Cutaneous T cell lymphoma

Belgian Hematology Society (BHS) course on "indolent lymphomas"

05-02-2015

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Overview:

I. Cutaneous T cell lymphoma (CTCL)
   1. Introduction and definition
   2. Epidemiology in Belgium
   3. Risk factors
   4. Clinical picture
   5. Pathology and Molecular genetics
   6. Staging and prognosis
   7. Diagnosis and differential diagnosis
   8. Treatment
   9. References and further reading

Introduction

- Primary cutaneous lymphomas = cutaneous T-cell lymphomas (CTCLs, ~ 75%) and cutaneous B-cell lymphomas (CBCLs, ~ 25%) presenting in the skin without any evidence of extracutaneous disease at time of diagnosis
  - Often completely different clinical behavior and prognosis from histologically similar systemic counterparts
  - Recent classification systems (WHO, EORTC, …) include primary cutaneous lymphomas as separate entities
  - Correct classification only possible by integrating clinical picture, histopathologic, immunophenotypic and molecular data (i.e. lymphomatoid papulosis)

Cerroni L et al An illustrated guide to skin lymphoma Blackwell Science, London 1998
Willemze R et al WHO-EORTC classification for cutaneous lymphomas, Blood 105:3768-3785, 2005

Table 1. WHO-EORTC classification of cutaneous lymphomas with primary cutaneous manifestations

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30$^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma*
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8$^+$ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous CD4$^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4$^+$/CD56$^+$ hematodermic neoplasm (blastic NK-cell lymphoma)†

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Willemze R et al WHO-EORTC classification for cutaneous lymphomas, Blood 105:3768-3785, 2005

Table 2. Relative frequency and disease-specific 5-year survival of 1905 primary cutaneous lymphomas classified according to the WHO-EORTC classification

WHO-EORTC classification	No.	Frequency, %*	Disease-specific 5-year survival, %
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	< 1	100
Granulomatous slack skin	4	< 1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous $CD4^+$ small/medium pleomorphic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	< 1	NR
Primary cutaneous aggressive CD8+ T-cell lymphoma†	14	< 1	18
Primary cutaneous γ/δ T-cell lymphoma†	13	< 1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16
Cutaneous B-cell lymphoma			
Indolent clinical behavior			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95
Intermediate clinical behavior			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	< 1	50
Primary cutaneous intravascular large B-cell lymphoma	6	< 1	65

Willemze R et al WHO-EORTC classification for cutaneous lymphomas, Blood 105:3768-3785, 2005

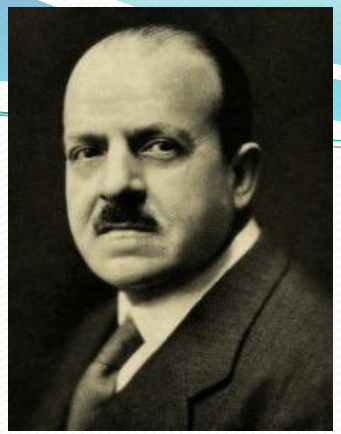
Definition

- Mycosis Fungoides (MF) = MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin but with potential involvement of the nodes, blood, and viscera, normal counterpart = peripheral epidermotropic CD4+ T-cell
  - 1806 (JL Alibert): first description of an unusual skin eruption developing into tumors having a mushroom-like appearance, "mycosis fungoides" misnomer since no association with fungal infection
  - 1870 (PAE Bazin): first description of natural progression through patches, plaques and tumor stage
  - 1975 (Edelson and Lutzner): first used the term 'cutaneous T cell lymphoma'

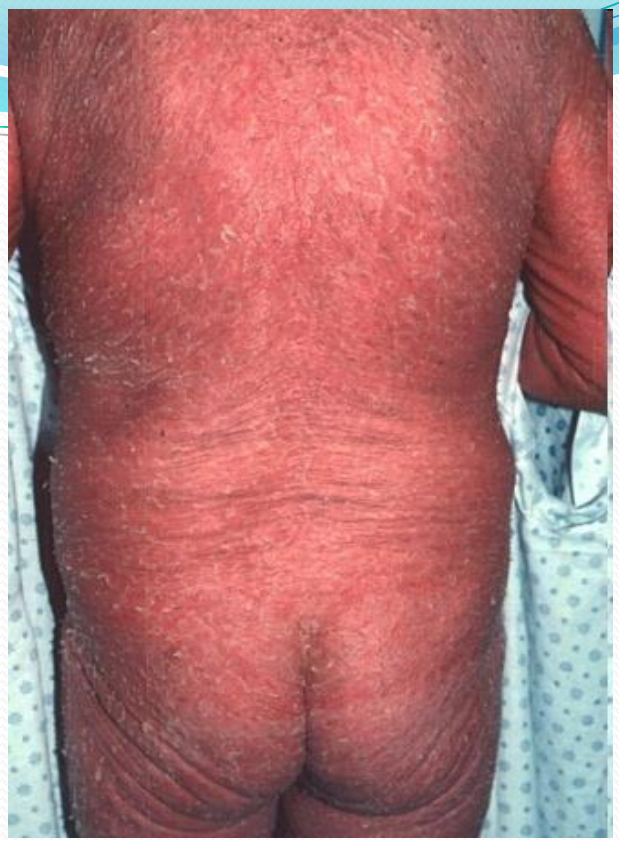
Jean – Louis Alibert (1768-1837)

Alibert's original drawing

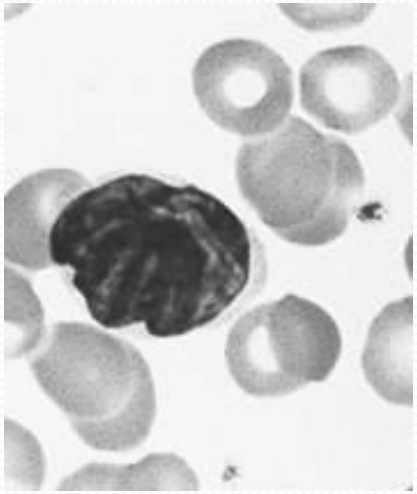
Definition

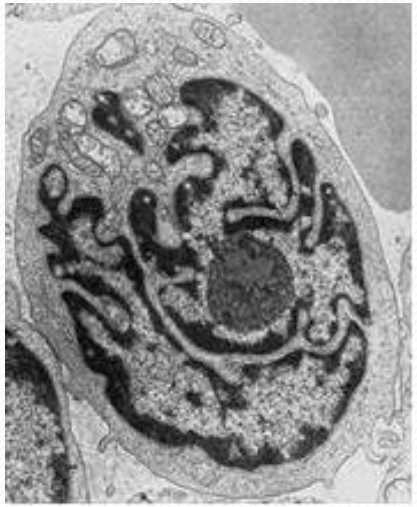


Albert Sézary (1880-1956)



- Sézary Syndrome (SS): distinctive erythrodermic CTCL with a leukemic involvement of malignant T cells clonally matching that in the skin
  - Historically : triad of
    - Erythroderma
    - generalized lymphadenopathy
    - malignant circulating T-cells (Sézary cells) in the peripheral blood (>5% of peripheral lymphocytes)
- Erythrodermic MF is differentiated from SS by absent / low circulating SS cells; regarded as progression of MF <=> SS typically arises de novo; high expression of PD-1 by neoplastic T cells in SS





Epidemiology

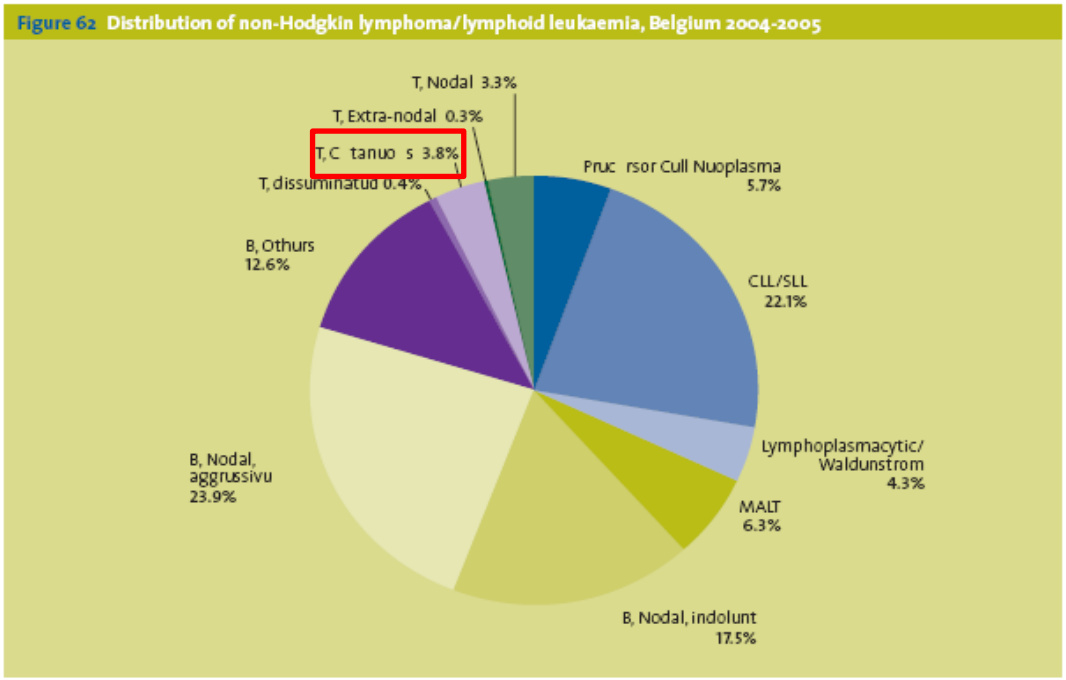
- Incidence of MF in Europe and US ~ 6 per million per year, accounting for about 4 percent of all cases of non-Hodgkin lymphoma

- SEER data: age-adjusted incidence of MF increasing since 1973 (due to improvements in detection, changes in the classification of this disease, or an increase in the underlying etiologic agent(s)?).

- The peak age at presentation is in excess of 55 to 60 years, with a 2:1 male:female ratio, can also be seen in patients under the age of 35 years

Epidemiology - Belgium

- With a total number of 4800 cases per year hematological malignancies represent 8,5% of all cancers in Belgium
- Lymphoid neoplasms account for 3411 new cases in Belgium in 2005.
- a total of 95 patients (60 males and 35 females) were diagnosed with cutaneous T cell lymphoma in 2005 in Belgium, crude incidence rate in males 1,2/100.000 person years and in females 0,7/100.000 person years, 3.8% of all NHL.



Cancer Incidence in Belgium 2004-2005
Belgian Cancer Registry

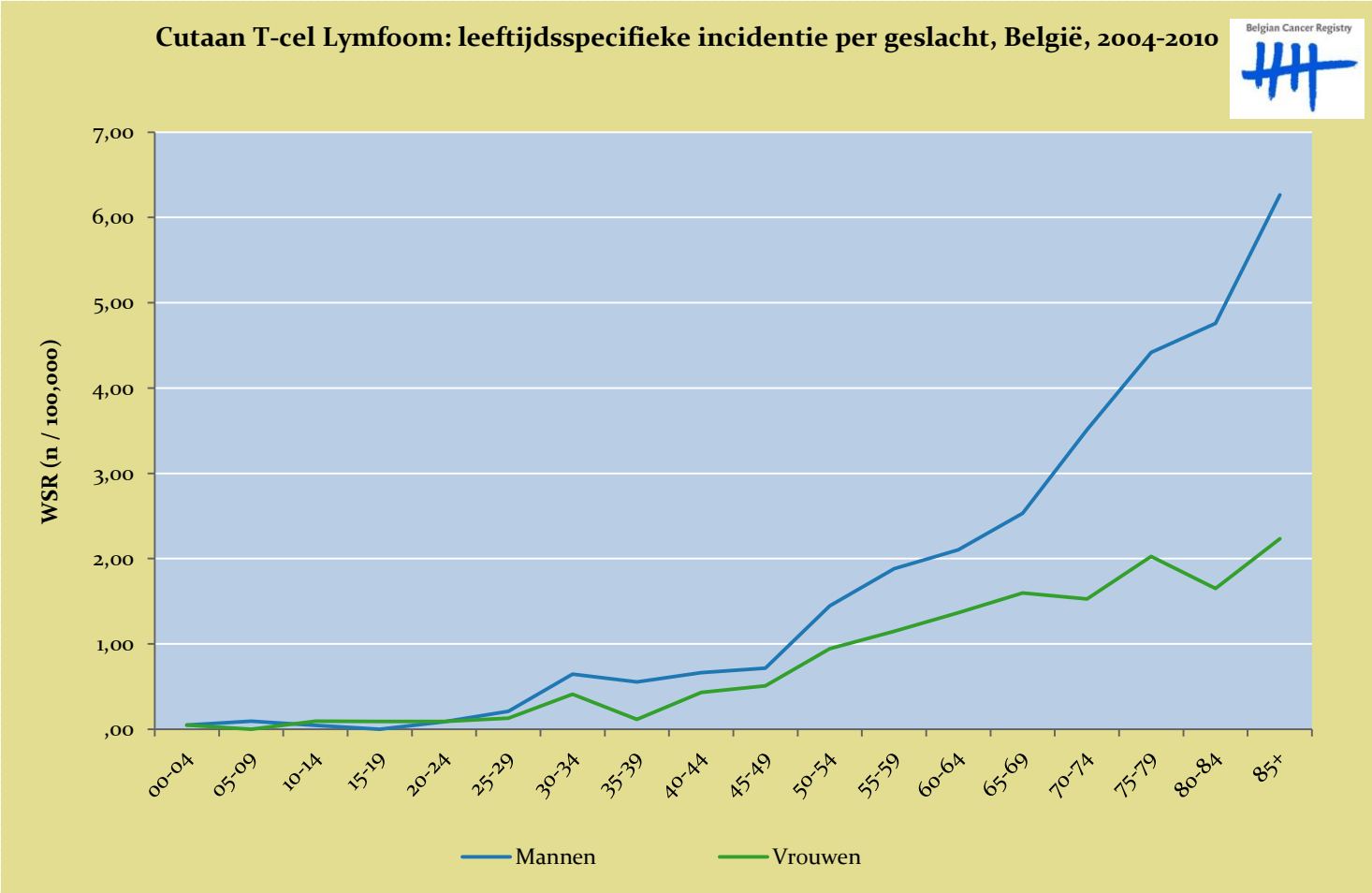
Epidemiology - Belgium

	2004		2005		2006		2007		2008		2009		2010	
	m	f	m	f	m	f	m	f	m	f	m	f	m	f
Absolute numbers (n)	59	32	60	35	44	25	63	39	61	42	58	41	58	44
CR, (n/100.000 person years)	1.2	0.6	1.2	0.7	0.9	0.5	1.2	0.7	1.2	0.8	1.1	0.7	1.1	0.8
ESR, (n/100.000 person years)	1.0	0.4	1.0	0.5	0.7	0.4	1.0	0.6	1.0	0.6	0.9	0.6	0.9	0.6
CRI, (%)	0.08	0.03	0.07	0.04	0.05	0.03	0.08	0.05	0.08	0.05	0.07	0.04	0.08	0.04

CR: crude (all ages) incidence rate (n/100.000 person years)
ESR: age-standardised incidence rate, using European Standard Population (n/100.000 person years
CRi: cumulative risk 0-74 years (%)

Cancer Incidence in Belgium 2004-2005, Belgian Cancer Registry

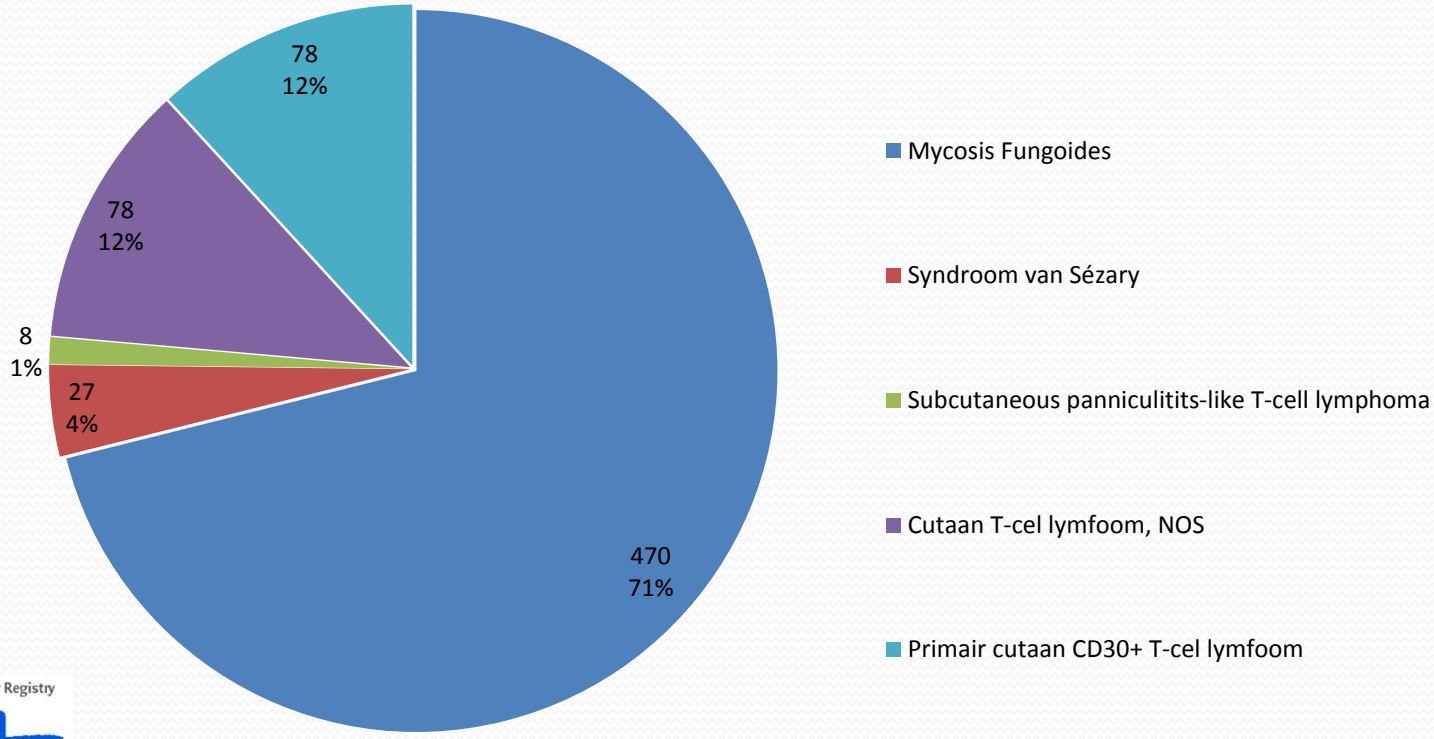
Epidemiology - Belgium



Cancer Incidence in Belgium 2004-2010, Belgian Cancer Registry

Epidemiology - Belgium

Cutaan T-cel lymfoom per histologie, België, 2004-2010



Cancer Incidence in Belgium 2004-2010, Belgian Cancer Registry

Risk factors and pathogenesis

- MF is believed to result from chronic antigen stimulation leading to uncontrolled clonal expansion and accumulation of T helper memory cells in the skin
- But precise etiology and risk factors of MF/SS are unclear
- Different risk factors have been investigated:
  - Exposure to solvents and chemicals (not confirmed)
  - Viral etiology: HTLV1, EBV, CMV (not confirmed)
  - Chromosomal abnormalities (deletions and translocations chromosome 1 or 6)

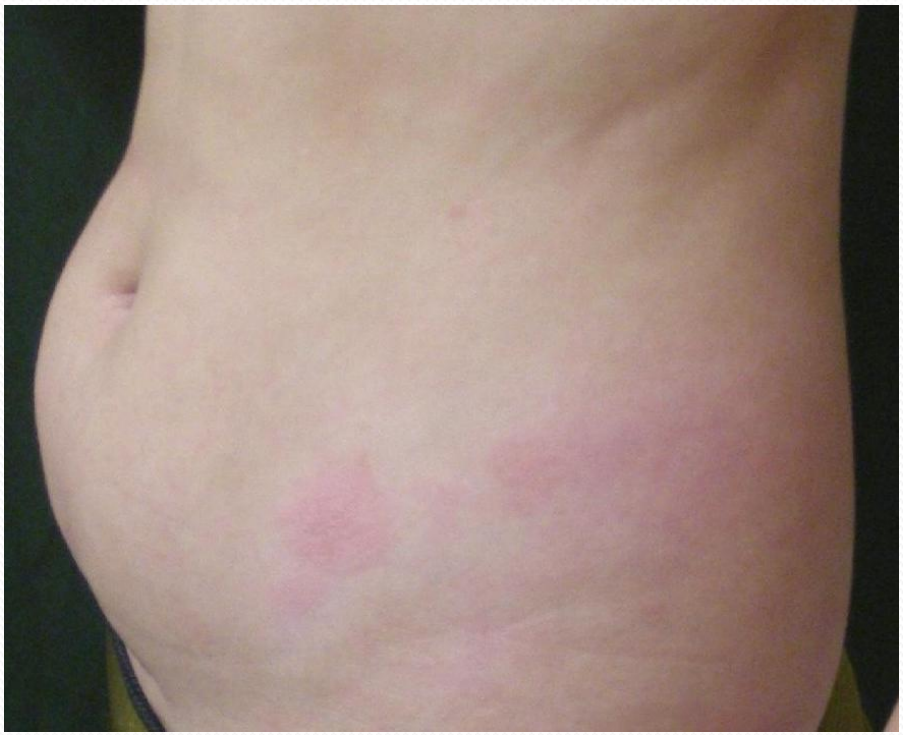
Hwang ST et al Mycosis fungoides and Sézary syndrome Lancet 371:945-957, 2008

Clinical Features

A. Cutaneous

1) *Patch – stage*

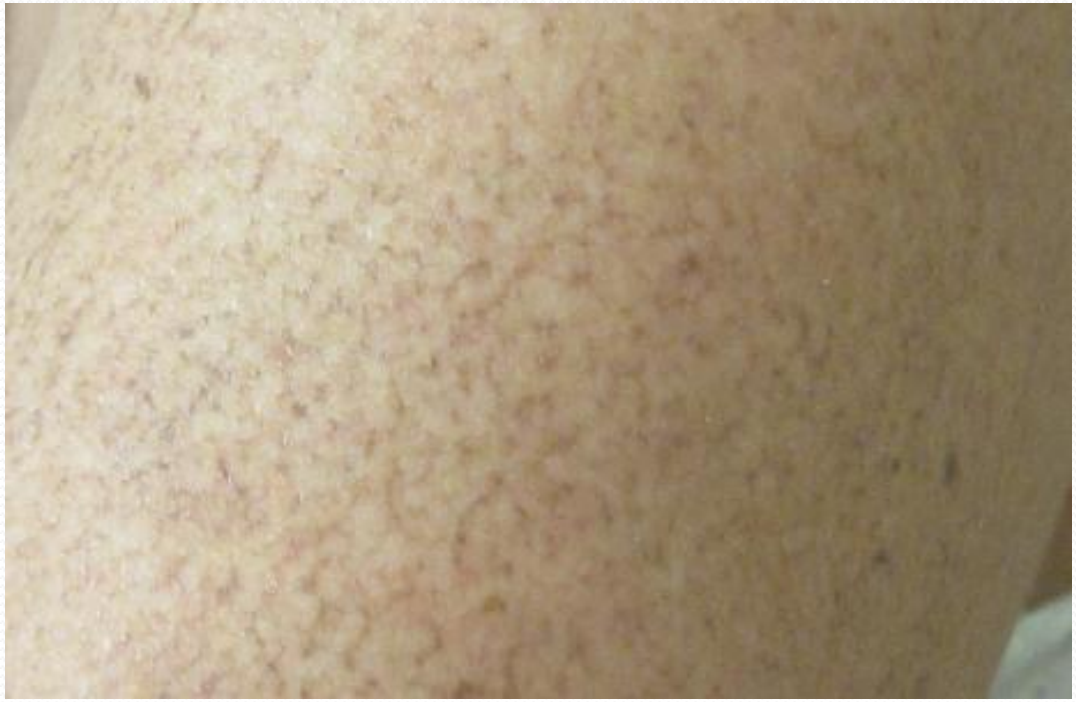
- Patch = a circumscribed area of discoloration, greater than 1 cm, which is neither elevated or depressed relative to the surrounding skin.



- Multipele lesions, scaly patches or plaques, sometimes pruritic
- Confined to bathing trunk distribution (buttocks and other sun-protected areas)
- Most patches >5cm
- Important variation in size, shape and color
- Wax and wane over years
- Sometimes preceded by "premycotic" period (nonspecific, scaling lesions and nondiagnostic biopsies)
- Only temporarily improvement with topical corticosteroids

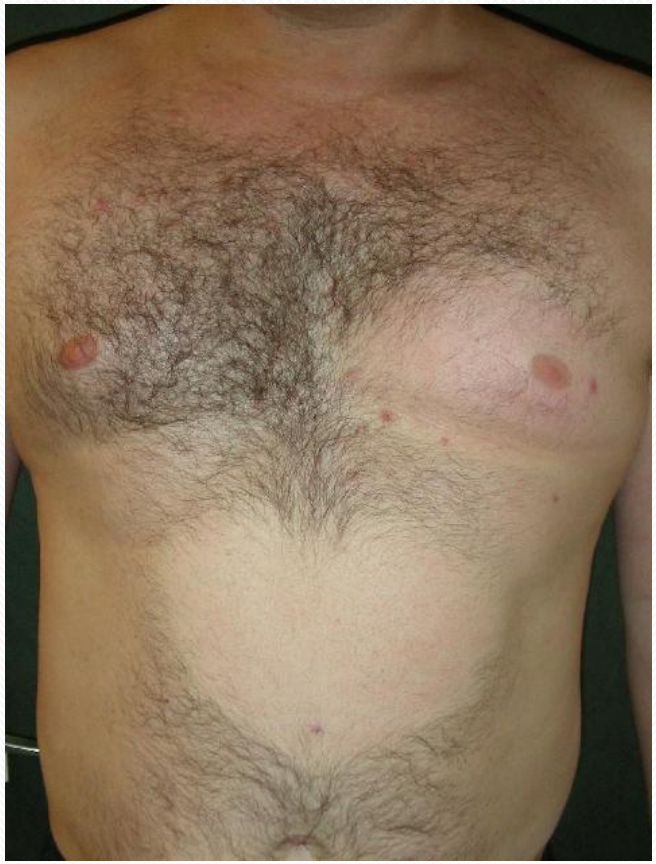
Cerroni L et al An illustrated guide to skin lymphoma Blackwell Science, London 1998

Clinical features



- Alopecia = common, reduced hair density diffusely over the scalp and body or as patches of alopecia

- Poikilodermia =presence of mottled pigmentation, epidermal atrophy, and telangiectasia associated with slight infiltration

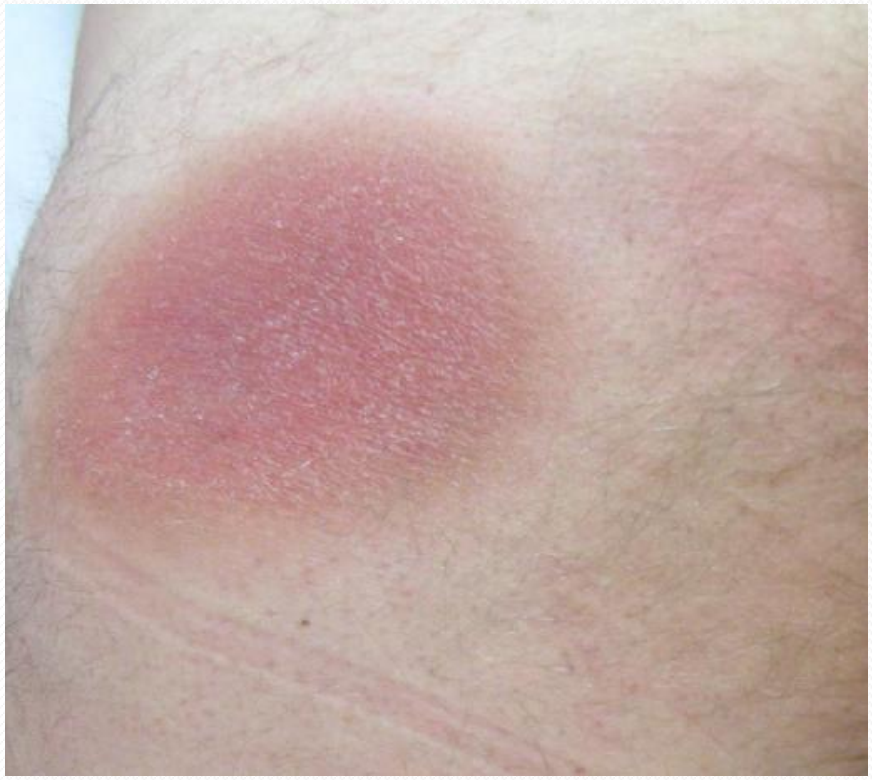


Clinical features

A. Cutaneous

1) *Plaque – stage*

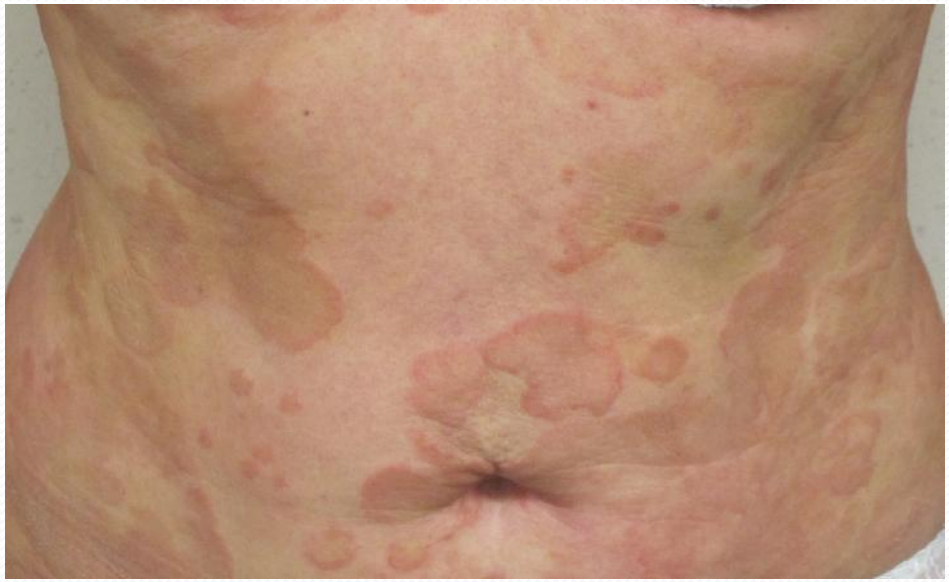
• Plaque = a well-circumscribed, elevated, superficial, solid lesion, greater than 1 cm in diameter. Usually "plateau-like" with a flat top.

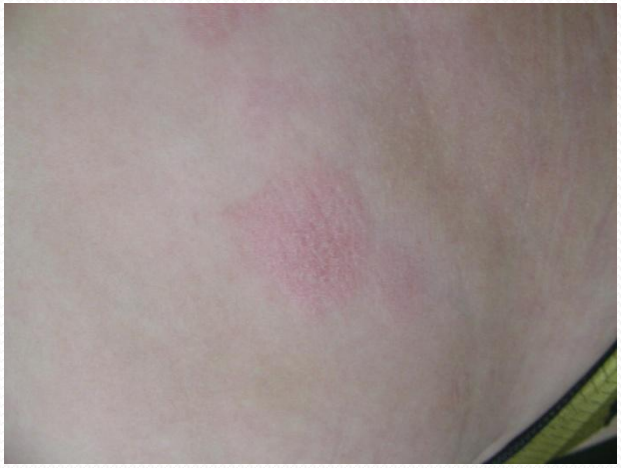


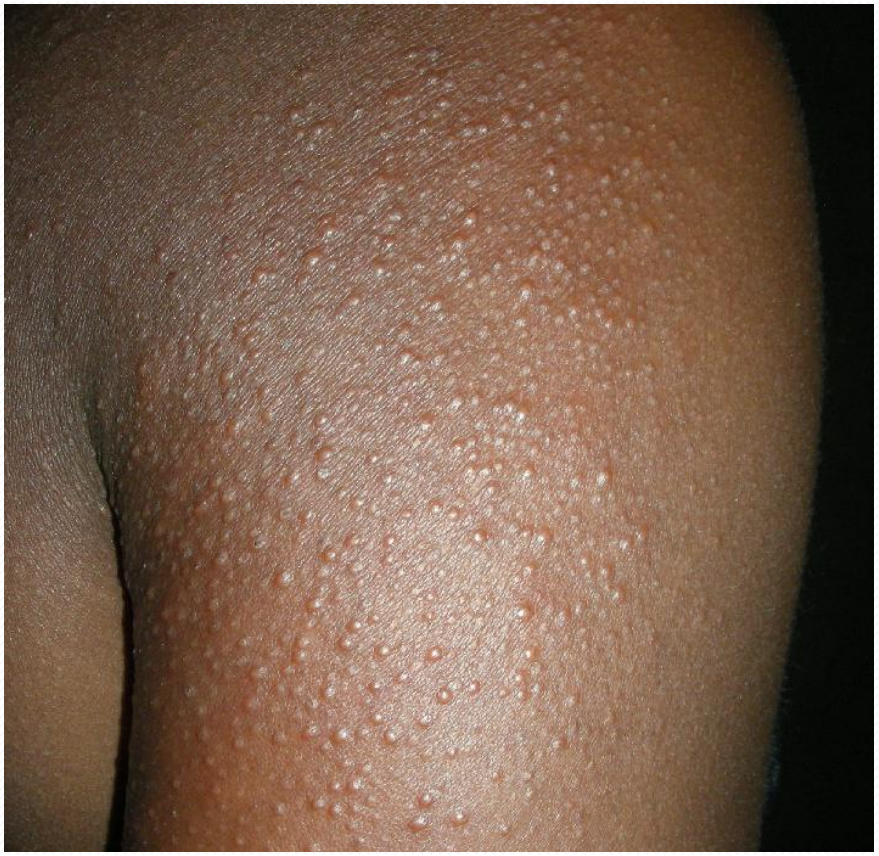
- Evolution to infiltrated plaques (infiltration, reddish - brown, scaly)
- Observed contiguous to plaques or at other sites

Cerroni L et al An illustrated guide to skin lymphoma Blackwell Science, London 1998

Clinical features







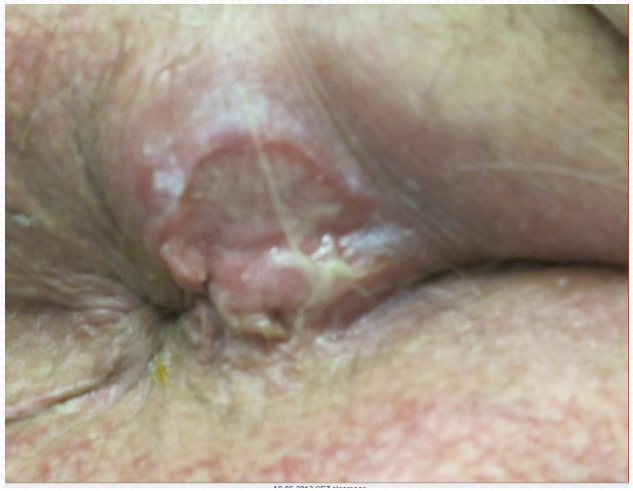
Folliculotropic MF: predilection for hair follicles

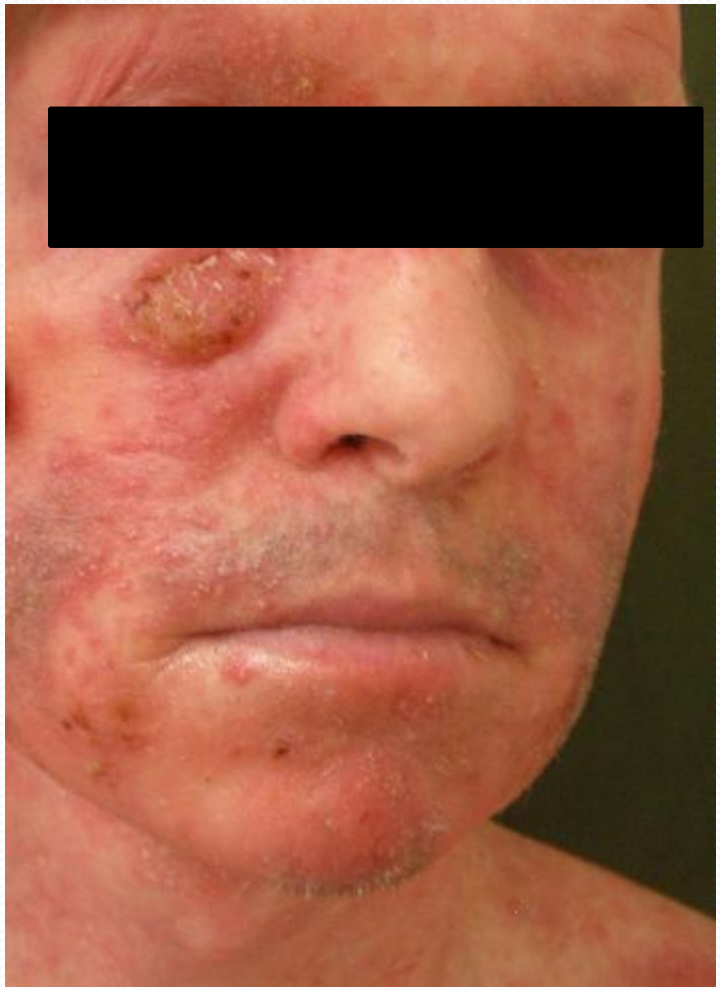
Clinical features

Tumor = any solid or nodular lesions ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth

2) Tumor phase

- Combination of patches, plaques and tumors, if tumor de novo, be careful with diagnosis -> other CTCL?
- may be localized or generalized
- Exophytic and ulceration common (CAVE: surinfection!)

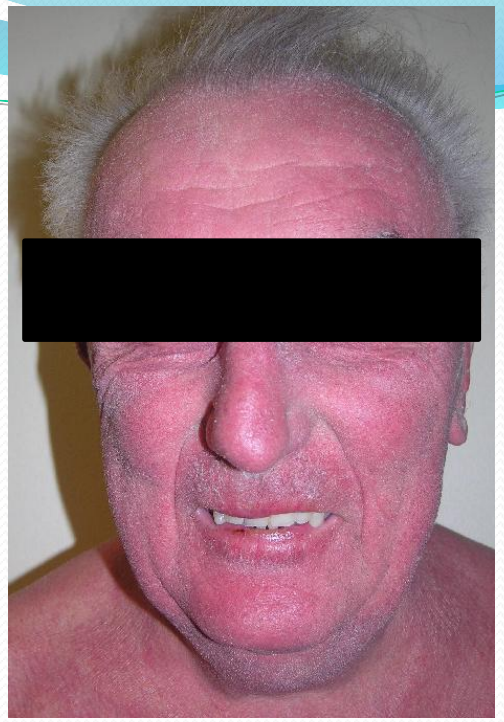


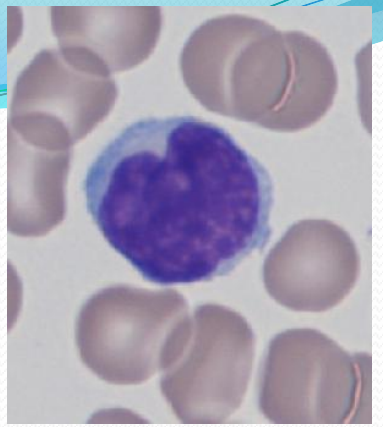


Clinical features

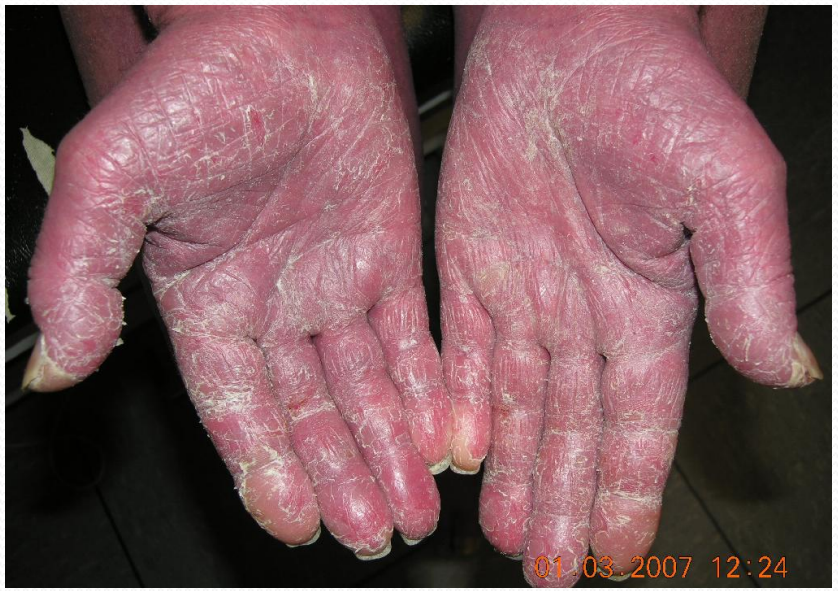
3) Erythrodermia

- Erythroderma covering at least 80% of body surface area
- Intense pruritus and scaling
- Palmoplantar hyperkeratosis, alopecia, onychodystrophy, ectropion
- Circulating SS cells with $CD4^+$, $CD7^-$, $CD26^-$ phenotype
- DD from non-neoplastic erythrodermia sometimes very challenging





Sézary cell with hyperconvoluted or cerebriform nucleus



Cerroni L et al An illustrated guide to skin lymphoma Blackwell Science, London 1998
Olsen EA et al J Am Acad Dermatol 64:352-404

Clinical features

B. **Extracutaneous disease**

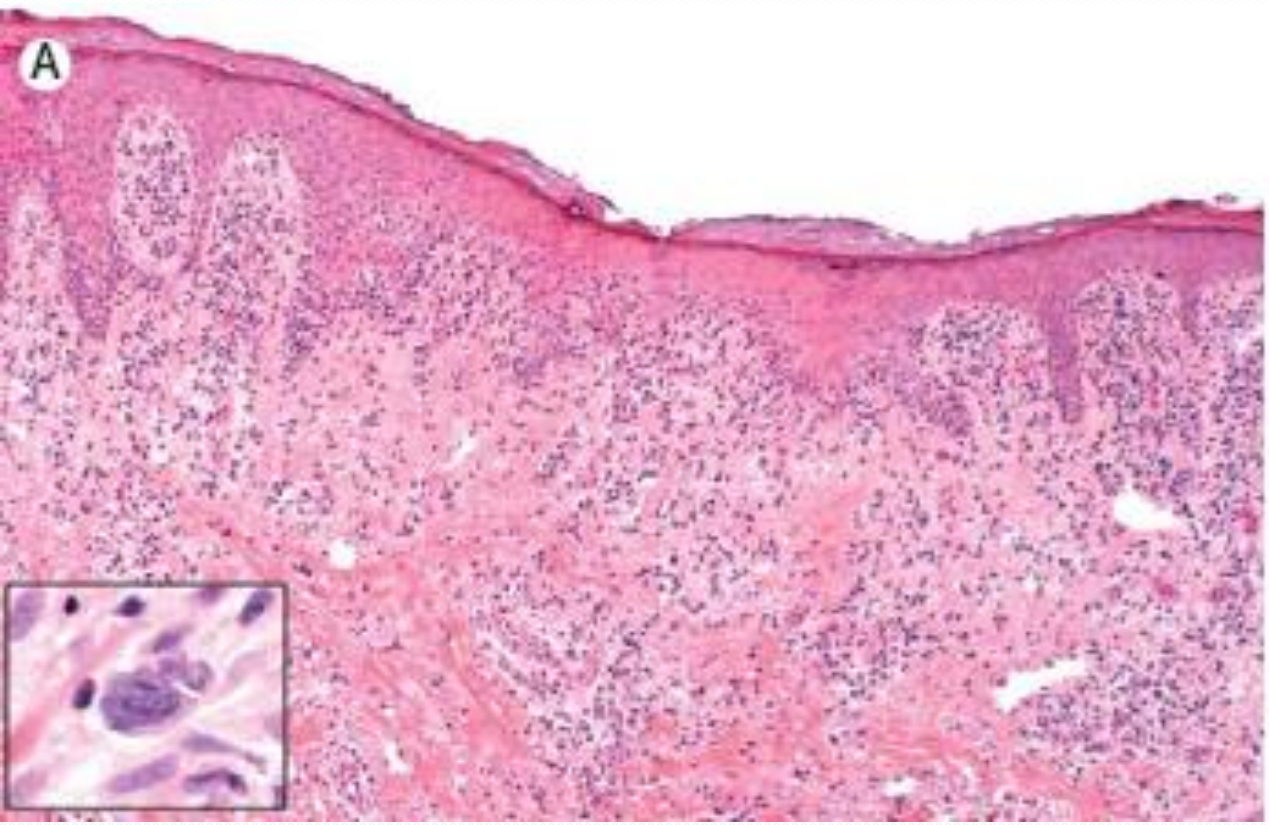
- correlates with extent of skin involvement
- more common with Sézary syndrome
- can include regional lymph node (30% in MF)
- Risk of developing extracutaneous disease (after 20 yrs)
    - limited patch/plaque (T1): 0%
    - generalized patch/plaque (T2): 10%
    - tumors (T3): 36%
    - Erythroderma (T4): 41%

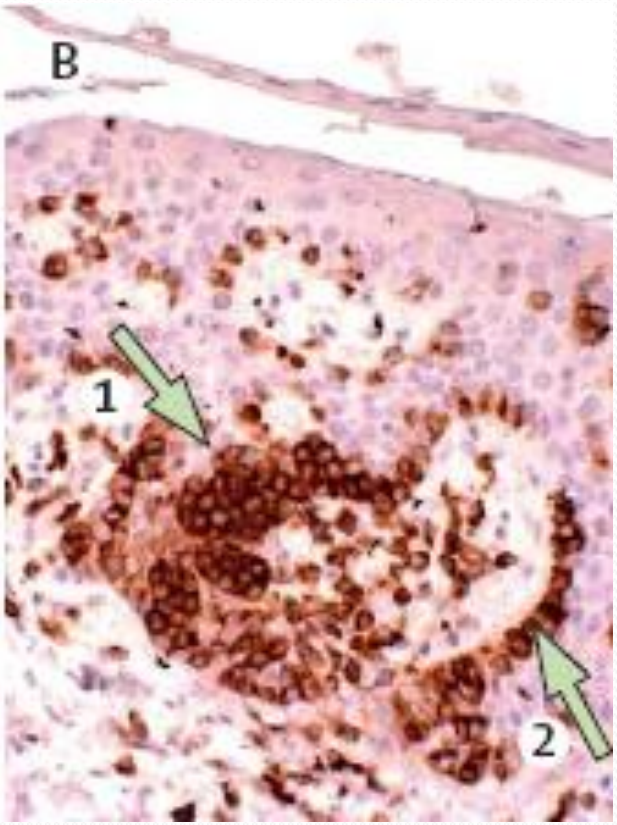
Pathology

- Patch en plaques
  - Small to medium-sized atypical lymphocytes infiltrating the upper dermis and epidermal keratinocytes (epidermotropism) or forming intraepidermal aggregates (Pautrier microabcesses 38%)
  - Lymfocytes aligned within the basal layer
  - Intraepidermal lymphocytes with avuoles around them (=haloed lymphocytes)

→ Problem:
often no clear picture, repeated biopsies necessary
time from first skin lesion to diagnosis of CTCL 3 - 6 yrs

2008, J Cut Pathol, Smoller et al
2002, Skin pathology, Weedon



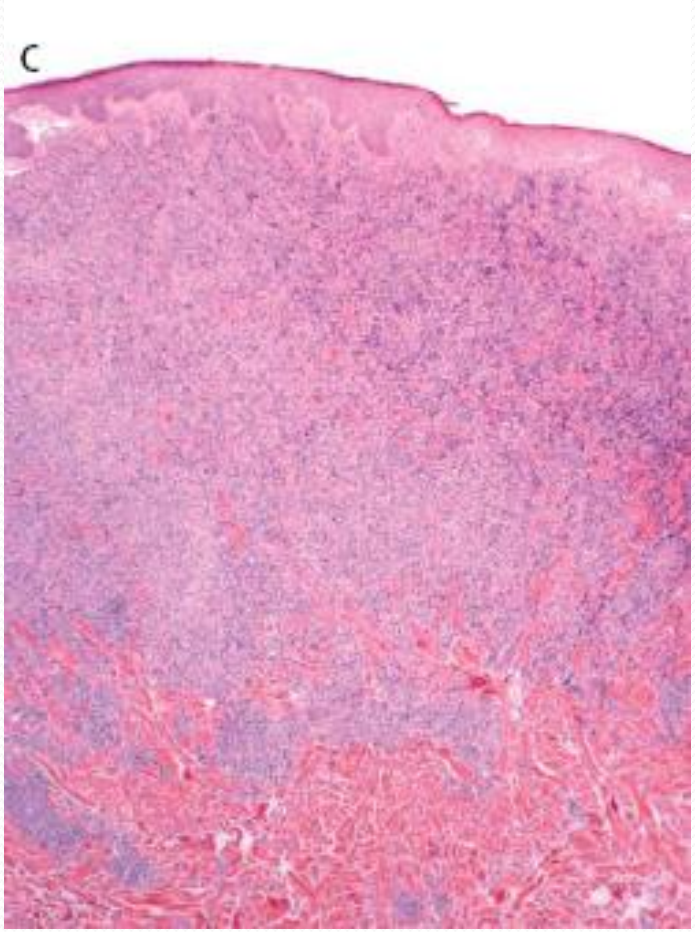


A: atypical cells in the epidermis (epidermotropism) and infiltrating lymphocytes in the papillary dermis.

B. Pautrier's microabces (1) and lymphocyts aligned with the basal layer in a CD2 staining

2008, The Lancet, Hwang et al

Pathology – tumor stage

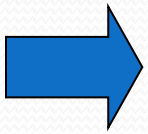


- Tumor
  - Dense infiltrates of atypical lymphocytes in the dermis
  - Diffus dermal infiltration
  - Epidermotropism gets lost
  - Frequent mitoses and apoptotic cells
  - Expression of CD30 in 40-50% of histologically transformed MF

2008, J Cut Pathol, Smoller et al

Pathology

- Immunohistochemistry
  - Phenotype of mature memory T-cells (CD3+, CD4+, CD8-), rarely CD8+
  - Loss of T-cell antigens: CD2, CD3, CD5, CD7, CD26
  - Elevated CD4:CD8 ration often seen in MF



Abberant phenotype in plaque or tumor stage

2008,The Lancet, Hwang et al
2005, Blood, Willemze et al

Molecular genetics

- T cell receptor gene rearrangement are utilized when the histology and immunophenotyping results are equivocal in patients whose clinical presentation is strongly suggestive of MF
- Examination of multiple biopsies from the same patient taken simultaneously or consecutively from two anatomically distinct skin sites usually, but not always, demonstrates the same TCR gene rearrangement
- The presence of TCR gene rearrangement among T cell clones is not diagnostic of MF. Instead, the presence of such abnormalities is only one component of a possible diagnosis. As an example, there are non-malignant disorders in which T cell clonality is observed:
- Some non-malignant or pre-malignant cutaneous conditions may be accompanied by evidence of an expanded T cell clone (i.e. lichen planus, lichen sclerosus et atrophicus, pityriasis lichenoides et varioliformis acuta (PLEVA), pseudolymfomen…

Diagnostic algorithm:

Table 3. Algorithm of diagnosing early MF developed by the ISCL[8]

	Criteria			Scoring system	
	Basic	Additional	Other	2 points	1 point
Clinical	Persistent and/or progressive patches/thin plaques	(1) Non–sun-exposed location (2) Size/shape variation (3) Poikiloderma		2 points for basic criteria and 2 additional criteria	1 point for basic criteria and 1 additional criteria
Histopathologic	Superficial lymphoid infiltrate	(1) Epidermotropism without spongiosis (2) Lymphoid atypia*		2 points for basic criteria and 2 additional criteria	1 point for basic criteria and 1 additional criteria
Molecular biologic			Clonal T-cell receptor gene rearrangement		1 point for clonality
Immunopathologic			< 50% $CD2^+$, $CD3^+$, and/or $CD5^+$ cells < 10% $CD7^+$ cells Epidermal/dermal discordance of CD2, CD3, CD5, or CD7†		1 point for 1 or more criteria

A total of 4 points is required for the diagnosis of MF based on any combination of points from the clinical, histopathologic, molecular biologic, and immunopathologic criteria.

*Lymphoid atypical is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours.

†T-cell antigen deficiency confined to the epidermis.

Olsen E et al Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the EORTC, Blood 110:1713-1722, 2008

Differential diagnosis

1. Benign common skin disorders
   - eczema, psoriasis, parapsoriasis, photodermatitis, drug reaction
2. Benign skin disorders with similar histology
   - Lymphomatoid contactdermatitis, lymphomatoid drug reaction, chronic actinic dermatitis
3. Other subtypes of CTCL
   - Pagetoid reticulosis, lymfomatoid papulosis, primary cutaneous ALCL, subcutaneous panniculitis-like T cell lymphoma, adult T-cel leukemie/lymphoma, …

Diagnostic work-up

Table 6. Recommended evaluation/initial staging of the patient with mycosis fungoides/Sézary syndrome

Complete physical examination including
Determination of type(s) of skin lesions
If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions
If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered, or fixed
Identification of any organomegaly
Skin biopsy
Most indurated area if only one biopsy
Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered.
Evaluation for clonality of TCR gene rearrangement
Blood tests
CBC with manual differential, liver function tests, LDH, comprehensive chemistries
TCR gene rearrangement and relatedness to any clone in skin
Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$)
Radiologic tests
In patients with $T_1N_0B_0$ stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with $T_2N_0B_0$ disease with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy
In all patients with other than presumed stage IA disease, or selected patients with limited T_2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted.
Lymph node biopsy
Excisional biopsy is indicated in those patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
Site of biopsy
Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value (SUV).
If there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas.
Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement.

Olsen E et al Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the EORTC, Blood 110:1713-1722, 2008

mSWAT scoring in MF/SS

Table 3. Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Staging of Mycosis fungoides/SS

Table 4. ISCL/EORTC revision to the classification of MF and SS[11]

TNMB classification	Characteristics
Skin	
T1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface; may further stratify into T1a (patch only) versus T1b (plaque ± patch)
T2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T2a (patch only) versus T2b (plaque ± patch)
T3	One or more tumors‡ (≥ 1 cm diameter)
T4	Confluence of erythema covering ≥ 80% BSA
Node	
N0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N1a	Clone negative‖
N1b	Clone positive‖
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative‖
N2b	Clone positive‖
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells#
B0a	Clone negative‖
B0b	Clone positive‖
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B1a	Clone negative‖
B1b	Clone positive‖
B2	High blood tumor burden: ≥ 1000/μL Sézary cells# with positive clone‖

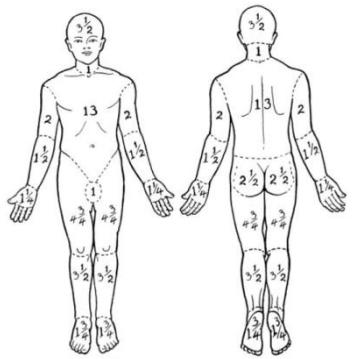


Figure 1. Regional percent body surface area (BSA) in the adult. Adapted from Lund and Browder[35] with permission.

*For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypopigmentation or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

†For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features, such as folliculotropism or large-cell transformation (> 25% large cells), $CD30^+$ or $CD30^-$, and clinical features, such as ulceration, are important to document.

‡For skin, tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

§For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed, or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

‖A T-cell clone is defined by polymerase chain reaction or Southern blot analysis of the T-cell receptor gene.

¶For viscera, spleen and liver may be diagnosed by imaging criteria.

#For blood, SCs are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If SCs are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of 10 or more; or (2) expanded $CD4^+$ cells with abnormal immunophenotype including loss of CD7 or CD26.

Staging of Mycosis fungoides/SS

Table 7. ISCL/EORTC revision to the staging of mycosis fungoides and Sézary syndrome

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

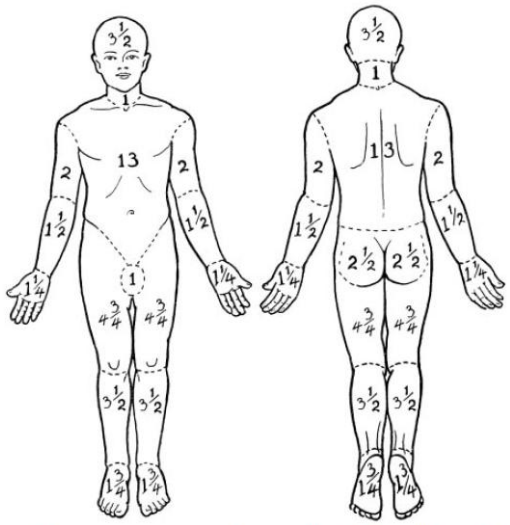


Figure 1. Regional percent body surface area (BSA) in the adult. Adapted from Lund and Browder[35] with permission.

Table 5. Histopathologic staging of lymph nodes in mycosis fungoides and Sézary syndrome

Updated ISCL/EORTC classification	Dutch system[58]	NCI-VA classification[13,57,59]
N_1	Grade 1: dermatopathic lymphadenopathy (DL)	LN_0: no atypical lymphocytes LN_1: occasional and isolated atypical lymphocytes (not arranged in clusters) LN_2: many atypical lymphocytes or in 3-6 cell clusters
N_2	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei > 7.5 μm)	LN_3: aggregates of atypical lymphocytes; nodal architecture preserved
N_3	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells (CMCs) Grade 4: complete effacement	LN_4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

Olsen E et al Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the EORTC, Blood 110:1713-1722, 2008

Prognosis

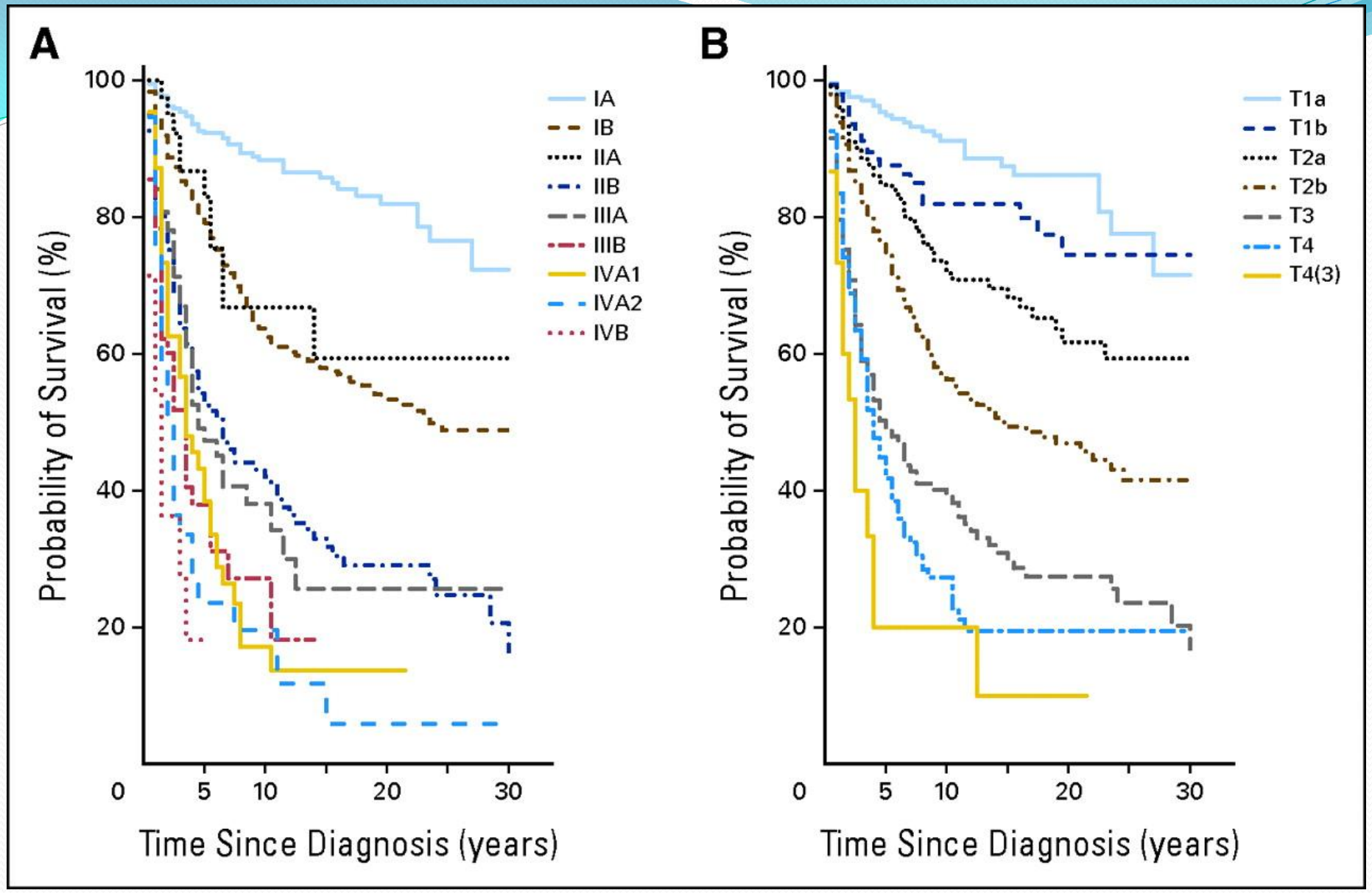
Stadium	TNM	Median survival	Risk of progression to higher stage (T_3/T_4)	10-year survival
Stage IA	T1 No Mo	Normal life expectancy	9%	84-100%
Stage I B	T2 No Mo	10-12 years	25%	58-67%
Stage IIA	T1-2 N1 Mo	10-12 years	25%	45-49%
Stage II B	T3 No-1 Mo	3 years		20-39%
Stage III A	T4 No Mo	4,5 years		20-40%
Stage III B	T4 N1 Mo	4,5 years		20-40%
Stage IV A	T1-4 N2-3 Mo	< 1,5 years		5-20%
Stage IV B	T1-4 No-3 M1	< 1,5 years		0-5%

2008, Crit Rev Onc Hematal, Zinzani et al
2003, Br J Dermatol, Whittaker et al

Prognosis

- Analysis of outcome of mycosis fungoides (MF) and Sézary syndrome (SS) 1502 patients using the ISCL/EORTC revised staging proposal.
- Most important findings:
  - 71% of patients with early-stage disease, disease progression occurred in 34%, 26% of patients died due to MF/SS
  - significant difference in survival and progression was noted for patients with early-stage disease with patches alone (T1a/T2a) compared with those having patches and plaques (T1b/T2b)
  - Poorer outcome with:
    - advanced skin (T) stage, the presence in peripheral blood of the tumor clone without Sézary cells (Bob), increased LDH, and folliculotropic MF

Agar NS et al Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal JCO 2010 Nov 1;28(31):4730-9



Disease-specific survival according to (A) clinical stage and (B) T classification (ISCL / EORTC)

Agar N S et al. JCO 2010;28:4730-4739

Treatment

- Depending on stage and general performance status
- CAVE: treatment is not curative but try to ease symptoms like itching or burning of patches and plaques
- Problem: very few randomized controlled trials.
  - Conclusion of recent Cochrane Review: *"This review identified trial evidence for a range of different topical and systemic interventions for MF. Because of substantial heterogeneity in design, small sample sizes, and low methodological quality, the comparative safety and efficacy of these interventions cannot be established on the basis of the included RCTs. Taking into account the possible serious adverse effects and the limited availability of efficacy data, topical and skin-directed treatments are recommended first, especially in the early stages of disease. More aggressive therapeutic regimens may show improvement or clearance of lesions, but they also result in more adverse effects; therefore, they are to be considered with caution. Larger studies with comparable, clearly-defined end points for all stages of mycosis fungoides, and a focus on safety, quality of life, and duration of remission as part of the outcome measures, are necessary."*

Table 4. Treatment Recommendations for Mycosis Fungoides (level of evidence III)

Stage	First-Line	Second-Line	Comments
IA (T1N0M0)	Watch-and-wait PUVA[92] Topical corticosteroids class III–IV[10] Topical HN2/BCNU[93,94] UVB/UVB narrow band[95–97]	Bexarotene gel[98] Hexadecyphosphocholine solution[99]	PUVA favored in Europe
Unilesional MF pagetoid reticulosis	Radiation therapy (soft x-rays or electron beam, total dose 30–40 Gy; 2 Gy 5x weekly)[100–103]	Topical PUVA Intralesional IFN Topical corticosteroids class III–IV Bexarotene gel[98]	These disorders represent special presentation forms of CTCL in stage IA
IB–IIA (T2N0M0–T1-2N1M0)	PUVA Topical HN2/BCNU[93,94]	PUVA + IFN-α[104–107] Oral bexarotene[108]	
IIB (T3N0-1M0)	PUVA + IFN-α[104–107] and radiation therapy for tumors Topical HN2/BCNU[93, 94]	Low-dose methotrexate[109] Oral bexaroten[22] Total body electron beam[110,111] Denileukin diftitox[47]	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
III* (T4N0-1M0)	PUVA + IFN-α[104–107] Topical HN2/BCNU[93,94] Extracorporeal photopheresis[112–117]	Low-dose methotrexate[118] Oral bexarotene[22] Total body electron beam[110,111] Chlorambucil/corticosteroids[119] Low-dose long distance (2 m) soft x-rays[102] Vorinostat[39]	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
IVA (TanyN2-3M0)	PUVA + IFN-α[104–107] Extracorporeal photopheresis,[112–117] eg, combined with IFN or methotrexate	Low-dose methotrexate[118] Oral bexarotene[22] Total body electron beam[110,111] Chlorambucil/corticosteroids[119] Vorinostat[39] Low-dose long distance (2 m) soft x-rays[102]	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved
IVB (TanyNanyM1)	PUVA + IFN-α[104–107] Chlorambucil/corticosteroids[119] Liposomal doxorubicin[120] Soft x-rays or electron beam for tumors[102]	Oral bexarotene[22] Gemcitabine[121] CHOP polychemotherapy[122] Denileukin diftitox[123] Cladribine (2-chlorodeoxyadenosine)[124] Gemcitabine[125] Vorinostat[39] Alemtuzumab (anti-CD52)[55] Zanolimumab (anti-CD4)[53] Bortezomib[61] Forodesine[37]	Consider maintenance therapy with PUVA + IFN-α or bexarotene when remission is achieved

Abbreviations: PUVA, psoralen and UVA; HN2, nitrogen mustard; BCNU, carmustine; IFN, interferon; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone.
*Erythrodermic mycosis fungoides.

Belloni B et al Seminar in Oncology 39:150-162, 2012

Stage IA: Patch/plaque<10%: skin directed therapy

1. Topical corticosteroids (class 1-3)
    - Complete remission: 25-60%
2. Topical chemotherapy
    - Nitrogen mustard or metchlorethamine (HN2)
        - CR in 70-80% after 6-8 months
        - Cave: contactsensitivity and carcinogenic (BCC x 1.8 en SCC x 8.6)
    - Carmustine (BCNU)
        - Results comparable to HN2
        - CAVE: myelosuppression (30%), regular bloodsamples

2003, Br J Dermatol, Whittaker et al
2008, Crit Rev Onc Hematol, Zinzani et al
2007, Canc Treat Rev, Whittaker et al
2006, Eur J of Cancer, Trautinger et al

3. Phototherapy
   - PUVA:
     - 3x/week, as soon as decrease of lesions, frequency of PUVA can be reduced to 1x/2w
     - Remission in 90% of the patients after 2-6 months
   - UVB: broadband of narrowband
     - Shallow penetration, only slightly infiltrated patches
4. Electron beam radiotherapy
   - Only for rare MF patients with a single lesion
5. Topical bexarotene gel (not on the market in Belgium)
   - Response of 60%

2003, Br J Dermatol, Whittaker et al
2008, Crit Rev Onc Hematol, Zinzani et al
2007, Canc Treat Rev, Whittaker et al
2006, Eur J of Cancer, Trautinger et al

Topical therapy in MF:

Therapy	Level of Evidence	Design	Stage	Response rate	References
BCX-34 (peldesine)	2++	RCT	IA-IB	28% vs 24% (placebo)	Duvic 2001
Mechlorethamine	3	Case series	IA-IB	51-80% (IA) 26-68% (IB)	Hoppe 1987 Ramsey 1988 Vonderheid 1989 Kim 2003b Zachariae 1985
Mechlorethamine + Betamethasone	2+	Phase II	IA-IB	58% CR (Duration 7.7 months)	de Quatrebarbes 2005
Carmustine (BCNU)	3	Case series	IA-IB	76%	Zackheim 1990 Apisarntnanarax *2012*
Bexarotene gel	2+	Phase II	IA-IB	63%	Breneman 2002
Corticosteroids	3	Case series	IA-IB		Zackheim 1998

Phototherapy in MF:

Therapy	Design (All non randomised)	Level of Evidence	Stage	Response rate	Response duration	References
UVB	Retrospective	2-	IA-IB	74%	51 mos	Resnik 1993
UVB	Retrospective	2+	IA-IB	71%	22 mos	Ramsay 1992
NB UVB	Retrospective	2+	IA-IB	84%	12.5 wks	Gathers 2002
NB UVB	Retrospective	2+	IA-IB	84% (IA) 78% (IB)		Pavlotsky 2006
PUVA	Retrospective	2+	IA-IB	95%	43 mos	Herrmann 1995
PUVA	Prospective	2++	IA-IB	100%	20 mos IA 17 mos IB	Honigsmann 1984
PUVA	Retrospective	2+	IA-II	63% (CR)	39 mos	Querfeld 2005

TSEB Therapy in MF/SS:

Therapy	Dose	Level of Evidence	Stage	ORR %	CR %	Median RFS/PFS (months)	References
High dose	30-36Gy	2+	IA	100	97	50	Quiros 2007
High dose	30-36Gy	2+	IB	100	59-75	18 - 29	Navi 2011 Morris2013
High dose	30-36Gy	2+	IIB	95-100	47	9	Navi 2011 Morris 2013
High dose	30-36Gy	2+	III	100	33 -60	6-9	Morris 2013 Jones 1999
Low dose	5 - <10Gy	2+	IB-III	85-100	0 - 25	12	Harrison 2011 Kamstrup 2012
Low dose	10Gy	2+	IB-IV	90	70*	5.2m	Kamstrup 2012
Low dose	10 - <20Gy	2+	IB-III	96-100	7-52	25.7	Harrison 2011
Low dose	20 - <30Gy	2+	IB – III	83-100	29 – 37	29.3	Harrison 2011

(* VGCR is very good CR with mSWAT < 1)

Combination Phototherapy in MF & SS

Therapy	Design	Level of Evidence	Stage	ORR (CR)	Duration (months)	5yr RFS	References
PUVA + Interferon	Case series	2-	IA-IV	68% (45%)		20-75%	Nikolaou 2011
PUVA + Interferon	Prospective Phase II	2++	IB-IIA	98% (84%)	14		Rupoli 2005
PUVA + Interferon	Prospective Phase II	2++	IA-IVA	81% (75%)	32	75%	Chiarion-Sileni 2002
PUVA + Bexarotene	RCT EORTC 21011	2++	IB-IIA	77.% (31%)	5.8	25%	Whittaker 2012
PUVA + Bexarotene	Case Series	2-	I-III	67% (29%)	2-10		Papadavid 2008

Biologic Therapies in MF/SS

Therapy	Design	Level of Evidence	Stage	ORR	CR	Duration	References
Alpha Interferon	Case series	2-	IA-IVB	45-74%	10-27%	NA	Bunn 1989
Alpha Interferon	Case series	2-	IA-IIA	88%	?%	NA	Olsen 1989
Alpha Interferon	Case series	2-	IIB-IVB	29-63%	<?	NA	Kohn 1990
Bexarotene	Phase II	2+	IA-IIA	54%	0%	516d	Duvic 2001b
Bexarotene	Phase II	2+	IIB-IVB	45-51%	0%	299d	Duvic 2001c
DenileukinDiftitox	Phase II	2+	IB-IVA	30%	10%	6.9m	Olsen 2001
DenileukinDiftitox	RCT Phase III	2++	IA-III	44%	10%	>2y (PFS)	Prince 2010
Alemtuzumab HD	Case series	2-	IIB-IV	37-100%	25-47%	6-9m	Lundin 2003; Kennedy 2003
Alemtuzumab LD	Case series	2-	IIB-IV	85%	21%	TTF 12m	Bernengo 2007; Alinari 2008
Zanolumimab	Phase II	2-	IB-IV	56%	0%	81w	Kim 2007
Vorinostat	Phase II	2+	IB-IVA	24-29.7%	0%	106-185d	Olsen 2007b
Romidepsin	Phase II	2+	IB-IVA	34%	6%	13.7-14.9m	Whittaker 2010
Bortezomib	Case series	3	III-IV	70%	10%	7-14m	Zinzani 2007

Stage III: Erythroderma

1. PUVA (+/-IFN alfa)
2. Extracorporeal photophoresis (ECP)
3. Systemic retinoid:
    - classical (isotretinoine) or new (bexarotene)
4. Chemotherapy: i.e low dose methotrexate

Stage IV: extracutaneous disease

1. Chemotherapy (singel agent or combination: MTX, pegylated liposmal doxorubicin, gemcitabine, chlorambucil, Cyclophosphamide, (Pralatrexate), …)
2. Biologicals: denileukin difitox, alemtuzumab, …
3. Hematopoietic stem cell transplantation (auto TX poor results, graft versus lymphoma effect in allo-TX?)

2003, Br J Dermatol, Whittaker et al
2008, Crit Rev Onc Hematol, Zinzani et al
2007, Canc Treat Rev, Whittaker et al
2006, Eur J of Cancer, Trautinger et al

Photopheresis (ECP) in MF/SS

Therapy	Design	Level of Evidence	Stage	ORR	CR	OS
ECP	Systematic review	2+	IB-IV	63%	20%	
ECP	Systematic review	2+	III	35-71%	14-26%	39-100m
ECP	Multiple case series	2+	III	31-86%	0-33%	

Adapted from Scarisbrick 2008

Chemotherapy in MF/SS

Therapy	Design	Level of Evidence	ORR	CR	Med RFS & PFS (mos)	References
Pentostatin	Case series	2+	35-71%	6-32%	9	Cummings 1991, Kurzrock 1999, Dearden 2000, Ho 1999, Foss 1992,
Cladaribine	Case series	2+	28-41%	14-19%	4.5	Kuxel 1996
Fludarabine	Case series	2+	51%	4/35	5.9	Foss 1994
Liposomal Doxorubicin	Case series	2+	80-88%	45-66%	15	Wollina 2003,
Liposomal Doxorubicin	EORTC 21012	2+	40.8%	6.1%	6	Dummer 2012
Gemcitabine	Case series	2+	70-75%	10-22%	10-15	Zinzani 2000, Marchi 2005
Methotrexate	Case series	2+	58%	41%	31	Zackheim, 1996,
Trimetrexate	Case series	2+	45%		Not recorded	Sarris 2002
Pralatrexate	Phase II	2+	45%		Not recorded	Horwitz 2012
Combination chemotherapy	Systematic review	2++	81%	38%	5-41	Bunn 1994)
Chlorambucil	Case series	2	89%	36%	Not recorded	Winkelmann 1984

Treatment Algorithm for MF/SS

Prognostic group (stage)	1st line	2nd line	Experimental
Low risk (IA-IIA)	Expectant or SDT	SDT	
Intermediate risk (IA-IIA)	SDT; PUVA+IFN; PUVA+Bex; TSEBT;	HDACi; Ontak;Trials;	
Stage III erythrodermic	MTX; ECP/IFN/Bex combinations; Trials;	Alemtuzumab;Chemo; TSEB;HDACi; Ontak; Trials;	RicAlloSCT
High risk (IIB/IV)	Radiotherapy (including TSEBT); Chemotherapy; Trials;	HDACi; Ontak; Trials; Palliative therapy;	RicAlloSCT

SDT - skin directed therapy: Topical therapy; Phototherapy (TLO1/PUVA); Radiotherapy;
TSEBT – total skin electron beam therapy; IFN – alpha interferon; Bex – bexarotene;
HDACi – histonedeacetylase inhibitors (vorinostat/romidepsin)*
ECP – extracorporeal photopheresis; MTX – methotrexate; Ontak – Denileukindifititox
RicAlloSCT – reduced intensity conditioned allogeneic stem cell transplant;

Ongoing studies in Belgium:

- **C25001:** A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell

  - U.Z. Leuven - Campus Gasthuisberg (Leuven)
  - Hôpitaux Universitaires Bordet-Erasme - Institut Jules Bordet (Brussels)

- **NCT01728805:** Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (Mogamulizumab) Versus Vorinostat in Subjects With Previously Treated Cutaneous T-Cell Lymphoma

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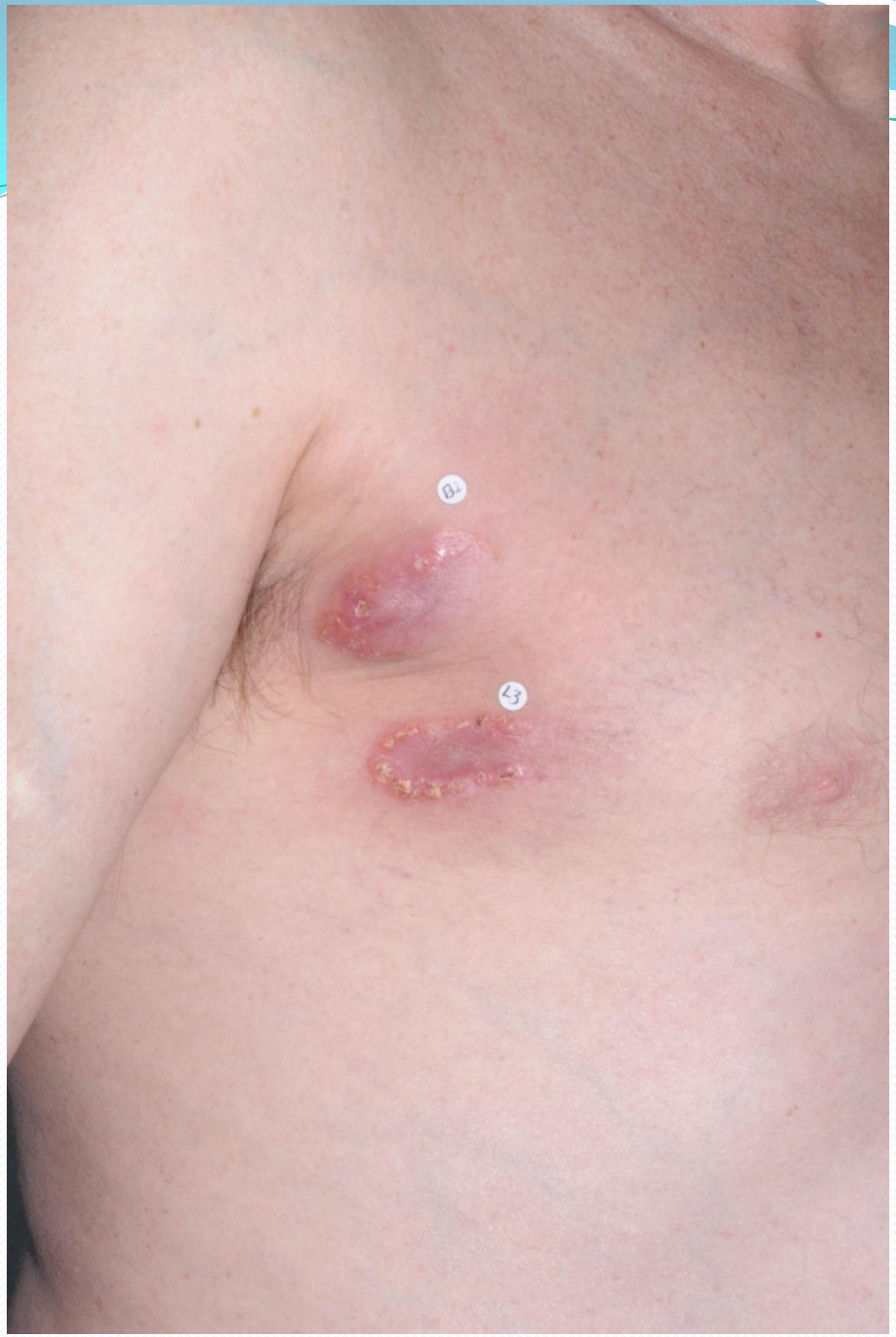

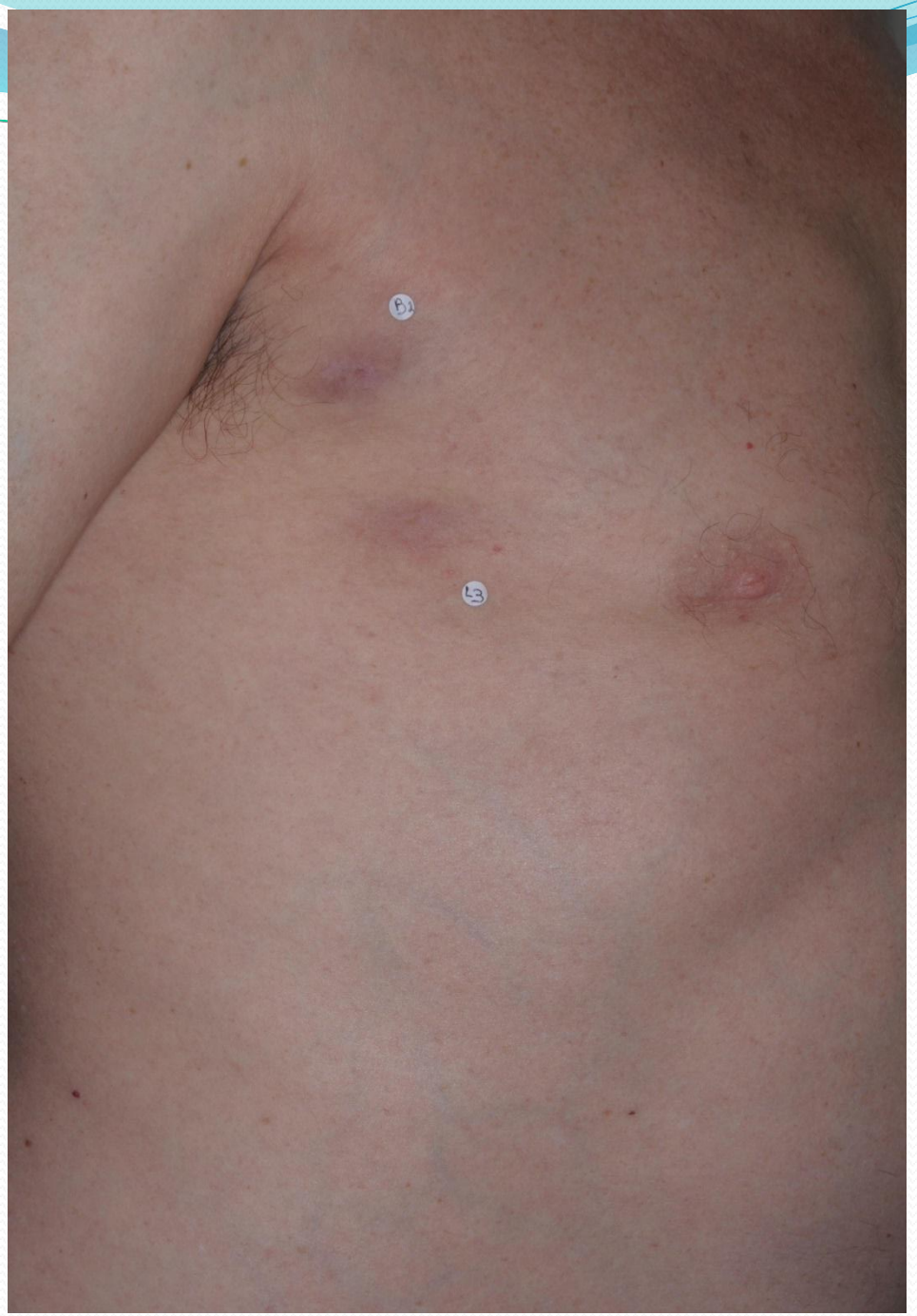

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Treatment Algorithm for Primary Cutaneous CD30+ Lymphoproliferative disorders

Disease	1st line	2nd line	Exp
Lymphomatoid papulosis	Expectant; SDT; Radiotherapy	MTX; IFN;	
Anaplastic large cell lymphoma	Surgical excision; Radiotherapy; MTX	CHOP	Brentuximab

SDT - skin directed therapy: Topical therapy; Phototherapy (TLO1/PUVA); Radiotherapy;
IFN – alpha interferon; MTX – methotrexate; Surgical excision – solitary lesions

Treatment Algorithm for CBCL

Prognostic group (stage)	1st line	2nd line
pcFCL/pcMZL		
Localised T1-T2b	Excision; Expectant; RT	RT; intralesional Rituximab;
Extensive T2c-T3	Chlorambucil;	Rituximab; CVP-R or CHOP-R;
Advanced N1-3 or M1	CVP-R or CHOP-R;	RT; High dose chemo/Auto SCT;
pcDLBCL - leg	CHOP-R 3-6 cycles +/- RT	BSC; RT; High dose chemo/Auto SCT
pcDLBCL – other including Anaplastic/Pleomorphic T cell/Histiocyte rich and Intravascular Large B cell lymphoma	CHOP-R RT as palliation	High dose chemo and Auto SCT

RT: Local skin Radiotherapy;
CHOP-R: Cyclophosphomide Doxorubicin Vincristine Prednisolone Rituximab;
Auto SCT: Autologous Stem cell transplant