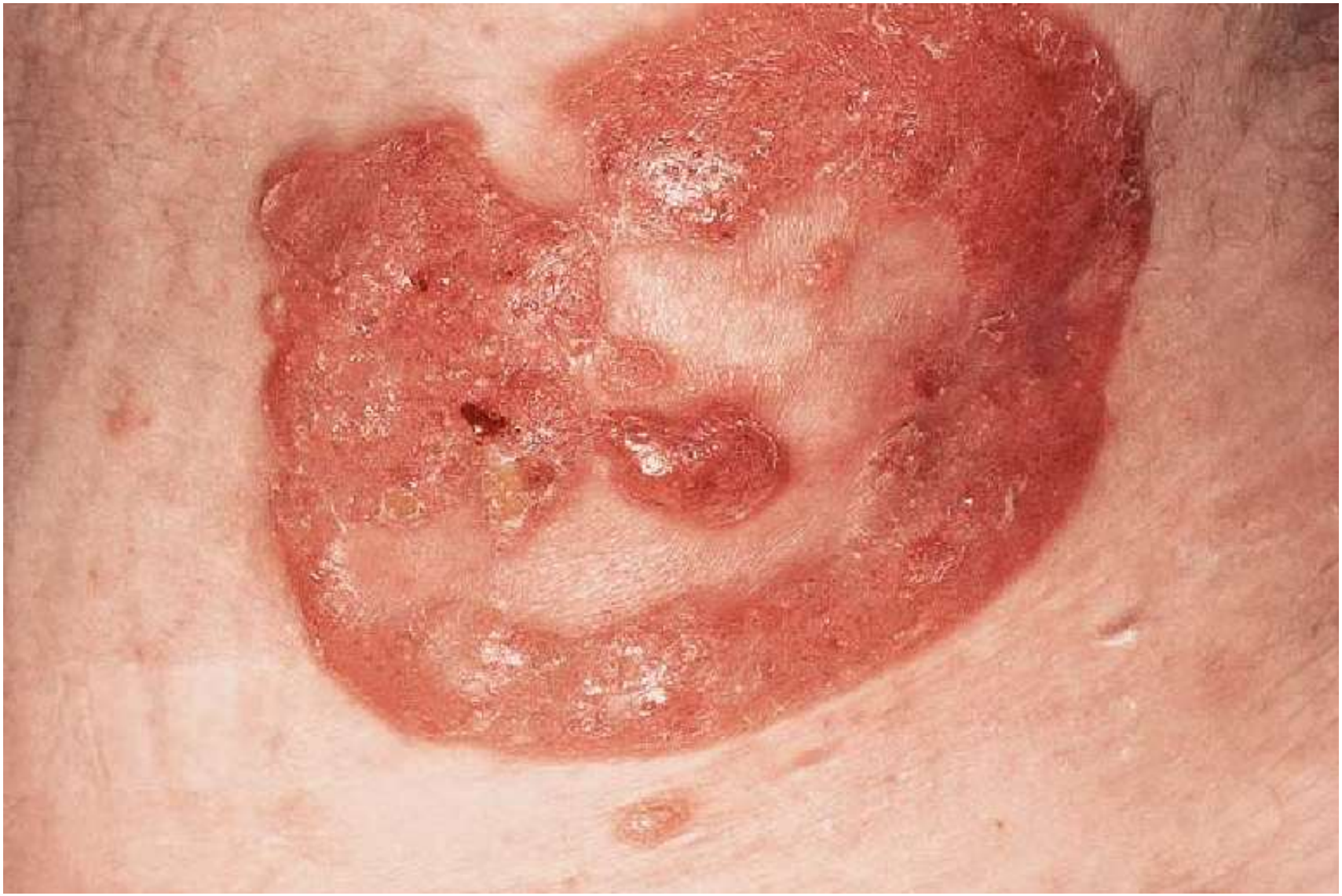
MF – plaque stage

- plaques are elevated, indurated, infiltrative, scaly, well demarcated
- annular, oval, kidney-shaped erythematous, reddish-brown plaques
- shape: oval, annular, arcuate, serpiginous
- pruritus +++
- median survival

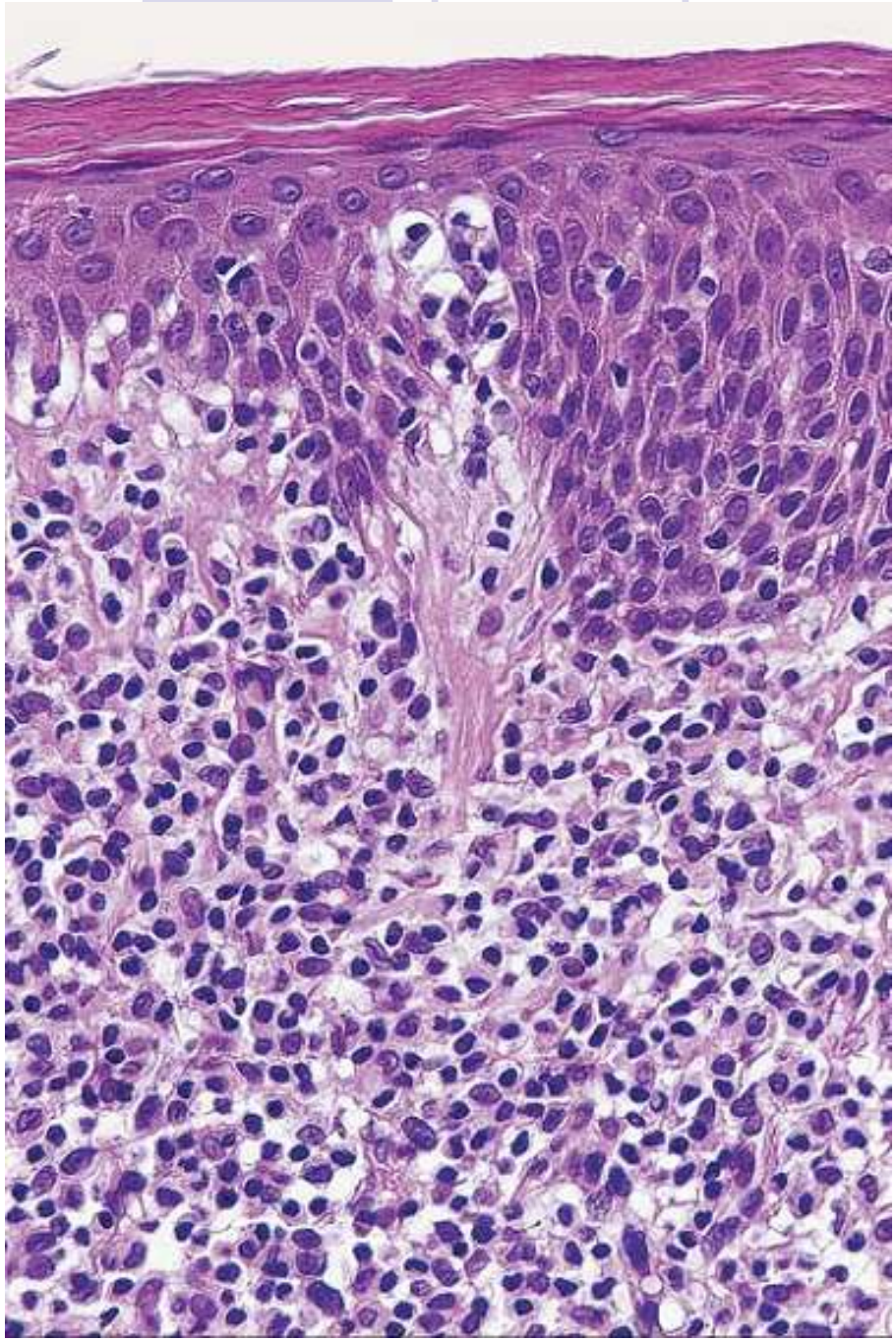
for person with patch- and plaque-stage MF disease is 12 years



Plaque of MF



Plaque MF in histology



- epidermotropism is less pronounced
- dense band-like lichenoid infiltrate
- lymphocytes with irregular convoluted nuclear membranes and hyperchromatic nuclei

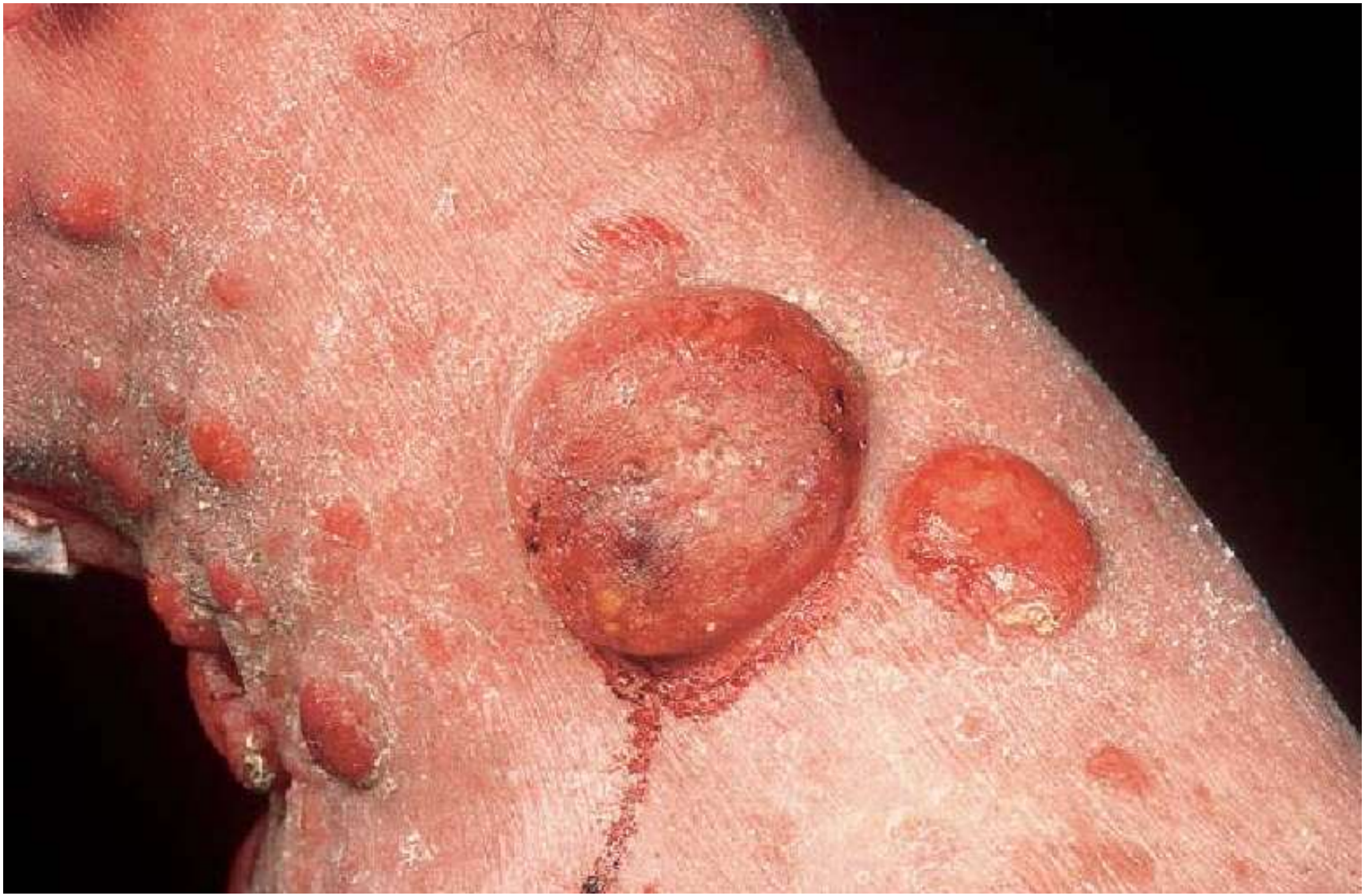
Tumor stage of MF – clinical presentation

- last, terminal stage of MF
- tumors are present on the normal looking skin or on the base of the erythematous patches or plaques
- exaggerated vertical growth phase, resulting in large, reddish-brown or bluish-red smooth-surfaced nodules
- on the face – characteristic appearance called *facies leontina*
- the big smooth-surfaced nodules gave the resemblance to mushrooms – therefore fungoides (Alibert, 1806)
- visceral involvement (nodal, blood, spleen, liver, lungs, GI tract)

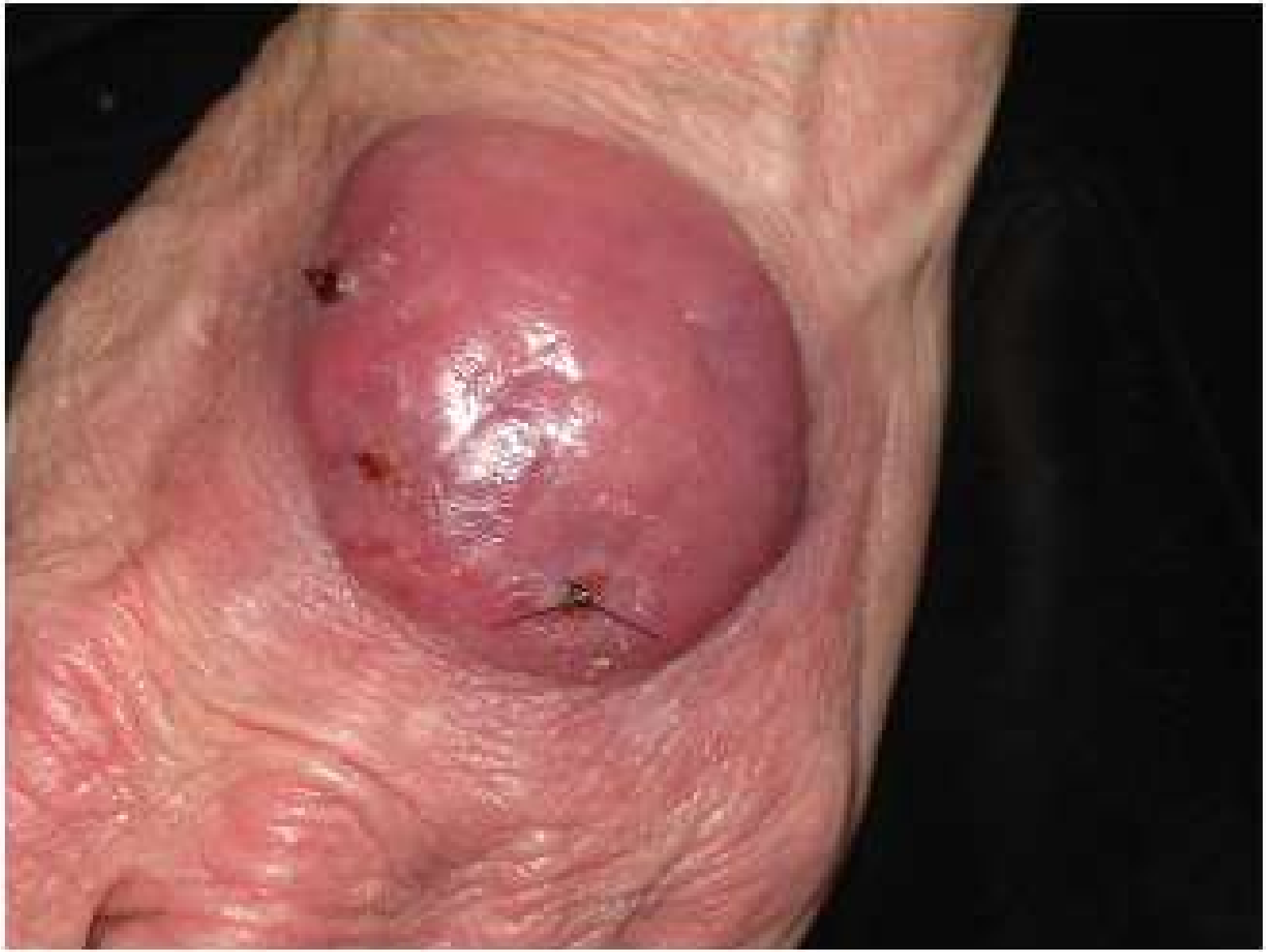
MF tumor stage – mushroom-like tumors (terminal stage of the disease)

1806, Alibert

Nodular MF



Nodular MF



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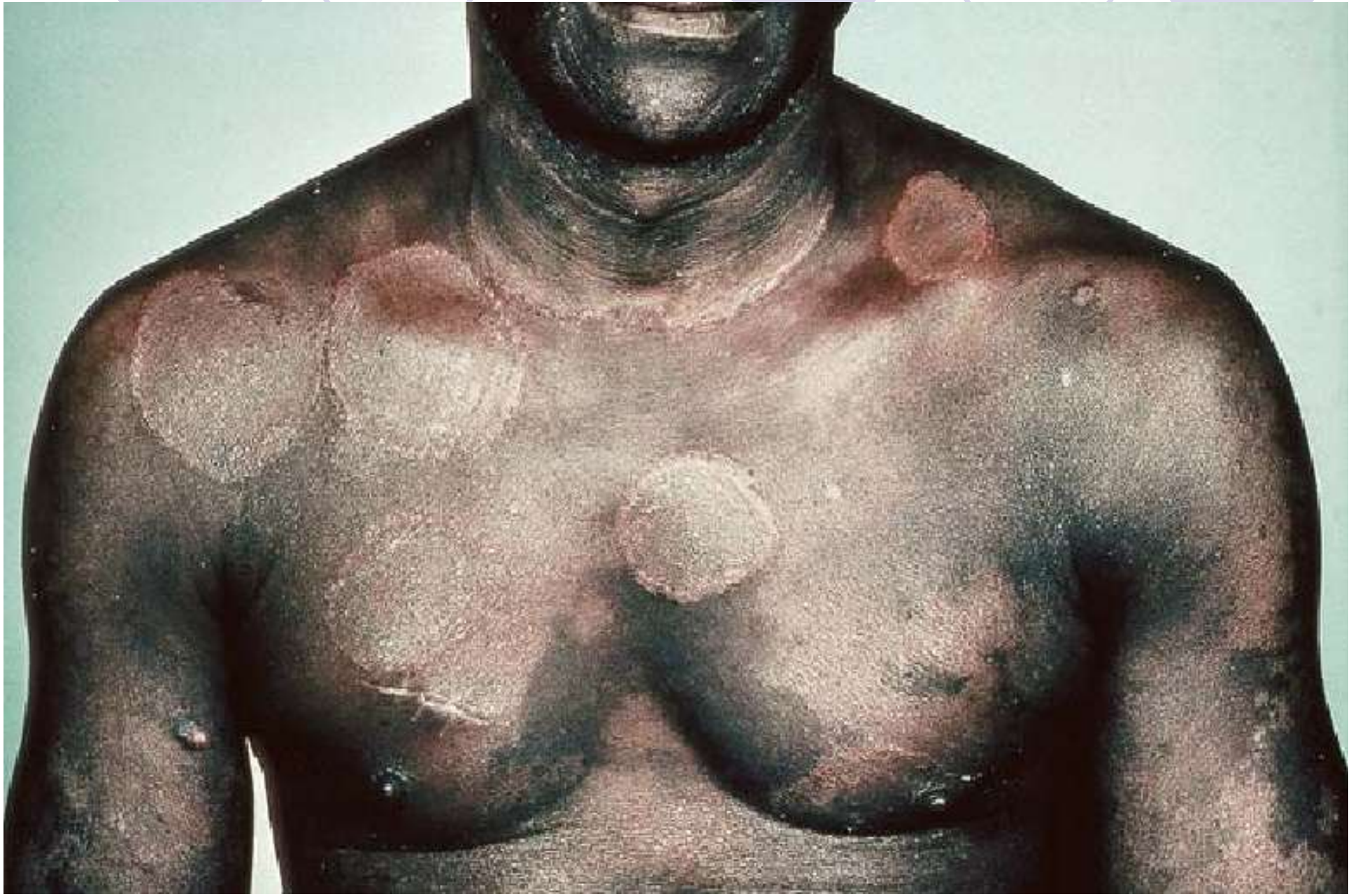
Types of mycosis fungoides

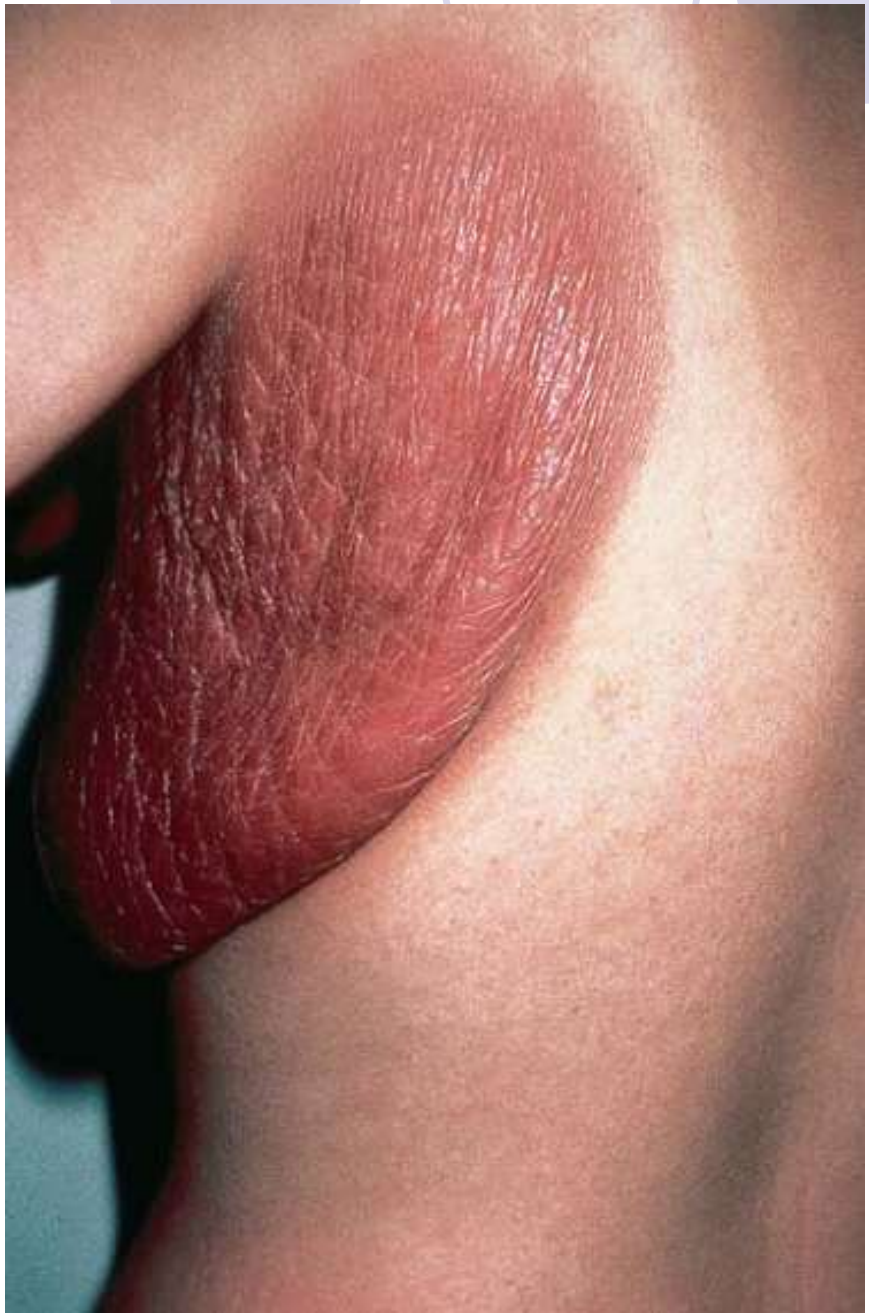
1. Erythrodermic
2. Hypopigmented
3. Folliculotropic +/- Follicular mucinosis
4. Syringotropic
5. Granulomatous slack skin
6. Pagetoid reticulosis

Hypopigmented MF

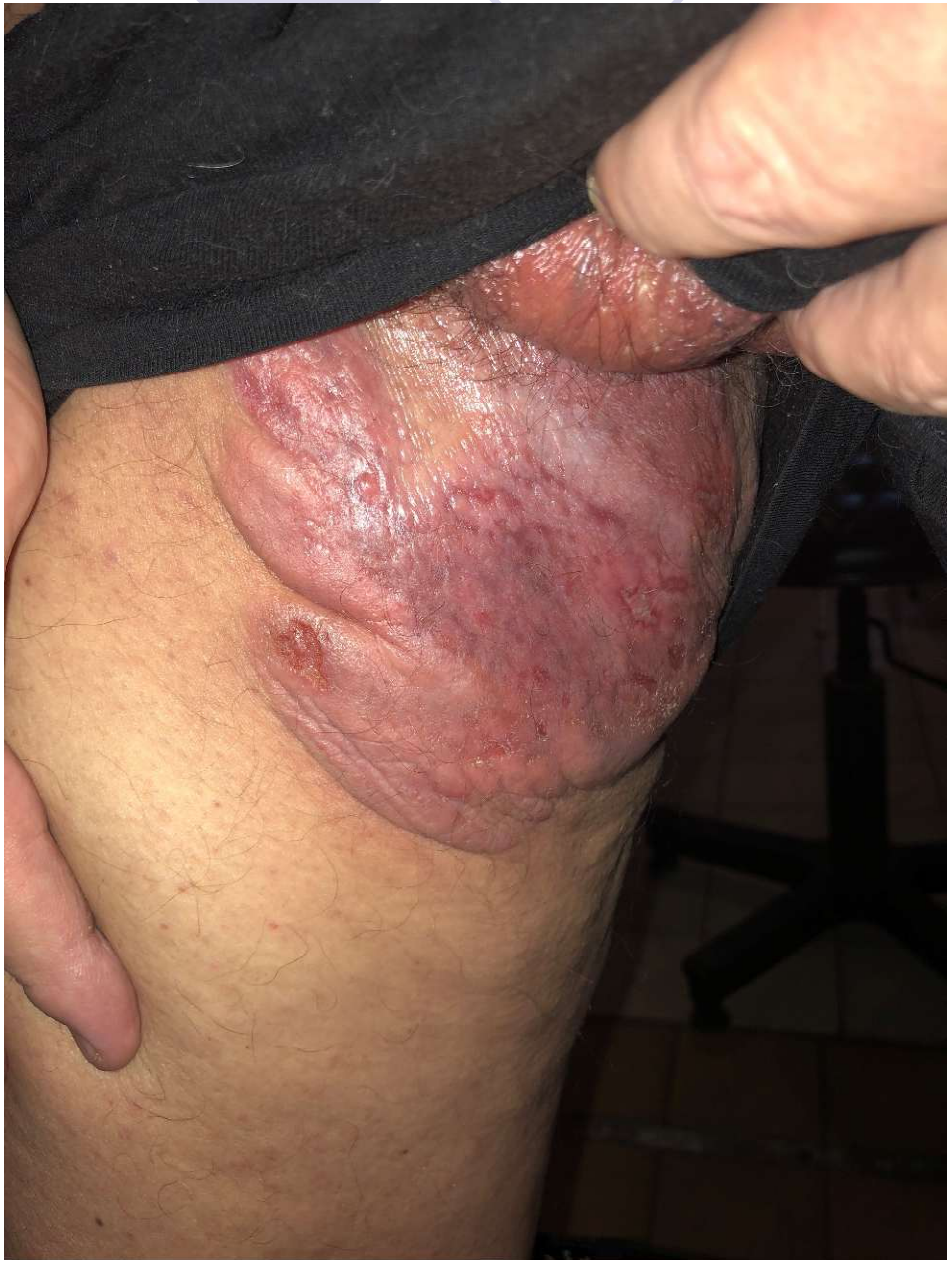


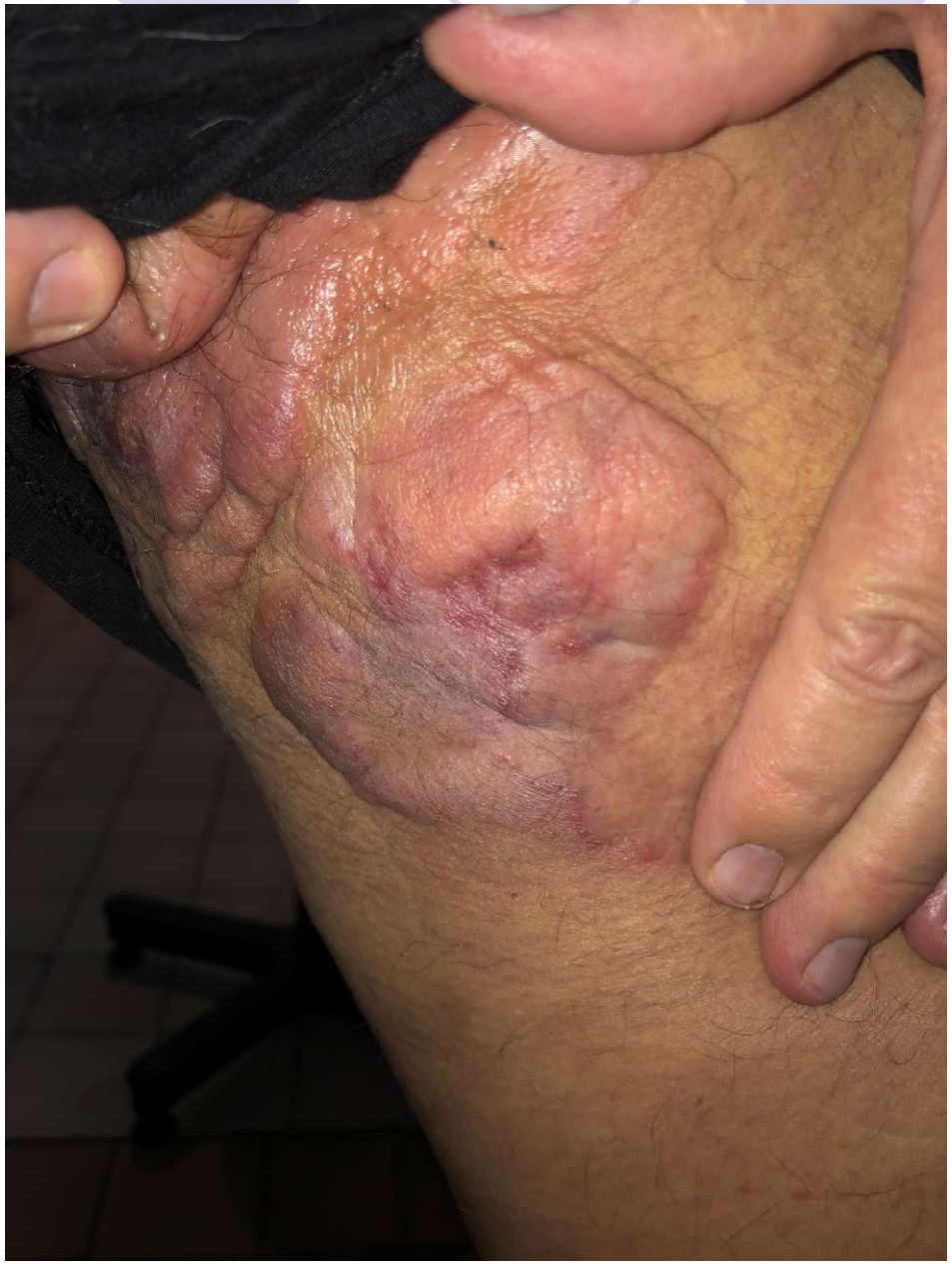
Granulomatous slack skin

- rare variant of MF
- affects folds and induces tremendous skin laxity
- dense diffuse granulomatous infiltrates composed of atypical lymphocytes and histiocytes

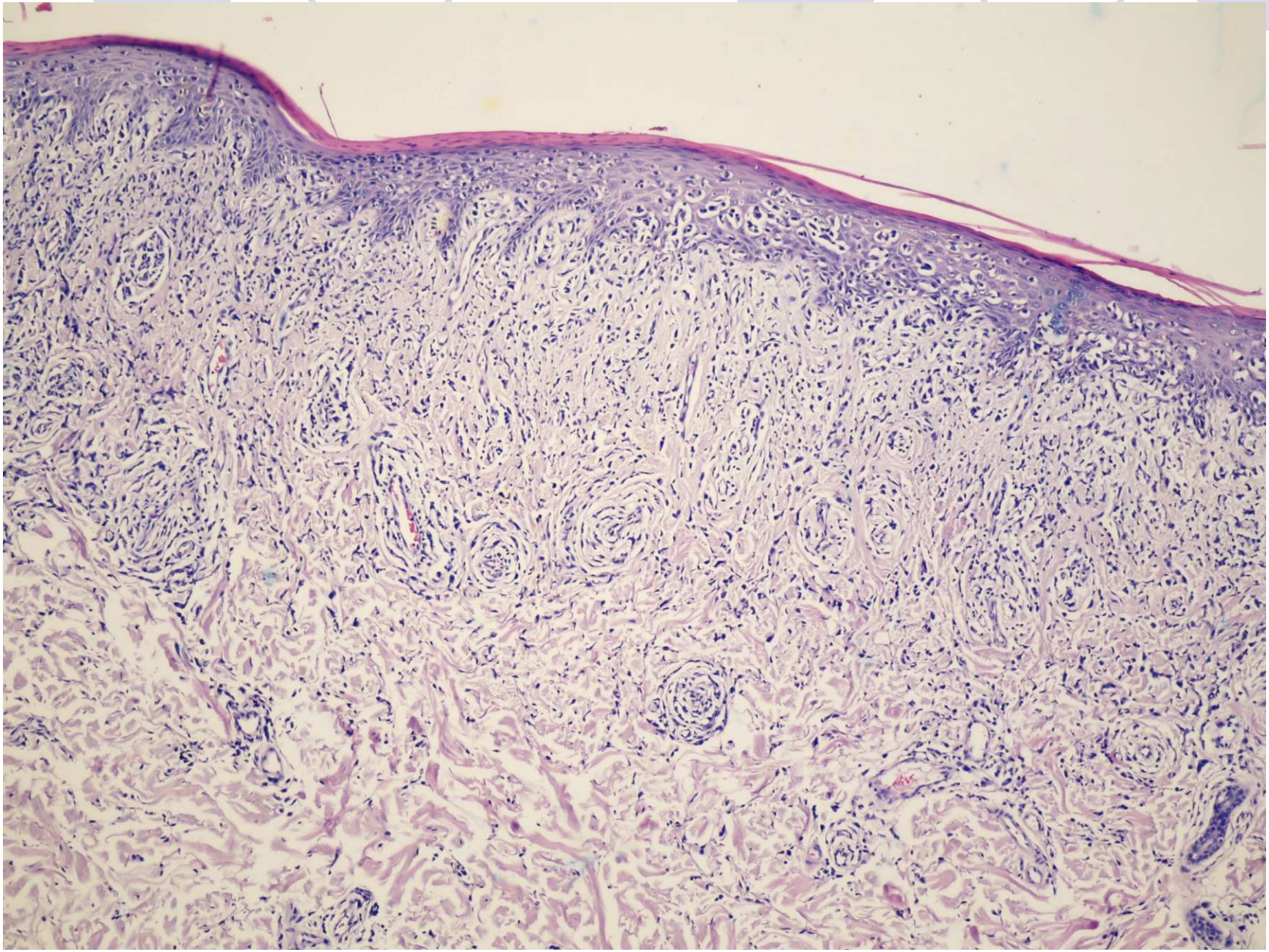


Granulomatous slack skin

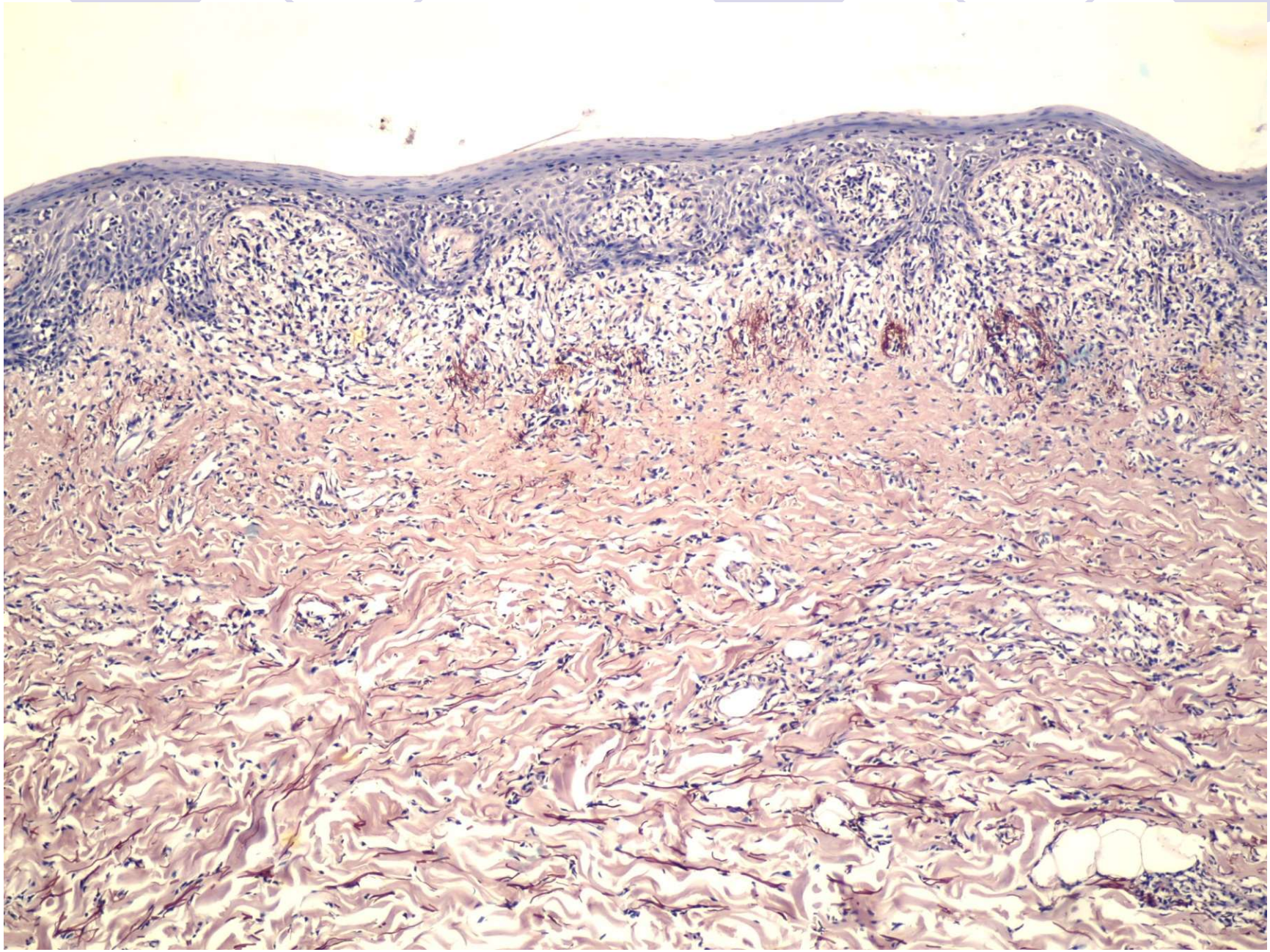




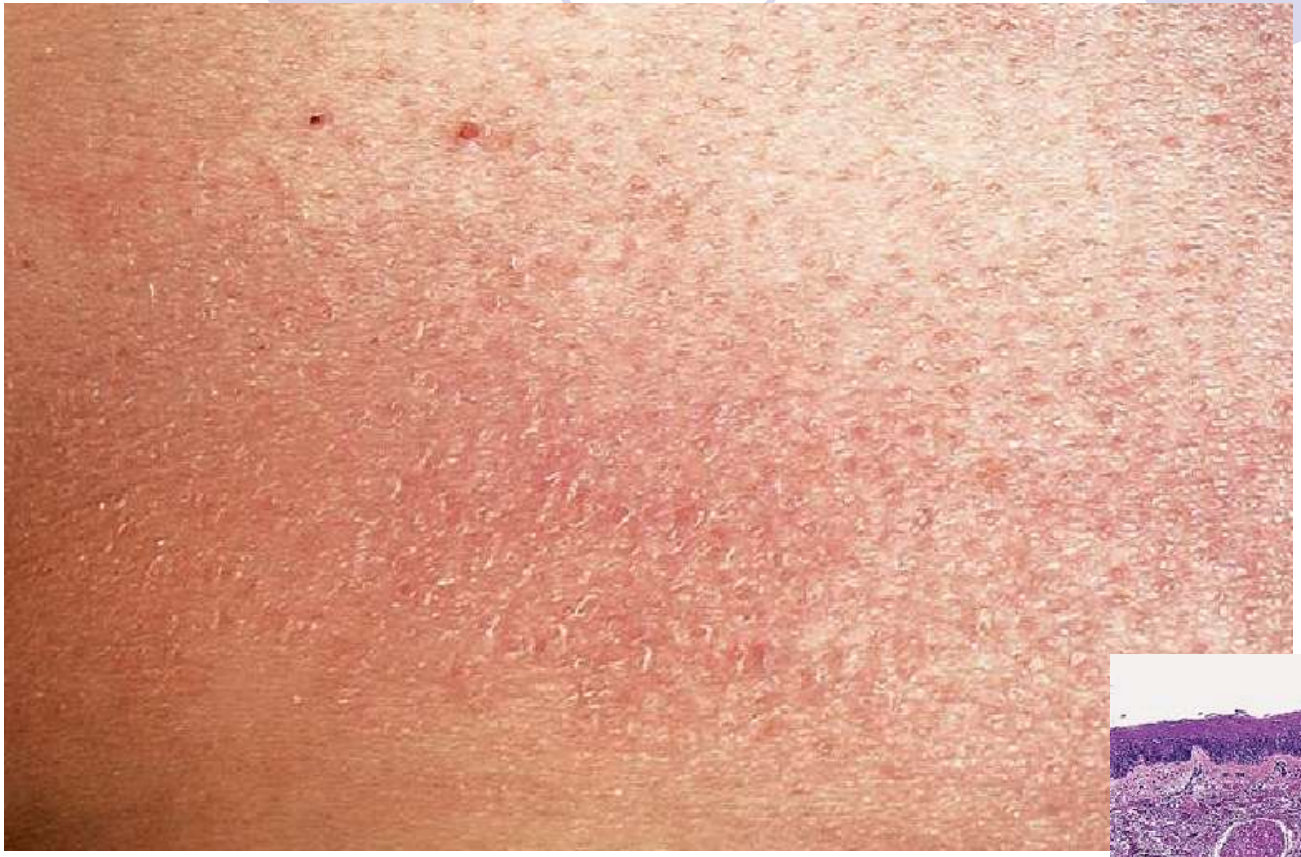
Granulomatous slack skin



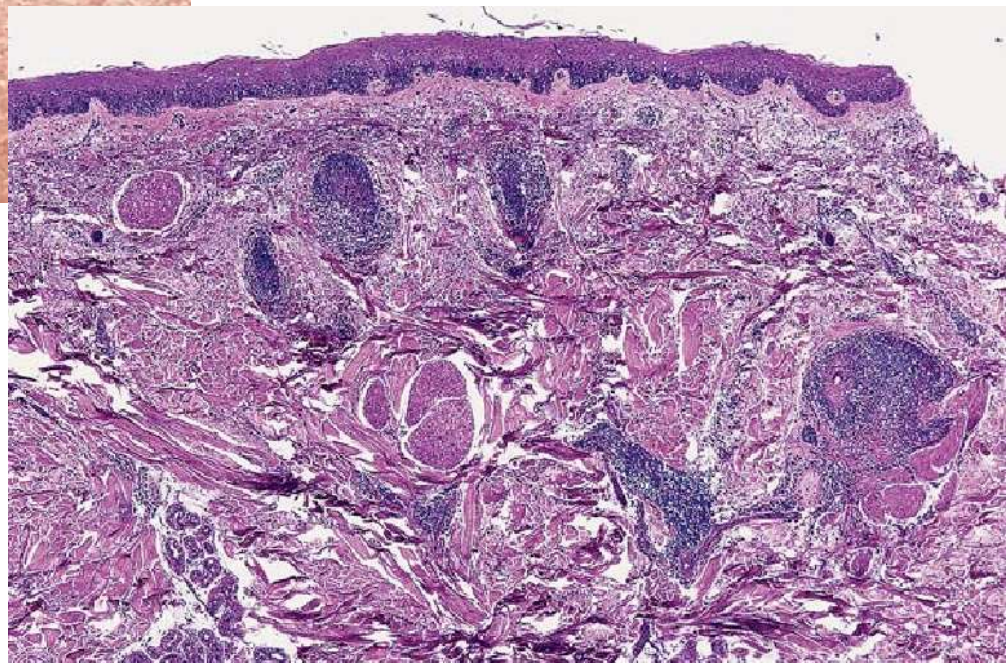
Granulomatous slack skin
(orcein stain for elastin)

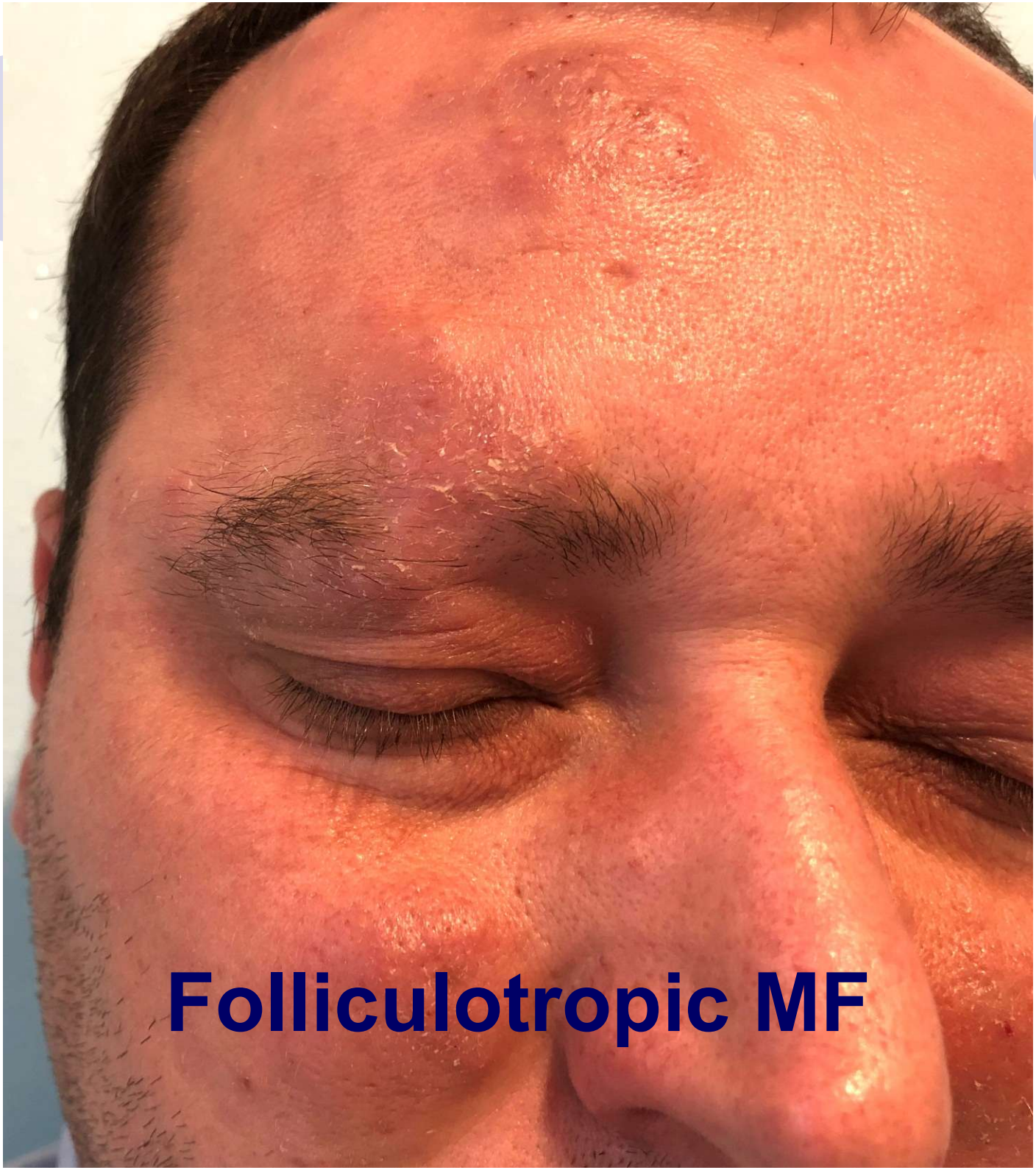


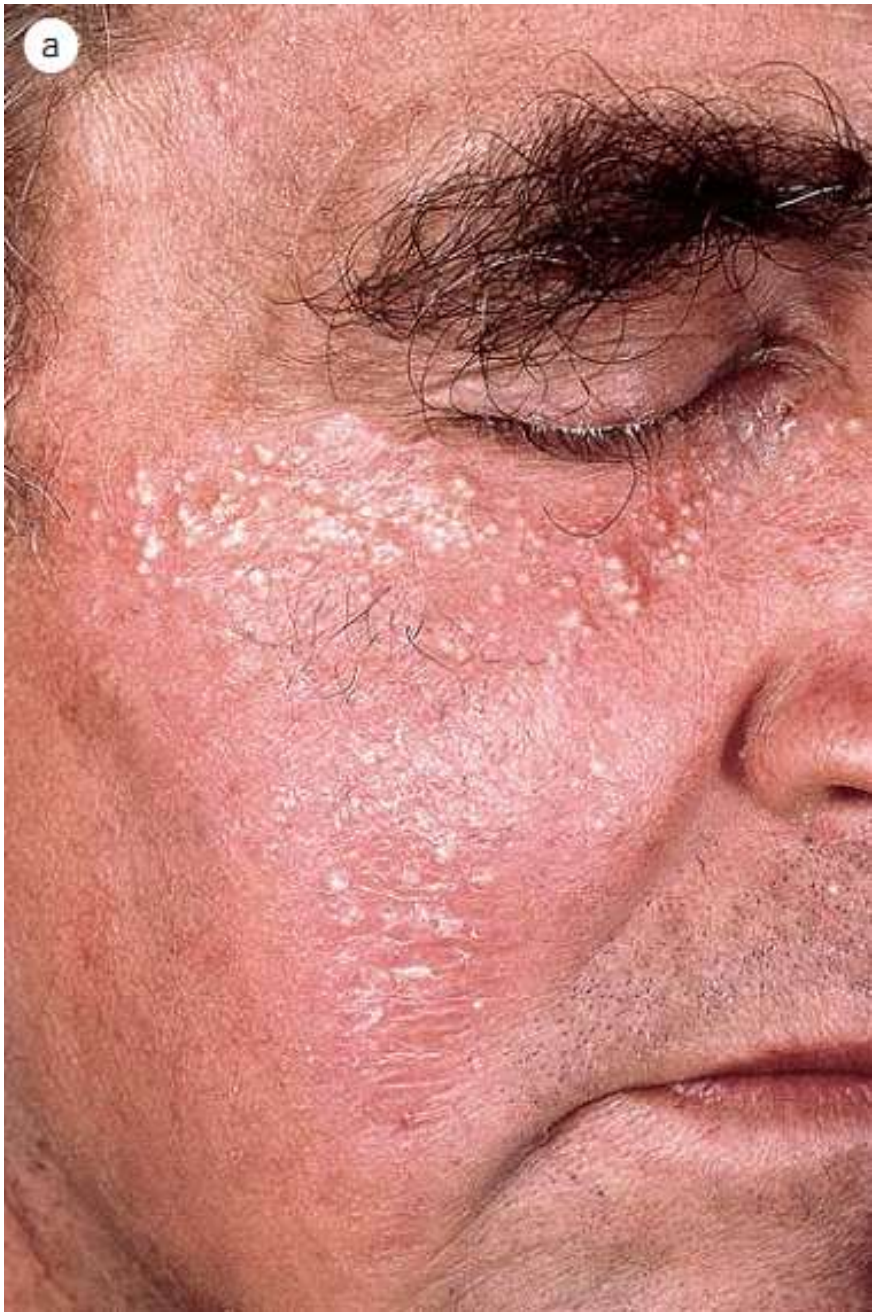
Folliculotropic MF



- head, scalp and neck location
- permanent alopecia
- severe pruritus

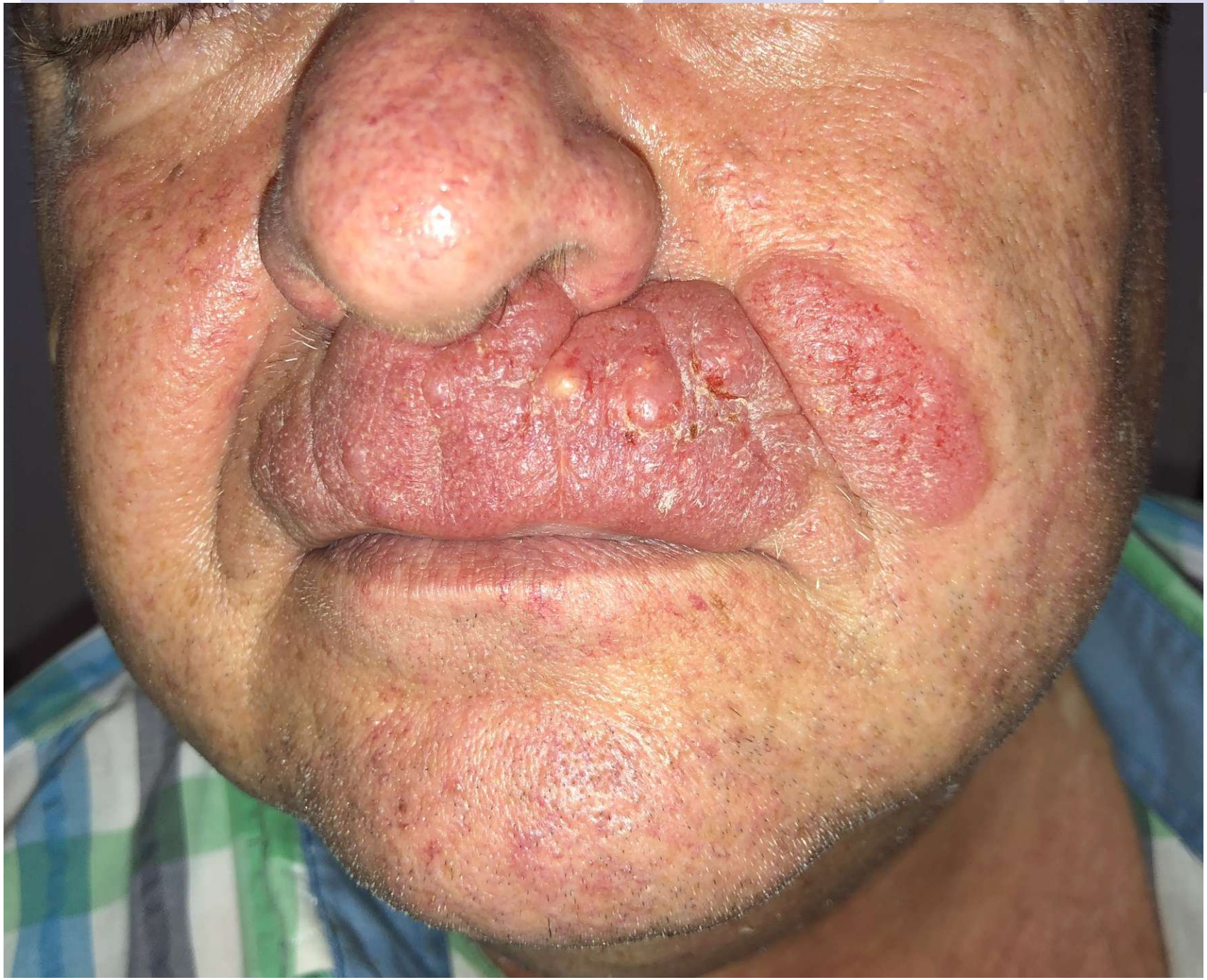


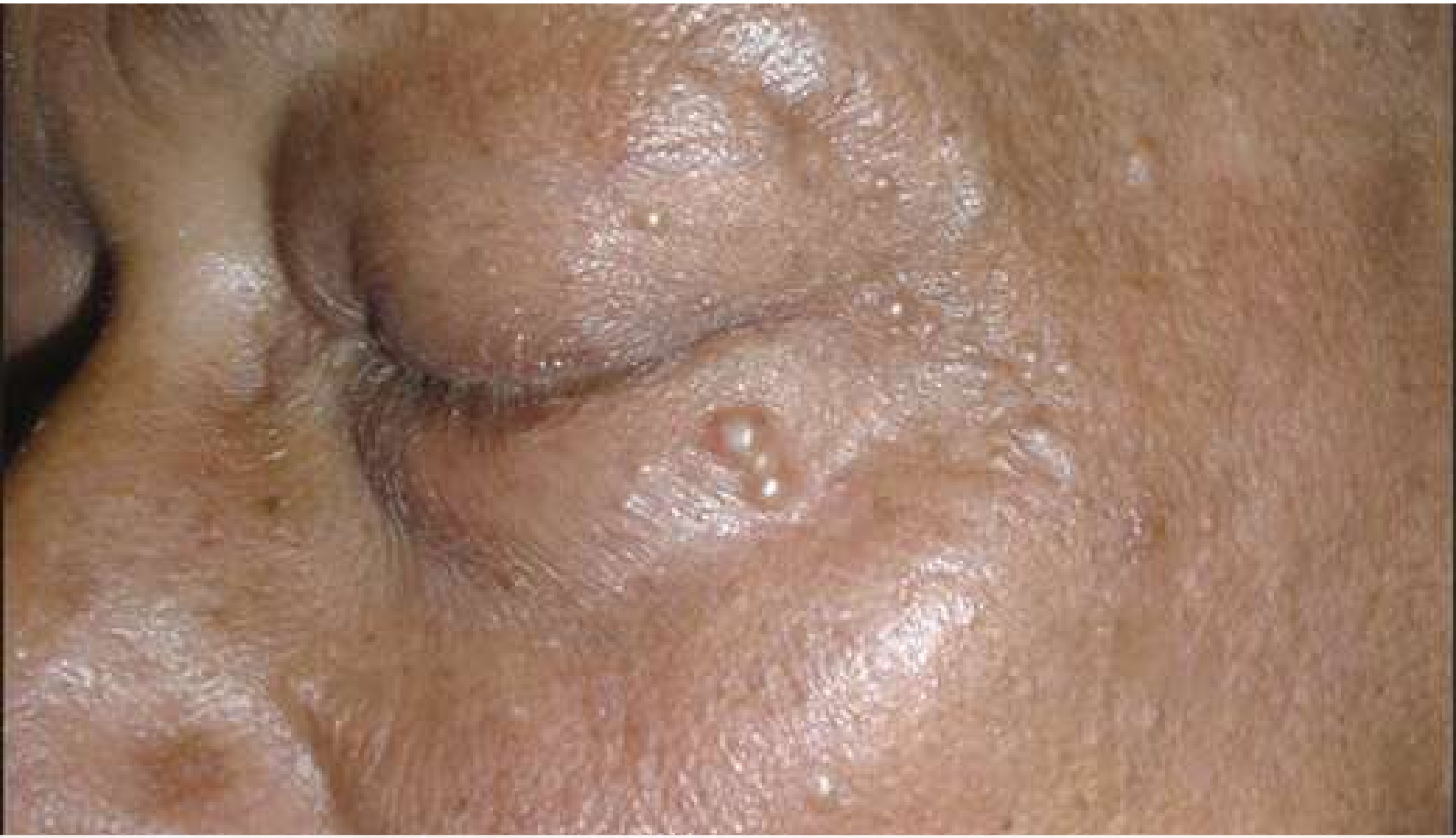

Folliculotropic MF



Folliculotropic MF with typical *comedo* formation from deformed hair follicles

Folliculotropic MF – facial location and involvement of hair follicles on the face of a man

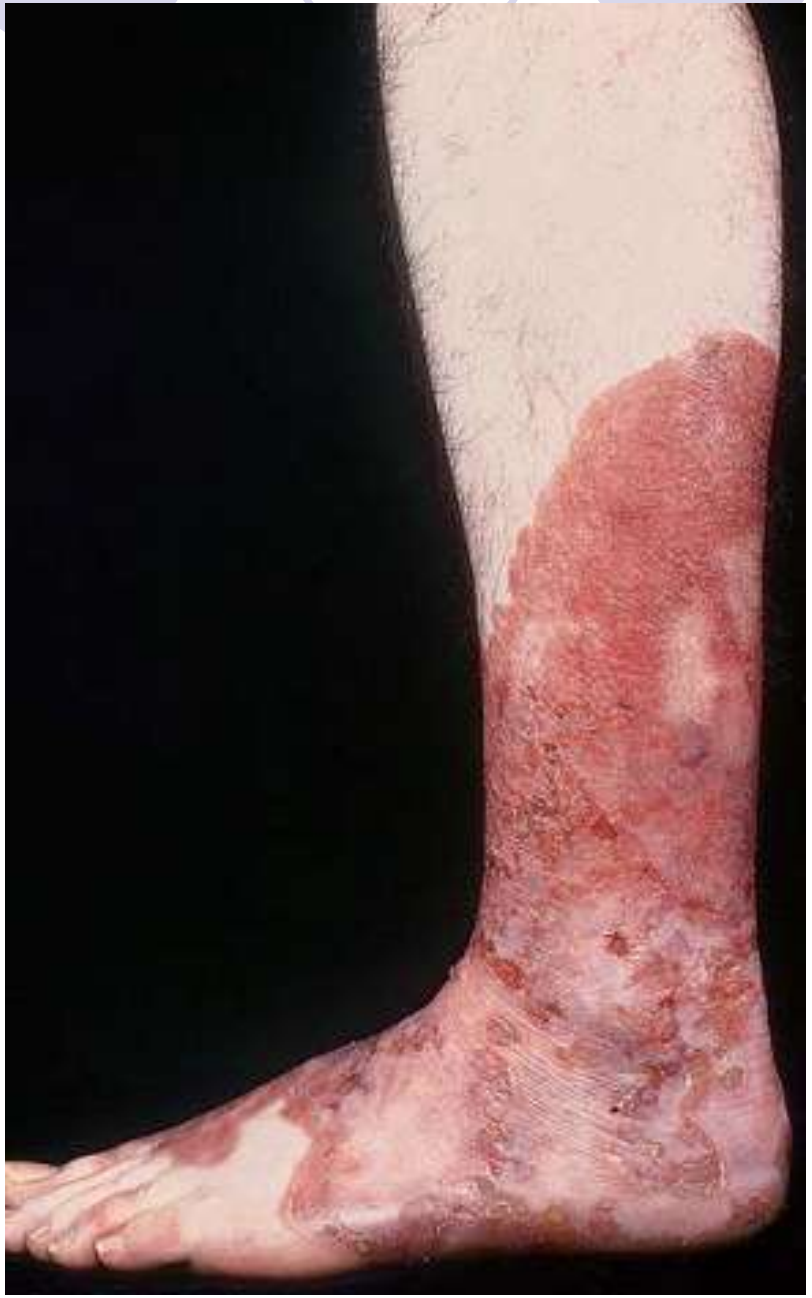




Syringotropic mycosis fungoides

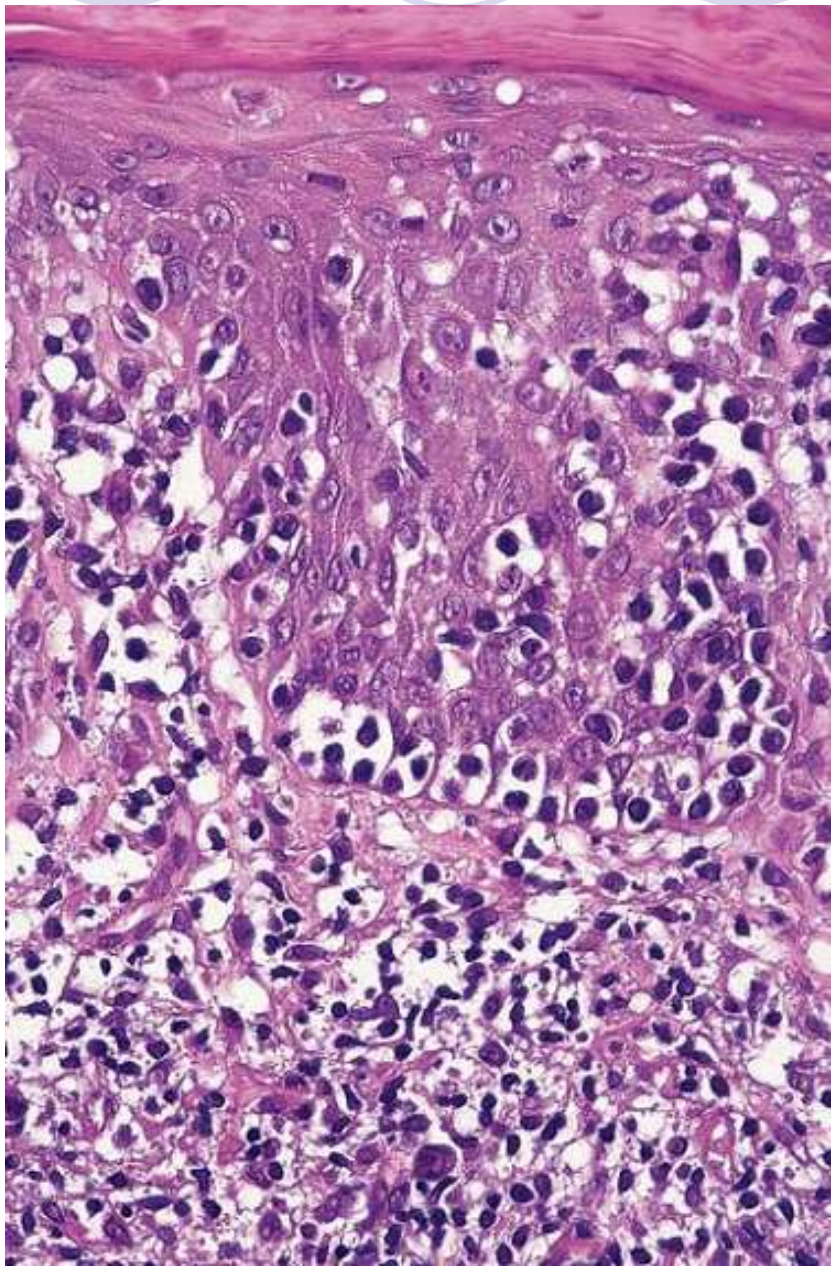
Pagetoid reticulosis

- indolent localized variant of MF
- solitary erythematous scaly or verrucous patch on the distal extremities or acral skin
- rare disease
- long, persistent and indolent course
- male predominance
- Histology: prominent pagetoid epidermotropism
- DDx: tinea, lupus vulgaris, neoplasm, metastasis
- good response to local radiation



Pagetoid reticulosis

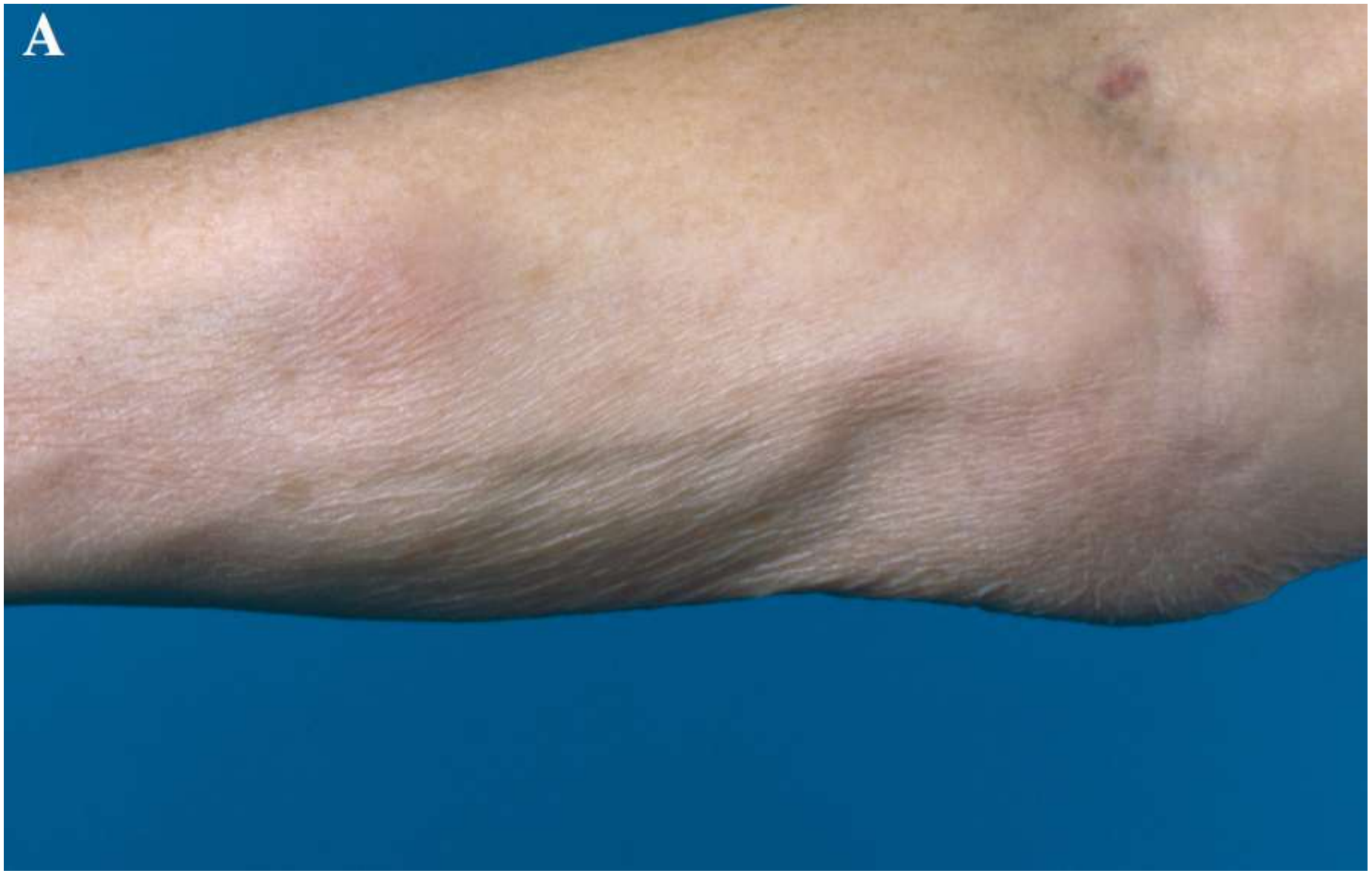
- striking epidermotropism
- numerous atypical mononuclear cells, singly or in clusters
- immunoprofile of lymphocytes: CD4+ or CD8+ or gamma/delta



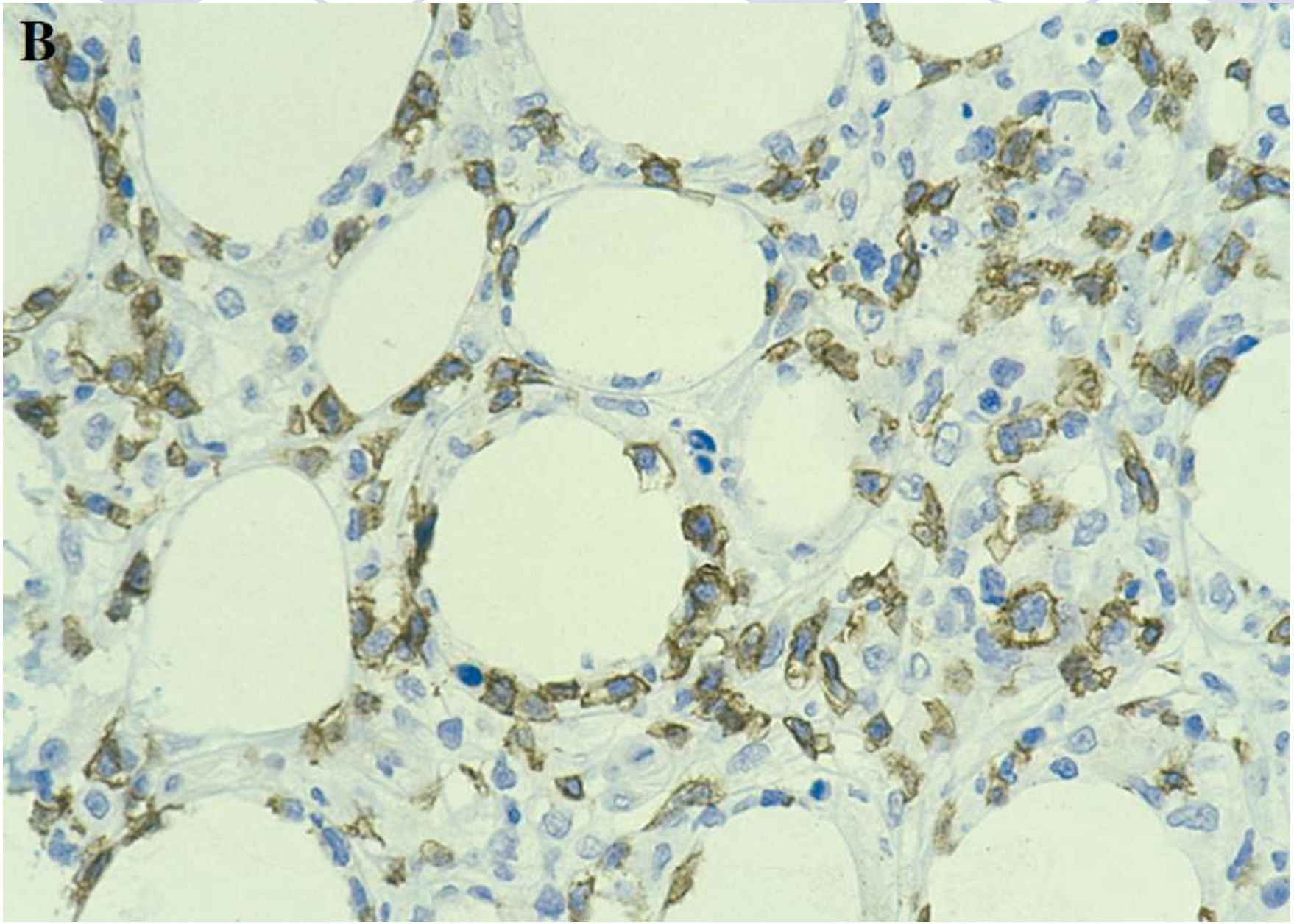
Lymphomas of a good prognosis with survival > 5 years

- mycosis fungoides
- pagetoid reticulosis
- granulomatous slack skin
- primary cutaneous small/moderate sized pleomorphic T-cell lymphoma
- primary cutaneous anaplastic large-cell CD30+ lymphoma
- lymphomatoid papulosis
- subcutaneous panniculitis-like T-cell lymphoma

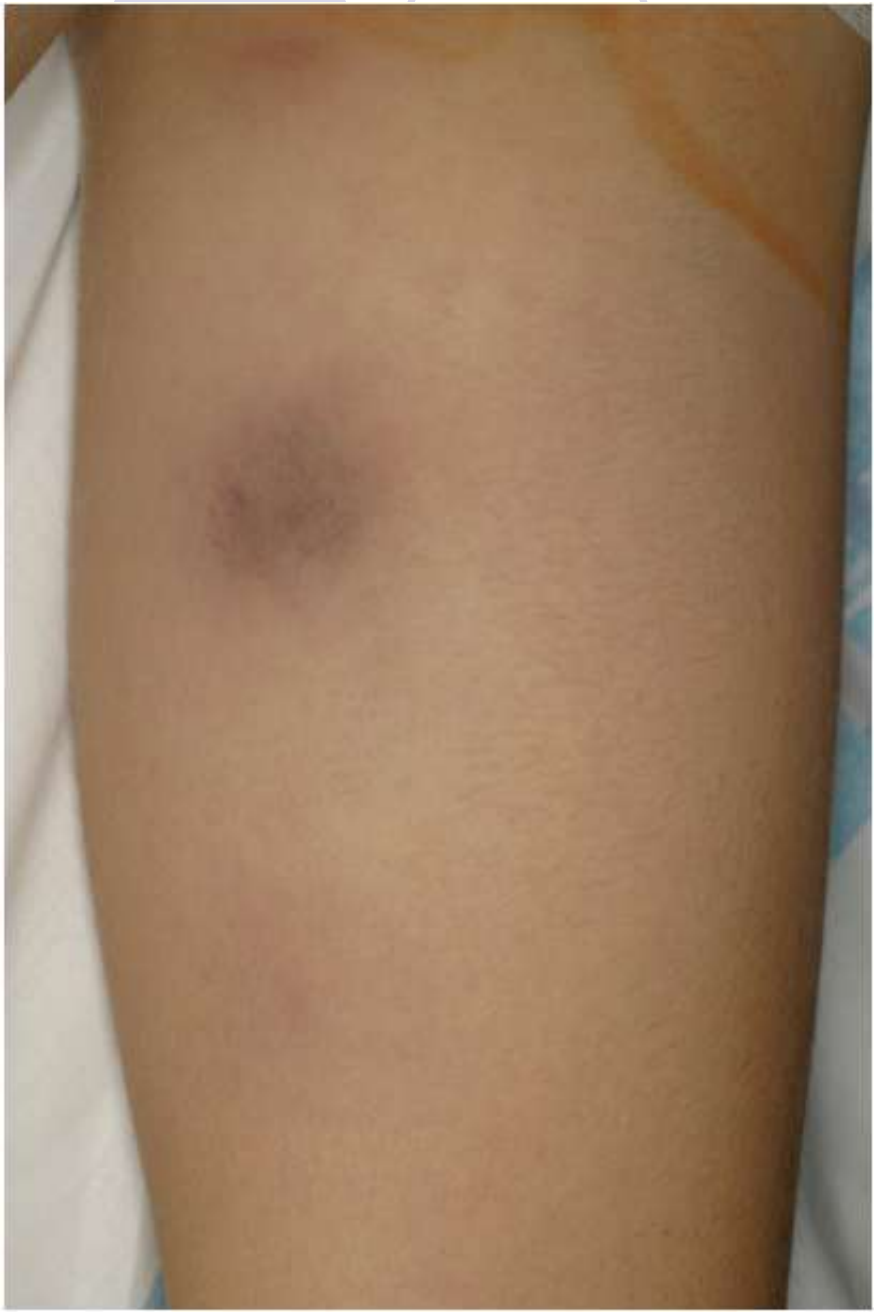
Subcutaneous panniculitis-like T-cell lymphoma (alpha/beta T-cell phenotype) – clinically nodules in the fat



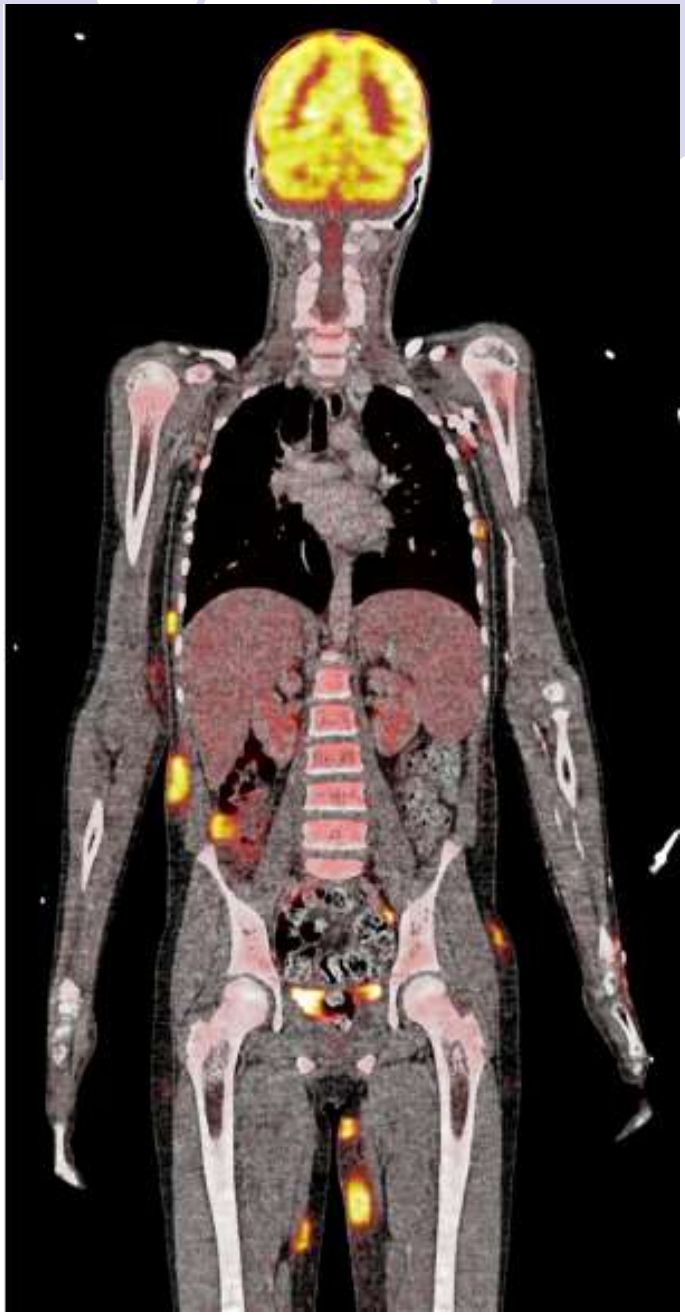
Subcutaneous panniculitis-like T-cell lymphoma (alpha/beta T-cell phenotype) – monomorphic atypical lymphocytes form a rim around adipocytes



Subcutaneous panniculitis-like T-cell lymphoma



Nodule imitating a bruise on the lower leg, present for a year



positron emission tomography reveals other tumors in adipose tissue

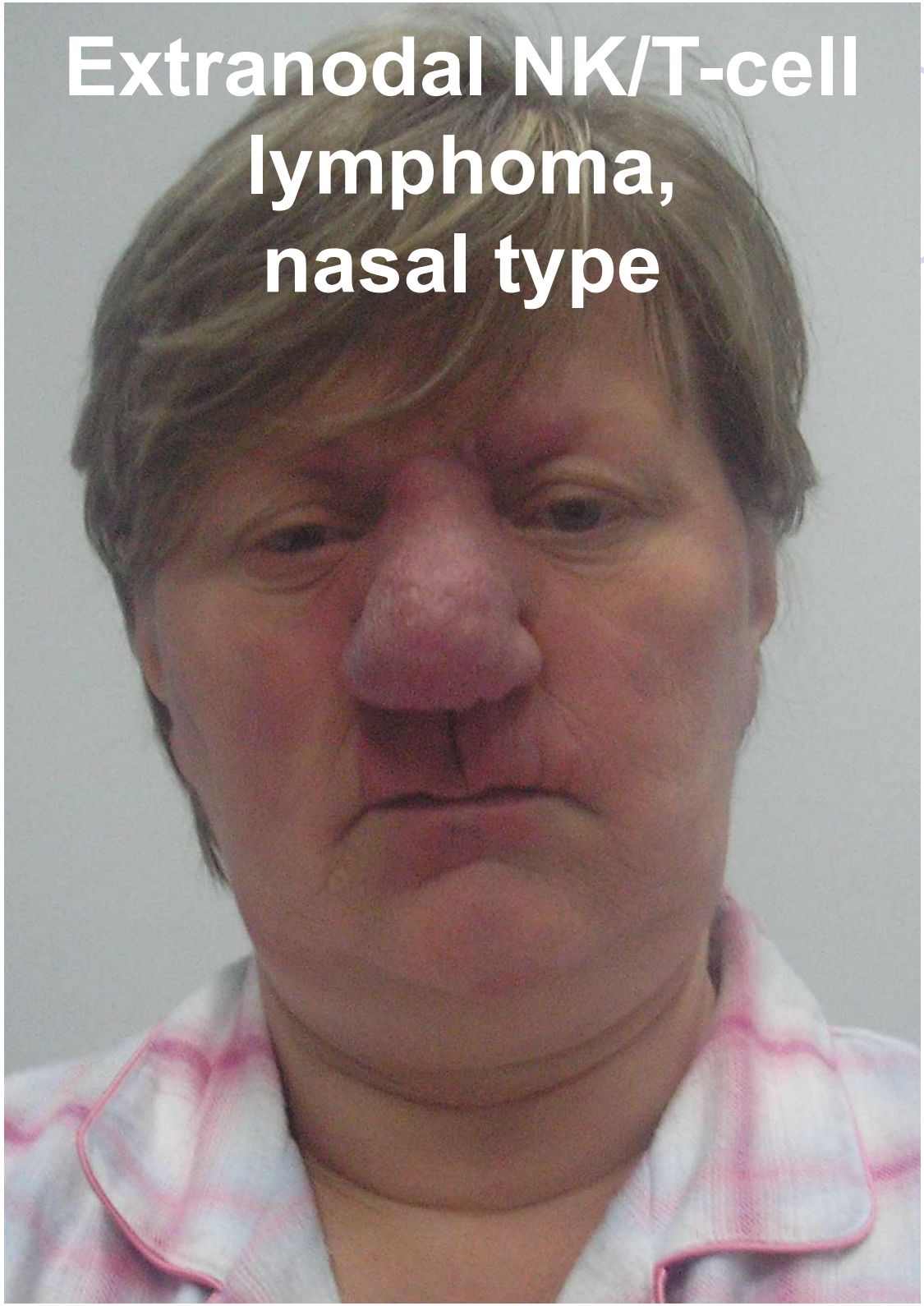
Lymphomas of moderate prognosis (2-5 years of survival)

- Sezary syndrome
- folliculotropic mycosis fungoides
- adult T-cell leukemia/lymphoma (HTLV+)
- primary cutaneous diffuse large B-cell lymphoma, leg type
- primary cutaneous diffuse large B-cell lymphoma, other types

Lymphomas of poor prognosis survival < 2 years

- extranodal natural killer (NK) T-cell lymphoma, nasal type
- primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
- primary cutaneous gamma/delta T-cell lymphoma
- primary cutaneous intravascular large B-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type



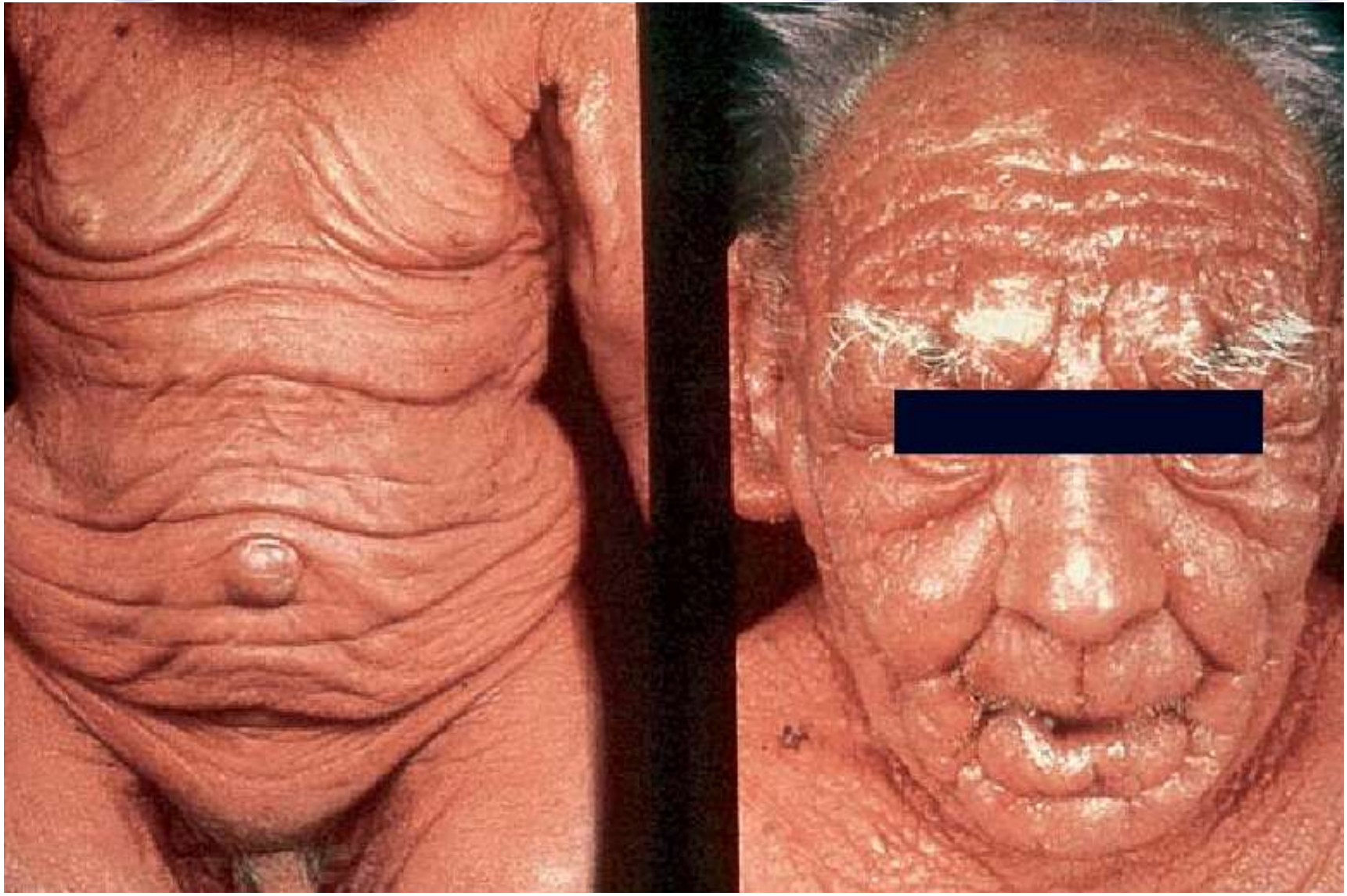
Sezary syndrome

Three symptoms – classic triad

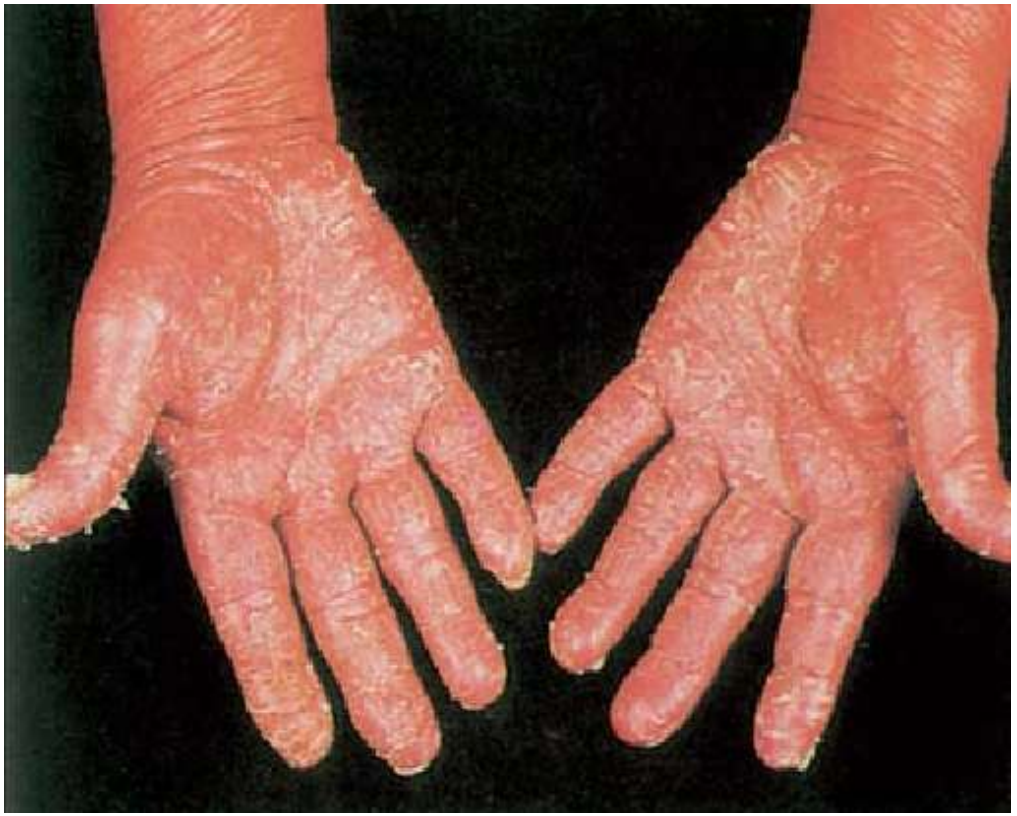
Erythroderma	Lymphadenopathy	Atypical lymphocytes circulating in the blood

This is an erythrodermic leukemic manifestation of T-cell lymphoma with worse prognosis than MF.
5-yr survival – 30%

Sezary syndrome



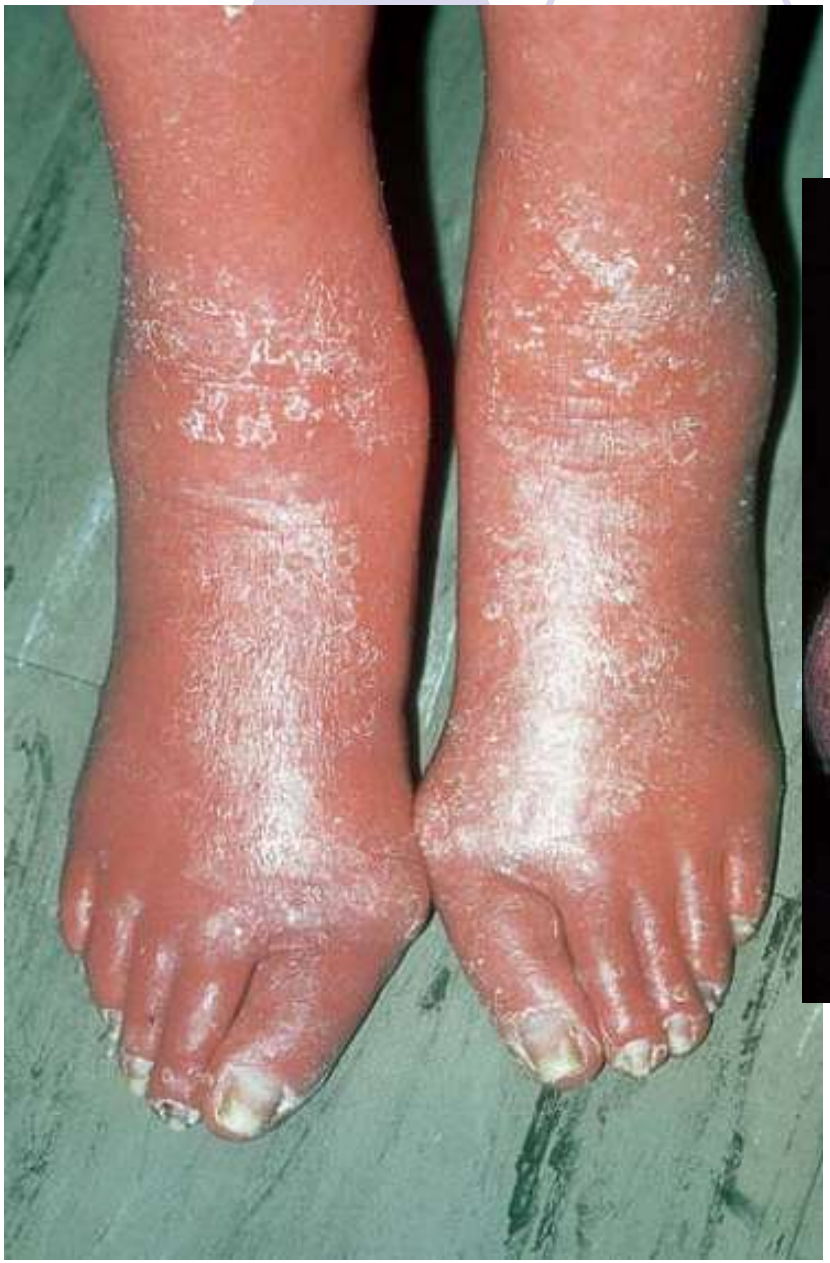
Sezary syndrome skin findings

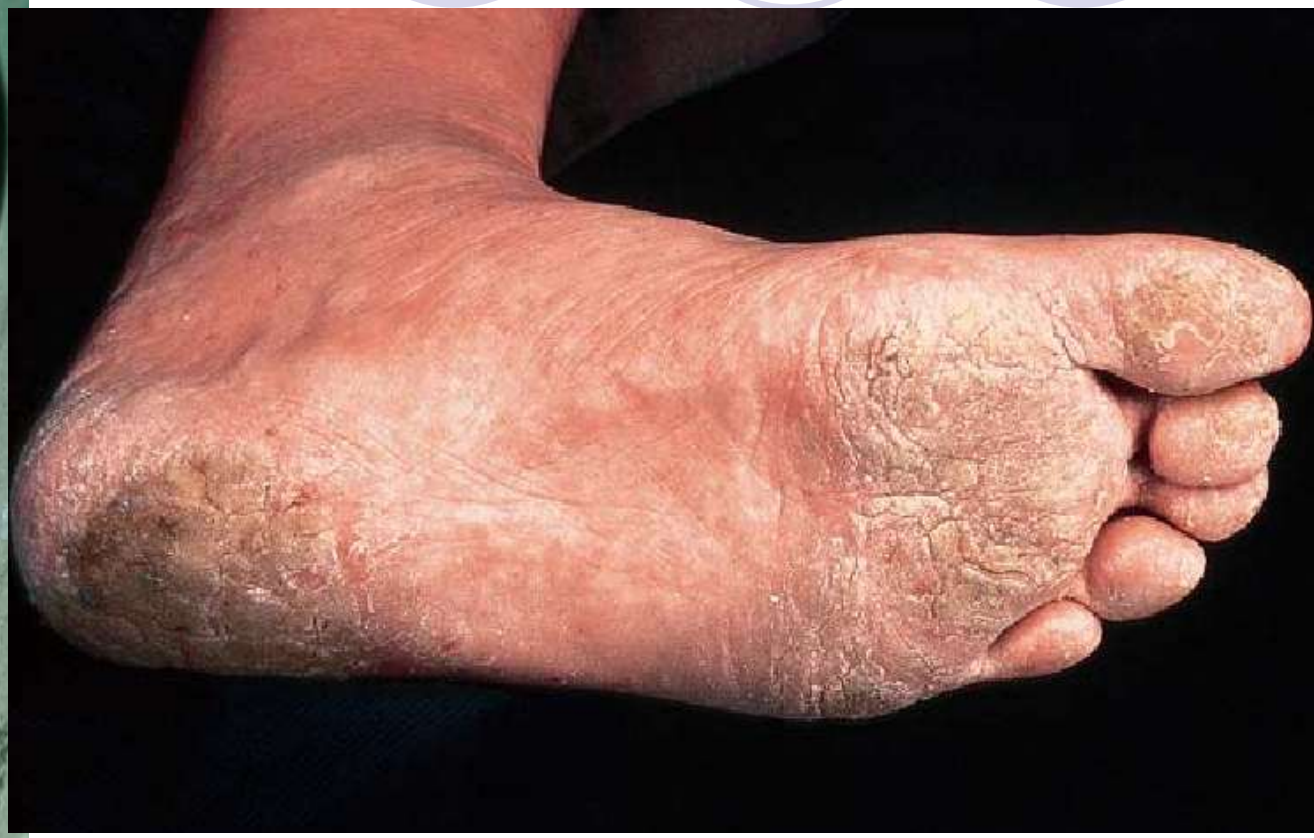


- classical triad

1. Erythroderma

- severe pruritus
- ectropion
- nail dystrophy
- peripheral edema
- alopecia
- keratoderma of the palms and soles





Sezary syndrome

Hematological abnormalities

- blood

- >1000/ml circulating atypical, big lymphocytes with cerebriform nuclei
- Increased number of CD4+
- Increased ratio of CD4+/CD8+ > 10
- Lost markers of CD5; CD7; CD26

- clonality of T lymphocytes (PCR confirmed rearrangement)

- Skin - erythroderma
- Lymphadenopathy

Sezary syndrome treatment

- Extracorporeal photopheresis (FDA-approved)
- INF-alfa
- Phototherapy: PUVA, Re-PUVA, NB-UVB
- Oral retinoids and rexinoids (bexaroten, acitretin)
- Methotrexate 5-75 mg/week
- Mogamulizumab
- Chlorambucil +/- prednisone
- Electron-beam therapy
- Chemotherapy
- Radiotherapy
- Allogeneic hematopoietic stem cell transplantation