Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Cutaneous CD30-positive lymphoproliferative disorders

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ERN-EuroBloodNet Cutaneous Lymphomas

Zürich, Switzerland

Sept 14th, 2020

Co-funded by
the Health Programme
of the European Union

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Advisory board	**Takeda Switzerland, member of the Swiss Advisory board (2018)**
Speaker honoraria	**Stemline, ADO meeting (2020)**

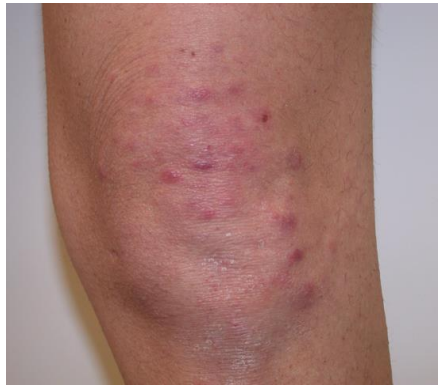
Learning objectives

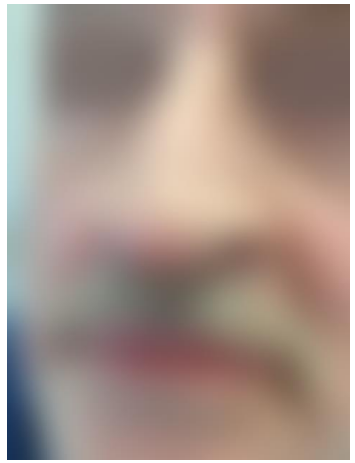
1. To get familiar with the spectrum of cutaneous CD30-positive LPD
2. To understand the importance of clínico-pathological correlation for the diagnostic work-up
3. To summarize the data on treatment of cutaneous CD30-positive LPD

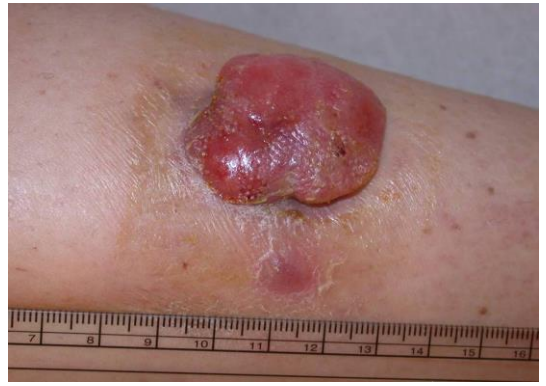
Primary cutaneous CD30+ lymphoproliferative disorders

20-25% of all cutaneous T-cell lymphomas (CTCL)
Second most common form of CTCL

Lymphomatoid papulosis — **Borderline lesions** — **Primary cutaneous anaplastic large cell lymphoma**







Classification

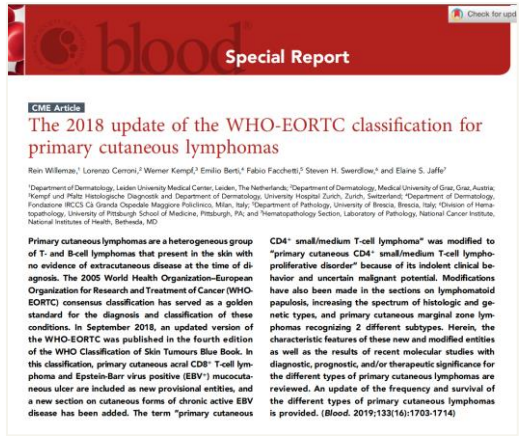
WHO classification (4th ed., 2018)

Swerdlow SH, Campo E, Harris NL et al. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue (revised 4th edition).
Lyon: IARC Press, 2017.

Elder DE, Massi D, Scolyer RA, Willemze R.
WHO Classification of Skin Tumours (4th edition).
Lyon: IARC Press, 2018.

Tumours of haematopoietic and lymphoid origin	
Mycosis fungoides	9700/3
Folliculotropic mycosis fungoides	9700/3
Granulomatous slack skin	9700/3
Pagetoid reticulosis	9700/3
Sézary syndrome	9701/3
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Cutaneous adult T-cell leukaemia/lymphoma	9827/3
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Cutaneous manifestations of chronic active EBV infection	
Hydroa vacciniforme–like lymphoproliferative disorder	9725/1
Extranodal NK/T-cell lymphoma, nasal type	9719/3
Primary cutaneous peripheral T-cell lymphomas, rare subtypes	
Primary cutaneous gamma-delta T-cell lymphoma	9726/3
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous acral CD8+ T-cell lymphoma	9709/3
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	9709/1

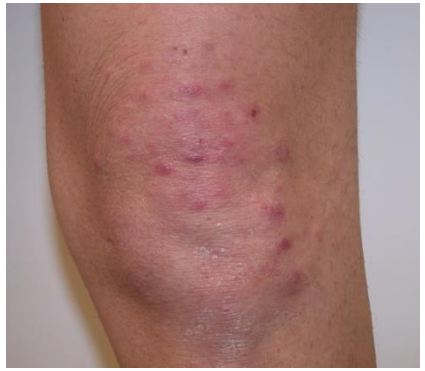
WHO-EORTC classification (updated 2018)



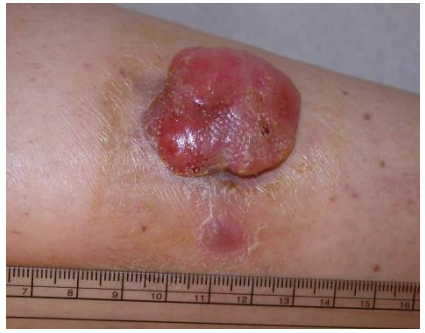
Willemze R, Cerroni L, Kempf W et al.
The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas.
Blood 2019

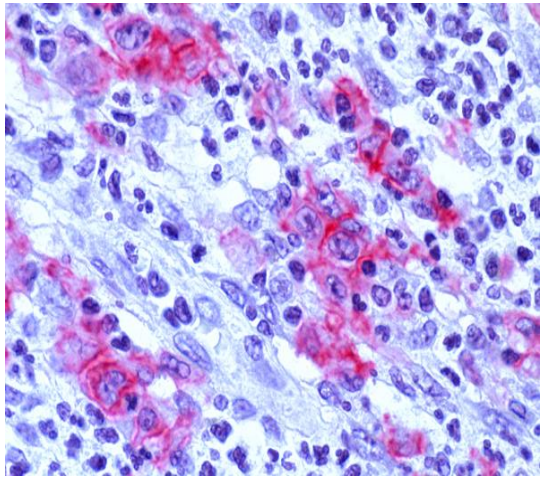
Primary cutaneous CD30+ lymphoproliferative disorders

LYP

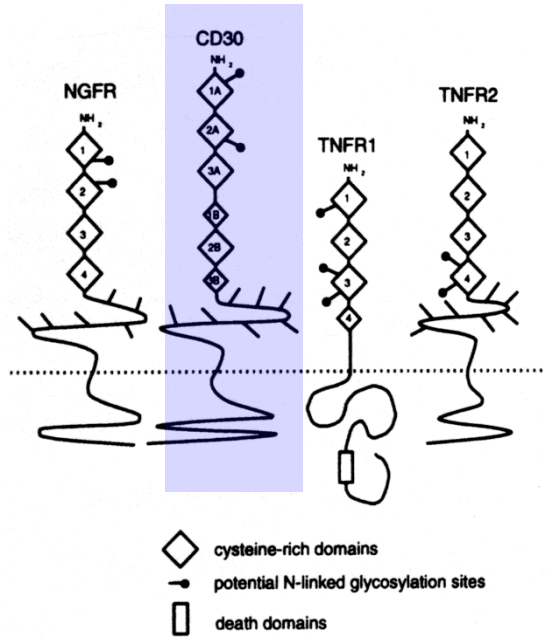


pcALCL





CD30



CD30 involved in growth regulation

Diagnostic marker and therapeutic target

Primary cutaneous anaplastic large cell lymphoma (C-ALCL)

Clinical presentation

Rapidly growing large nodule(s) with ulceration

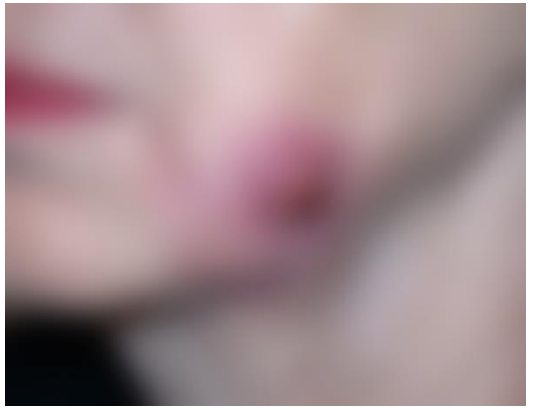
Predilection sites

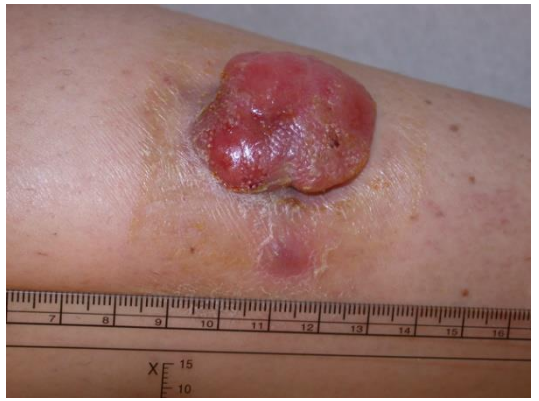
Head and neck, extremities

Distribution

T1: Solitary - 50%
T2: regional - 20-30%
T3: disseminated - 20-30%

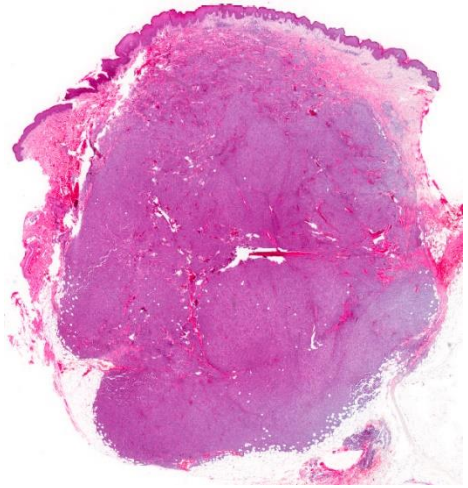
Spontaneous (partial) regression: 6-40%





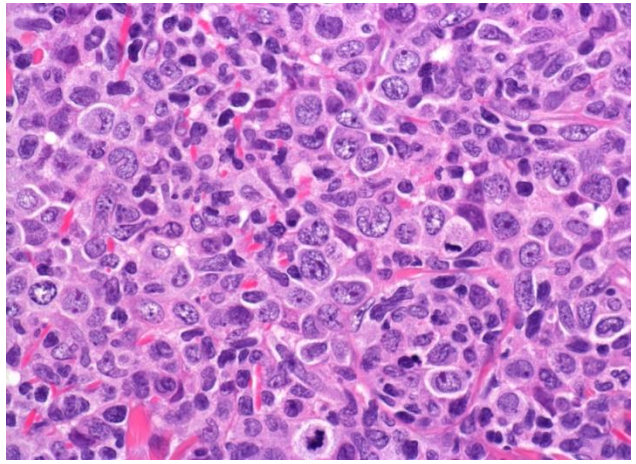
Bekkenk et al. 2000
Liu et al. 2003
Fernandez-de-Misa et al. JEADV 2019

Primary cutaneous anaplastic large cell lymphoma (C-ALCL)

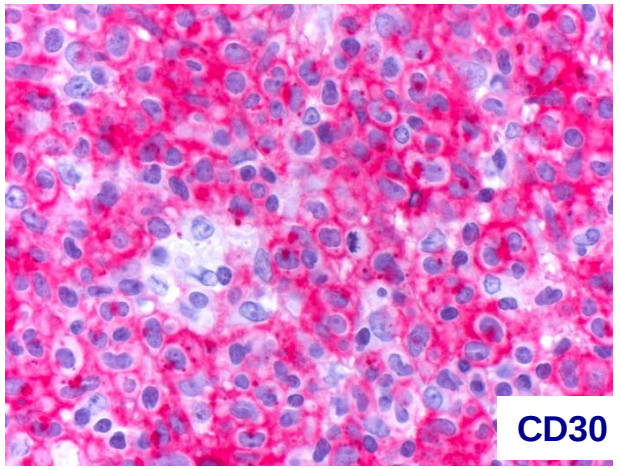


Nodular cohesive infiltrate

Ulceration



Medium-sized to large pleomorphic, anaplastic or immunoblastic tumor cells



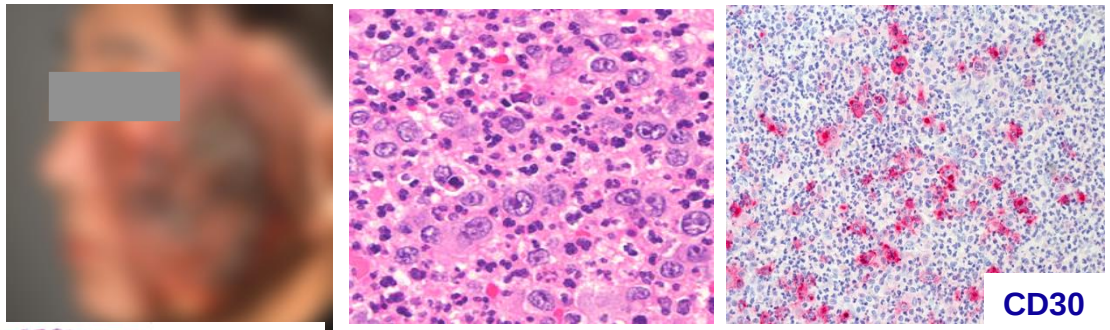
CD30 expressed by >75% tumor cells

Variable expression of T-cell makers

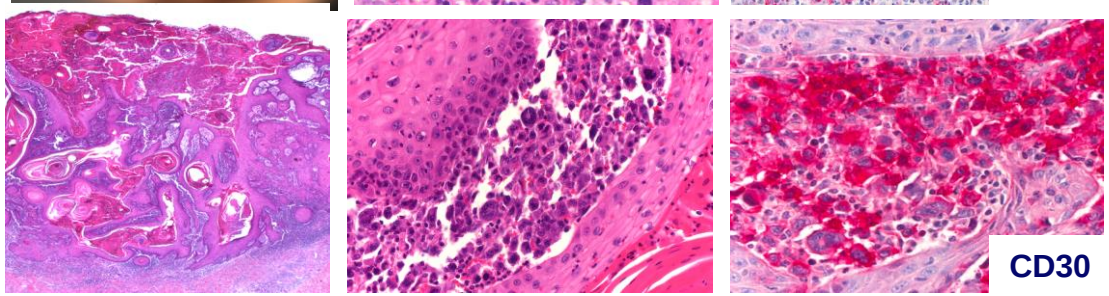
High mitotic activity

C-ALCL variants

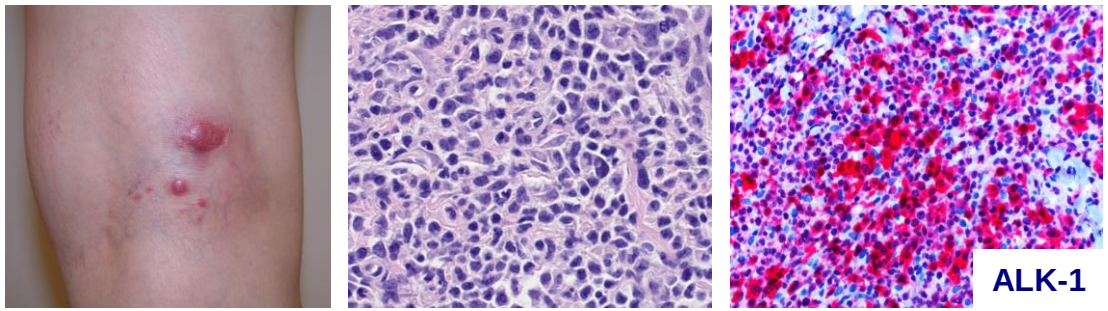
Neutrophil-rich



Epithelial hyperplasia



ALK-positive



Diagnostic marker

CD30+ LPD	**LyP** **ALCL: > 75% CD30+ tumor cells** **Borderline lesions**

CD30 expression in other cutaneous lymphomas

Mycosis fungoides and MF variants

Subcutaneous T-cell lymphoma

Cutaneous gamma/delta T-cell lymphoma

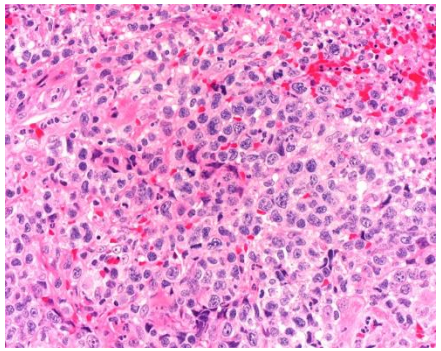
Extranodal NK/T-cell lymphoma

Cutaneous Hodgkin lymphoma

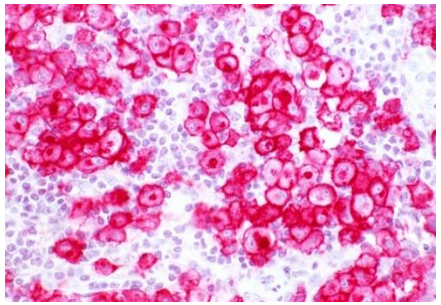
Adult T-cell lymphoma/leukemia

Diffuse large B-cell lymphoma

CD30+ lymphomas



CD30+



Indolent course

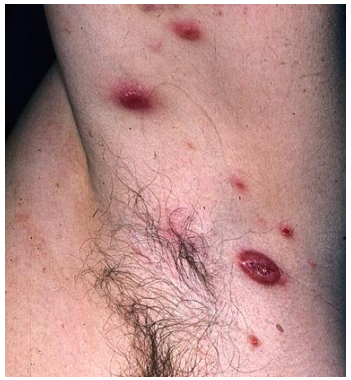
- Lymphomatoid papulosis (type C)
- Primary cutaneous anaplastic large-cell lymphoma

Aggressive course

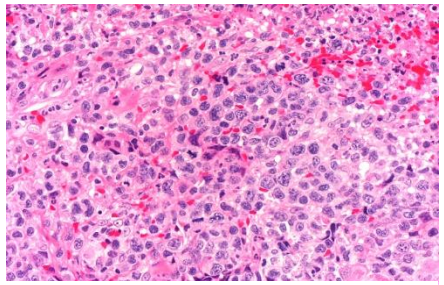
- CD30 LPD in immunosuppressed patients
- Mycosis fungoides (tumor stage)
- Systemic anaplastic large-cell lymphoma
- Adult T-cell lymphoma/leukemia
- Extranodal NK/T-cell lymphoma

Kempf Surg Clin Pathol 2014

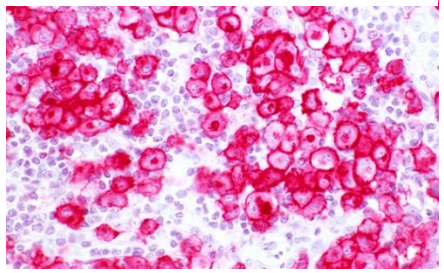
Differential diagnosis

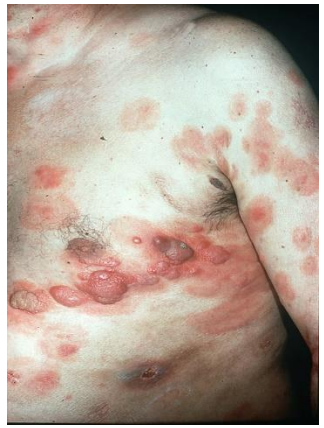


Lymphomatoid papulosis
Multiple papules
Spontaneous regression

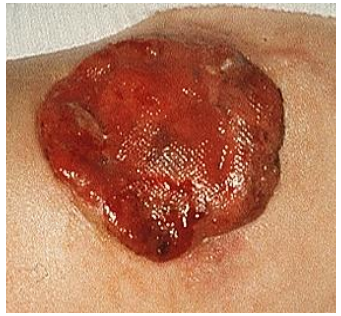


CD30

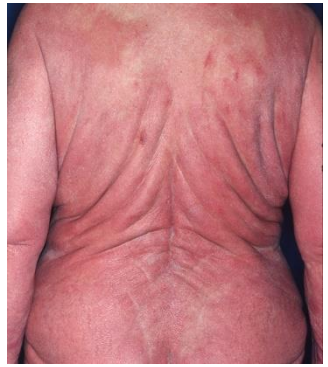




Mycosis fungoides
Patches - Plaques - Tumors



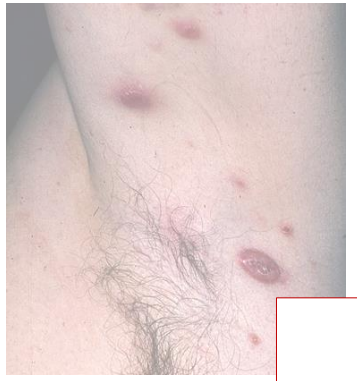
Prmary cutaneous
anaplastic large-cell lymphoma
Solitary nodule



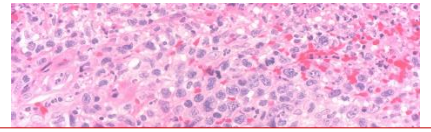
Sézary syndrome
Erythroderma

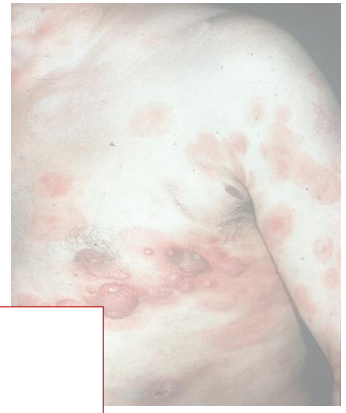
Differential diagnosis

LYP



Observation, UV lig
5-y-SR: 100%





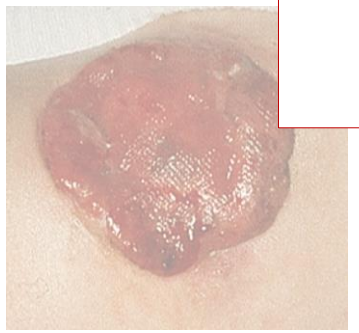
MF

ion, systemic tx
-SR: 20-40%

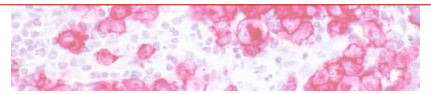
Clinico-pathological correlation

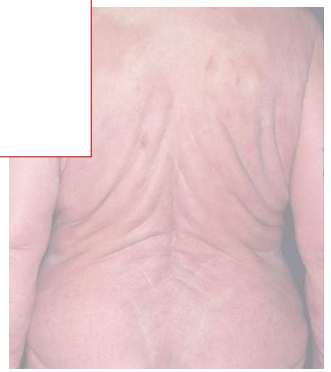
is crucial for the diagnosis

C-ALCL



Excision, radiation
5-y-survival > 90%

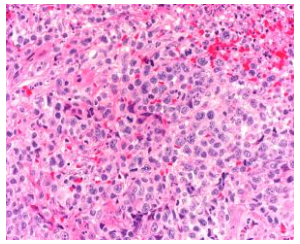




SS

SeS: ECP, Alemtuzumab
5-y-survival < 20%

C-ALCL - diagnostic work up



Clinicopathological correlation

Staging

CT / PET-CT
Peripheral blood
Bone marrow biopsy (?)

Final diagnosis

Exclude:

Mycosis fungoides
Transformation
Immunosuppression-related CD30+ ALCL

Hodgkin lymphoma
Systemic ALCL

C-ALCL – TNM classification

Table 1 ISCL/EORTC proposal on TNM classification of cutaneous lymphoma other than MF/SS

	Classification
T1	Solitary skin involvement.
T1a	A solitary lesion <5 cm diameter.
T1b	A solitary >5 cm diameter.
T2	Regional skin involvement: multiple lesions limited to one body region‡ or two contiguous body regions‡.
T2a	All-disease-encompassing in a <15-cm-diameter circular area.
T2b	All-disease-encompassing in a >15- and <30-cm-diameter circular area.
T2c	All-disease-encompassing in a >30-cm-diameter circular area.
T3	Generalized skin involvement
T3a	Multiple lesions involving two non-contiguous body regions.
T3b	Multiple lesions involving three or more body regions.
N	
N0	No clinical or pathologic lymph node involvement.
N1	Involvement of one peripheral lymph node region† that drains an area of current or prior skin involvement.
N2	Involvement of two or more peripheral lymph node regions† or involvement of any lymph node region that does not drain an area of current or prior skin involvement.
N3	Involvement of central lymph nodes.
M	
M0	No evidence of extracutaneous non–lymph node disease.
M1	Extracutaneous non–lymph node disease present.

†Definition of lymph node regions is consistent with the Ann Arbor system.
‡Refer to original study for detailed description of body areas.[6]

from: Fernandez-de-Misa et al. JEADV 2019

T1 - Solitary lesion

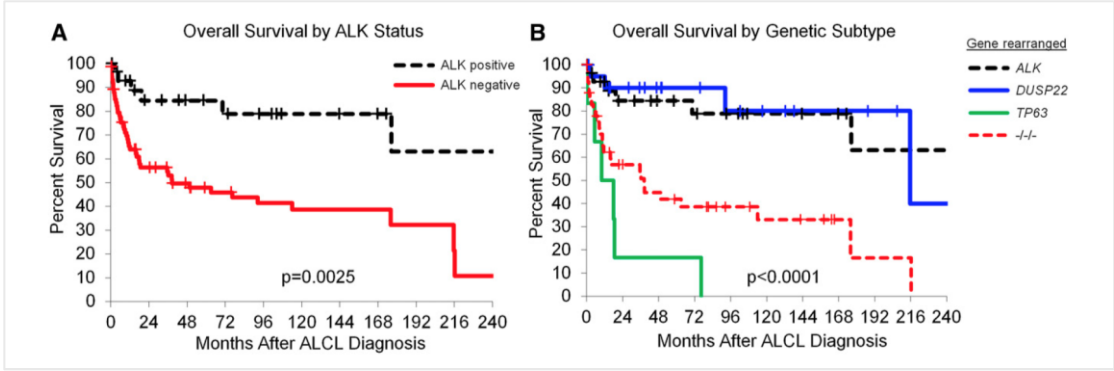
T2 - Regional (one or two contig. body areas): multiple lesions

T3 - Generalized (multiple body areas)

Kim et al. Blood 2007

C-ALCL - genetics and prognosis

Systemic ALCL



From: Parrilla Castellar et al. Blood 2014

PC-ALCL

DUSP22 approx. 30% of the cases.

TP63: very rare - impact (?)

ALK +: very rare - mostly excellent prognosis

Pham-Ledard et al. J Invest Dermatol 2010
Chavan et al. Cancer 2014
Schrader et al. Blood 2016

No impact of genetic alterations on the course and prognosis of pcALCL

C-ALCL – course and prognosis

Course

5-y-SR rate: 90-97%

Recurrence(s): 42-50%

Extracutaneous spread: 1-14%

Death (due to lymphoma): 5-8%

Prognostic factors

Multiple lesions at presentation

Extensive limb disease, esp. legs

Extracutaneous spread:

lymph nodes, visceral organs

Immunosuppression

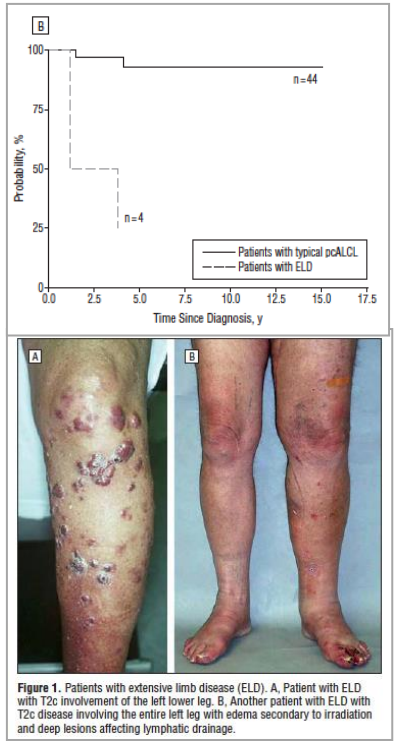


Figure 1. Patients with extensive limb disease (ELD). A, Patient with ELD with T2c involvement of the left lower leg. B, Another patient with ELD with T2c disease involving the entire left leg with edema secondary to irradiation and deep lesions affecting lymphatic drainage.

From: Woo et al. Arch Dermatol 2009

Bekkenk et al. Blood 2000;
Ravat et al. JAAD 2006
Benner and Willemze Arch Dermatol 2009
Woo et al. Arch Dermatol 2009
Seckin et al. Am J Transplant. 2013
Fernandez-de-Misa et al. JEADV 2019
Melchers et al. Blood 2020

CD30+ LPD - treatment

blood

2011 118: 4024-4035
Prepublished online August 12, 2011;
doi:10.1182/blood-2011-05-351346

EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma

Werner Kempf, Katrin Pfaltz, Maarten H. Vermeer, Antonio Cozzio, Pablo L. Ortiz-Romero, Martine Bagot, Elise Olsen, Youn H. Kim, Reinhard Dummer, Nicola Pimpinelli, Sean Whittaker, Emmilia Hodak, Lorenzo Cerroni, Emilio Berti, Steve Horwitz, H. Miles Prince, Joan Guitart, Teresa Estrach, José A. Sanches, Madeleine Duvic, Annamari Ranki, Brigitte Dreno, Sonja Ostheeren-Michaelis, Robert Knobler, Gary Wood and Rein Willemze

erative disorders (CD30+ LPDs) are the second most common form of cutaneous T-cell lymphomas and include lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Despite the anaplastic cytomorphology of tumor cells that suggest an aggressive course, CD30+ LPDs are characterized by an excellent prognosis. Although a broad spectrum of therapeutic strategies has been reported, these have been limited mostly to small retrospective cohort series or tive controlled or multicenter studies have been performed, which results in a low level of evidence for most therapies. The response rates to treatment, recurrence rates, and outcome have not been analyzed in a systematic review. Moreover, international guidelines for staging and treatment of CD30+ LPDs have not yet been presented. Based on a literature analysis and discussions, recommendations were elaborated by a multidisciplinary expert panel of the Cutaneous Organization for Research and Treatment of Cancer, the International Society for Cutaneous Lymphomas, and the United States Cutaneous Lymphoma Consortium. The recommendations represent the state-of-the-art management of CD30+ LPDs and include definitions for clinical endpoints as well as response criteria for future clinical trials in CD30+ LPDs. (*Blood*. 2011;118(15):4024-4035)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

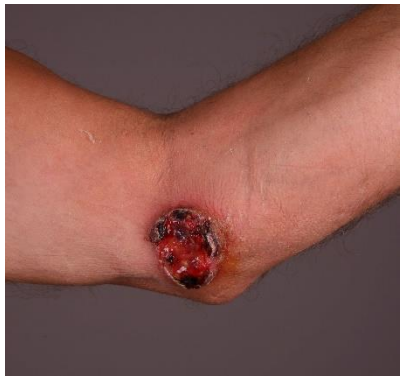
Annals of Oncology 29 (Supplement 4): iv30–iv40, 2018
doi:10.1093/annonc/mdy133

CLINICAL PRACTICE GUIDELINES

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

C-ALCL treatment



Solitary or localized tumors (T1/T2) (75-85%)

↓

Surgical excision
(Safety margins undefined)

Local radiation therapy
(20-46 Gy; 2-3 cm margin; altern. 2x4 Gy)

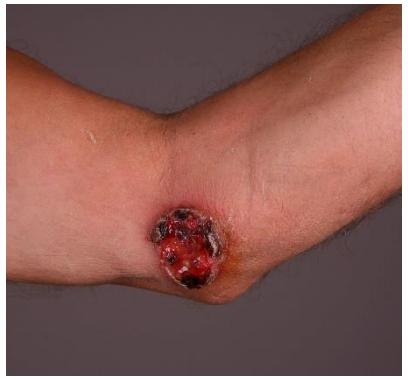
Evidence level:
IV A

Response rates: 95-100%

Relapse: 40%

Million et al. Int J Radiat Oncol Biol Phys 2016
Smith et al. Adv Radiat Oncol 2017
Melchers et al. Br J Dermatol 2018
Fernandez-de-Misa et al. JEADV 2019

C-ALCL treatment



Solitary or localized tumors (T1/T2) (75-85%)

↓

Surgical excision

(Safety margins undefined)

Local radiation therapy

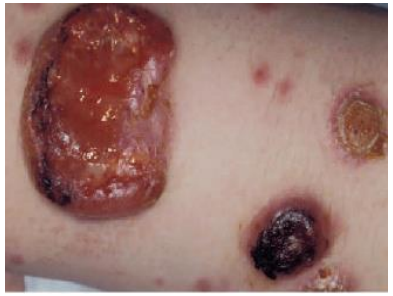
(20-46 Gy; 2-3 cm margin; altern. 2x4 Gy)

No chemotherapy (CHOP) for PC-ALCL !!

RR: 85% - Relapse rate: 90%

Bekkenk et al. Blood 2000
Kempf et al. Blood 2011

C-ALCL treatment



Multifocal tumoral lesions (T3) (15-20%)

MTX low-dose
(20 mg/wk, s.c.)(>5 lesions)

Radiotherapy (2x4Gy)

Brentuximab vedotin

Retinoids (acitretin)
Bexarotene (RXR agonist)
Interferon alpha

Extracutaneous spread (10-14%) *

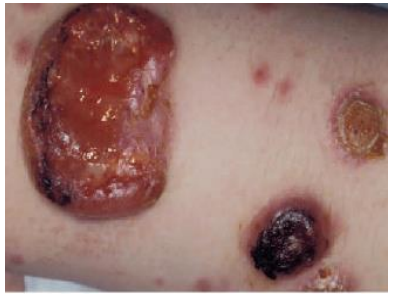
Brentuximab vedotin

Multiagent chemotherapy

Prince et al. Lancet 2017
Melchers et al. Br J Dermatol 2018
Willemze et al. Ann Oncol 2018
Melchers et al. Blood 2020

* **Locoregional LN involvement (4-16%): excellent prognosis -> radiotherapy**

Bekkenk et al. Blood 2000



Methotrexate (20mg/week): **ORR 57%, CR 43% in patients with C-ALCL (> 5 lesions)**

Melchers R et al. Br J Dermatol 2018

Brentuximab vedotin **in patients with CD30-positive LPD showed high response rates in C-ALCL (ORR4 75%; CR 31%)**

Duvic M et al. J Clin Oncol 2015

Prince M et al. Lancet 2017 (ALCANZA study)

Adverse effects **Peripheral sensory neuropathy (approx. 40-45%)**

Multiagent CT **Doxorubicin-based protocols**

CHOP +/- RT, ECHOP, VNCOP-B

Recurrence in 90% pat. -> not recommended for multifocal C-ALCL

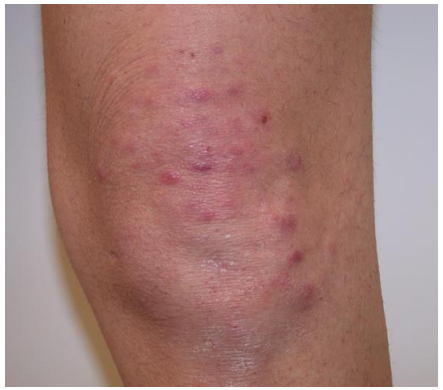
Bekkenk et al. Blood 2000

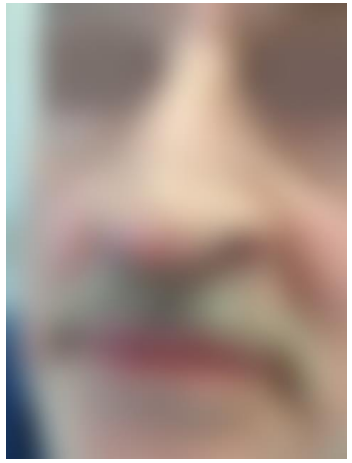
Shenan JAAD 2004

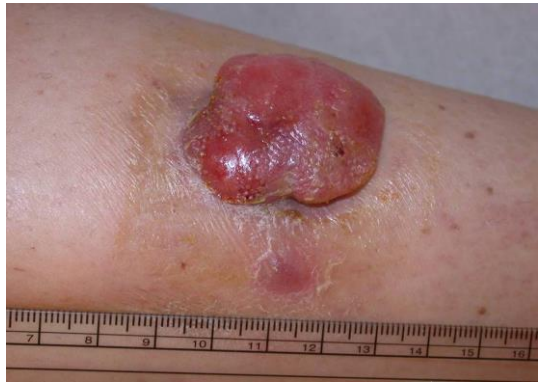
Primary cutaneous CD30+ lymphoproliferative disorders

20-25% of all cutaneous T-cell lymphomas (CTCL)
Second most common form of CTCL

Lymphomatoid papulosis — Borderline lesions — Primary cutaneous anaplastic large cell lymphoma





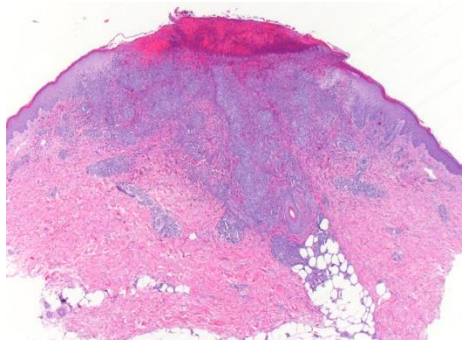


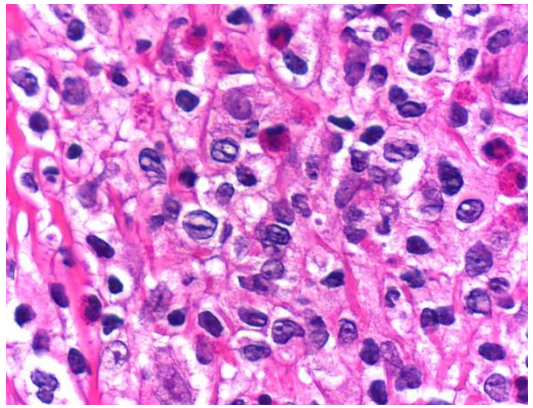
Lymphomatoid Papulosis

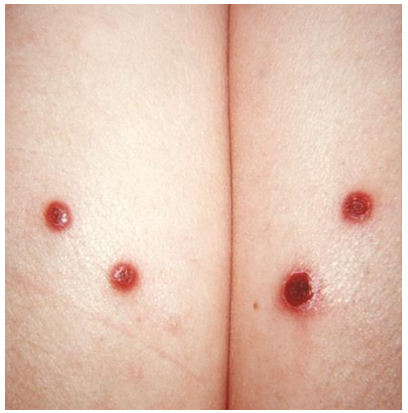
A Continuing Self-Healing Eruption, Clinically Benign—Histologically Malignant

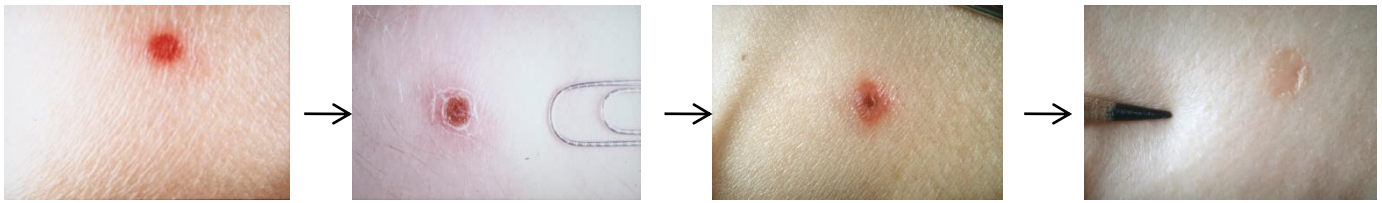
Warren L. Macaulay, MD, Fargo, ND

Arch Dermatol 1968; 97: 23-30





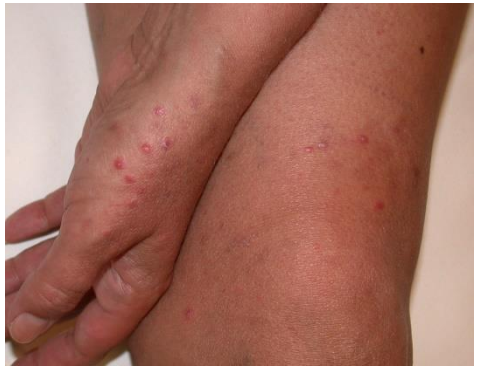


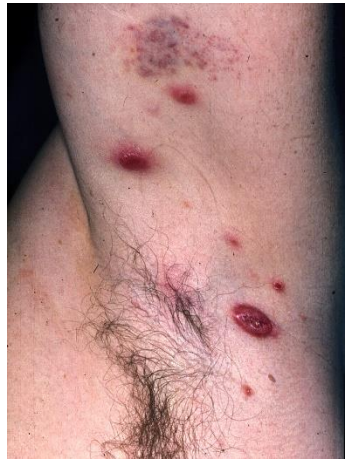


Clinical images by W. L. Macaulay, 1964

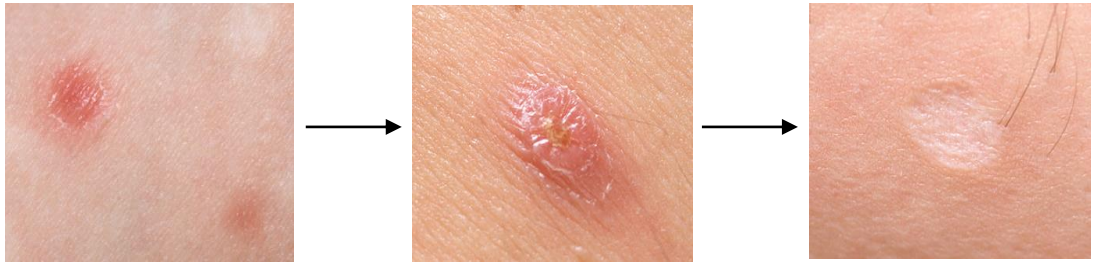
Lymphomatoid papulosis

Localized or multifocal (70%) papules and nodules
up to 1-2 cm, usually asymptomatic



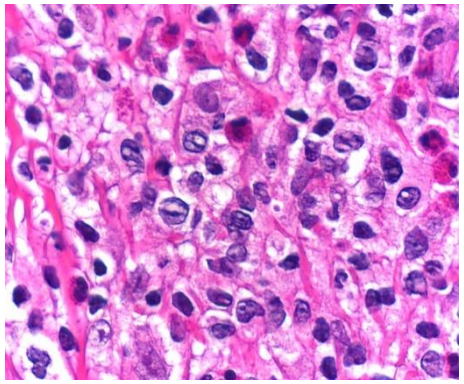


Spontaneous regression of skin lesions after weeks (to months)

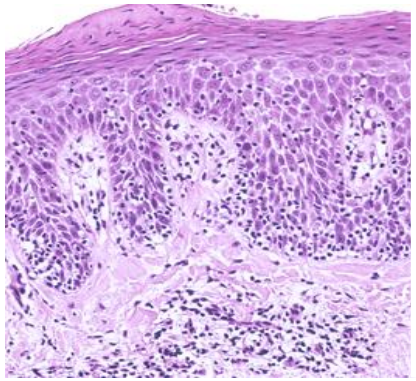


LyP – histological types (WHO classification 2018)

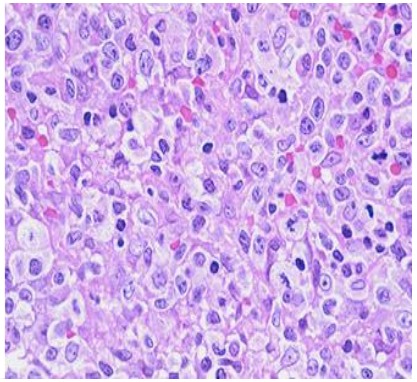
type A



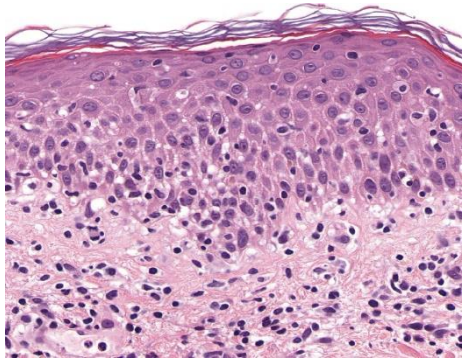
type B



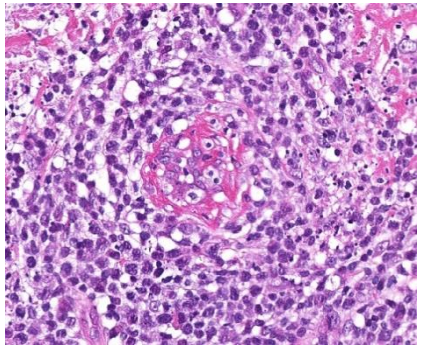
type C



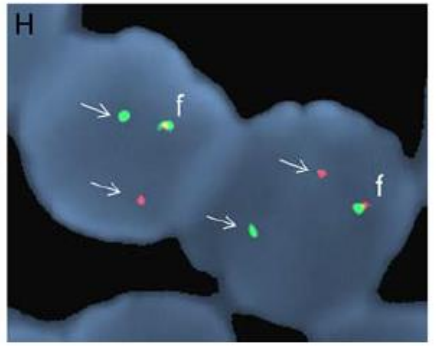
type D



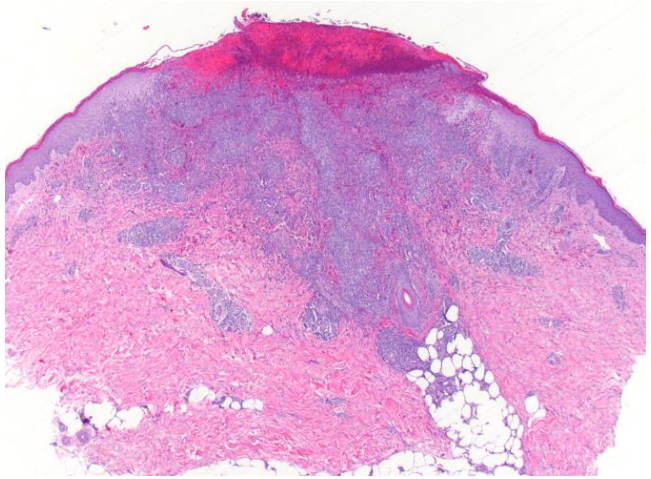
type E

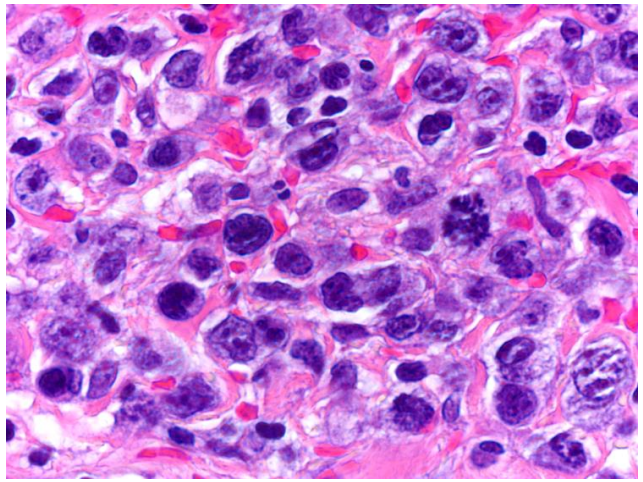


6p25.3



LyP type A

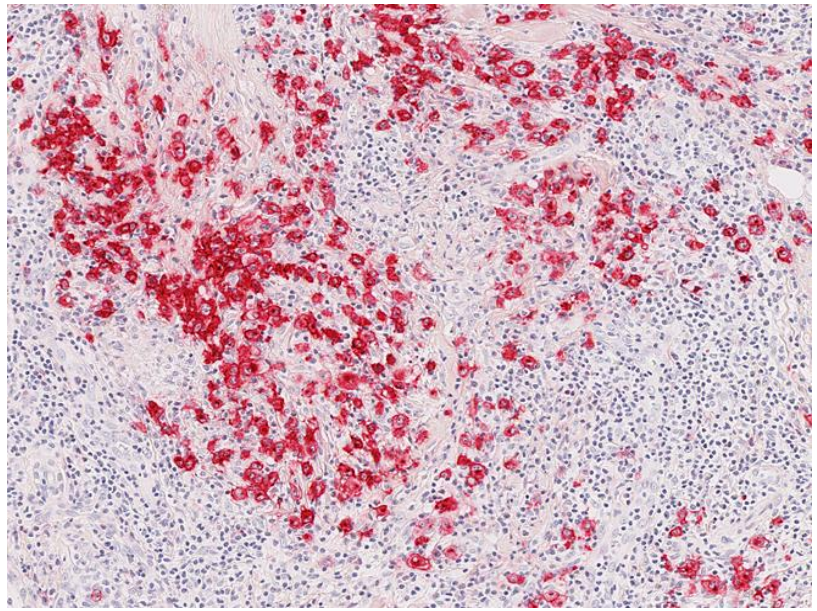




Most common histologic type (80%)

Scattered and in clusters arranged CD30+ pleomorphic or anaplastic cells

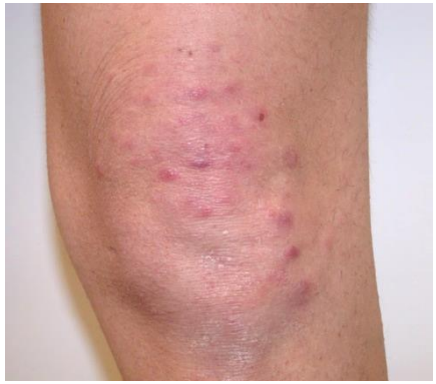
Numerous neutrophils and/or eosinophils

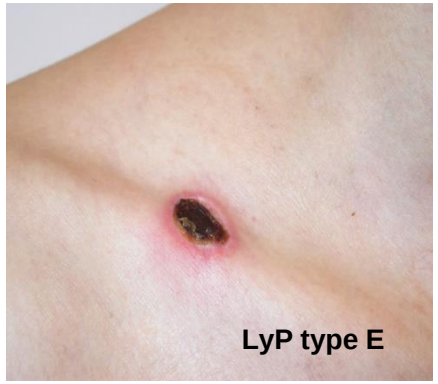


CD30

LyP histological types

- Overlapping histological features in individual lesions
- Various histological types occuring in an individual patient
- No significant differences in clinical presentation (except LyP type E: ulcers)
- All LyP types share the same biologic behaviour
- No prognostic impact

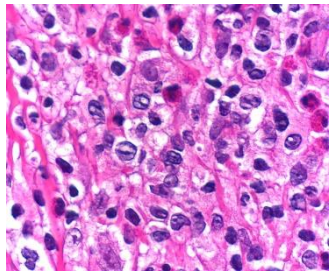
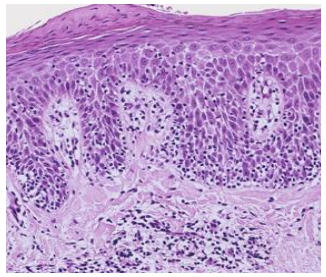
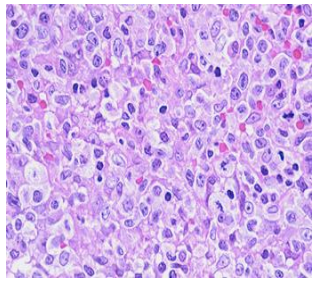
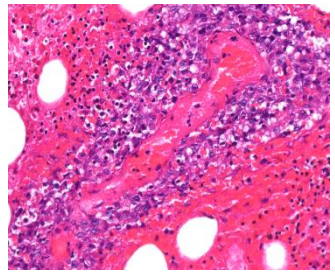




LyP type E

LyP types – differential diagnosis

Type	Histology	Differentialdiagnosis
Type A	Scattered CD30+, large	Hodgkin lymphoma
Type B	Epidermotropic CD30-/+ small	Mycosis fungoides, patch stage
Type C	Cohesive sheets CD30+, large	ALCL
Type D	Epidermotropic CD30+ CD8+ small	AE-CTCL (Berti lymphoma)
Type E	Angioinvasive CD30+ CD8+>CD4+	Extranodal NK/T, GD-TCL
6p25.3	Epidermotropic and dermal nodular	Mycosis fungoides, tumor stage

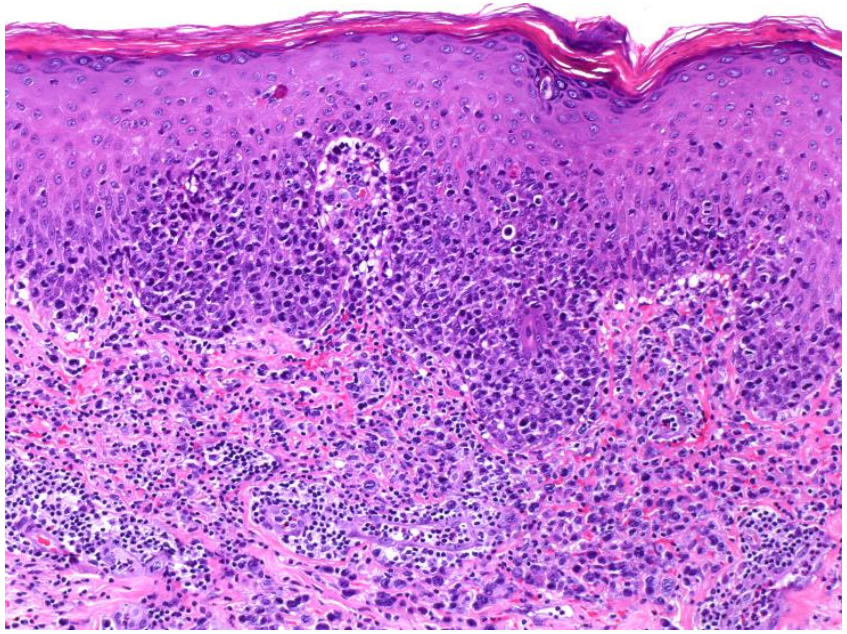





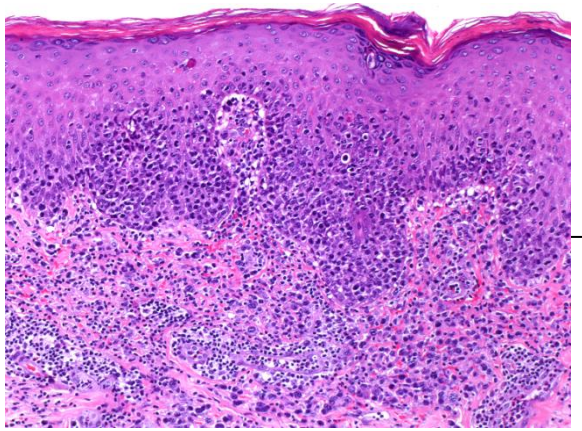
LyP type B

Rare histologic type (<5%)

Epidermotropic small to medium-sized lymphocytes

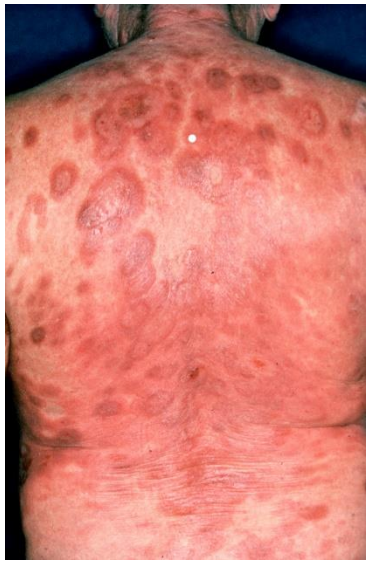
Phenotype: **CD4+ CD30 - / + (0-77%)**





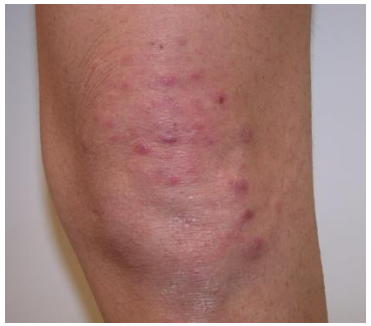
Mycosis fungoides

Patches – plaques

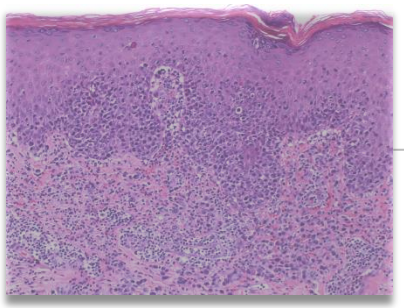


Lymphomatoid papulosis

Papulo-nodular lesions
Spontaneous regression



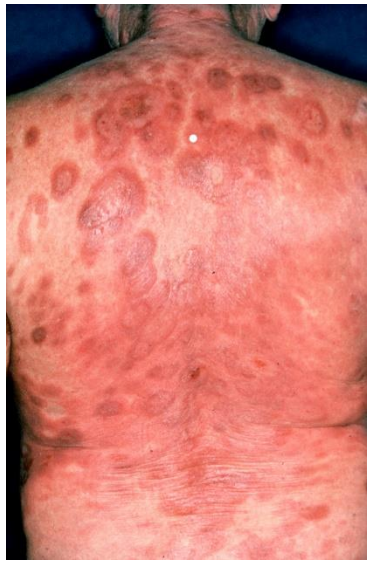
Diagnosis



Clinico-pathological correlation is crucial for the diagnosis

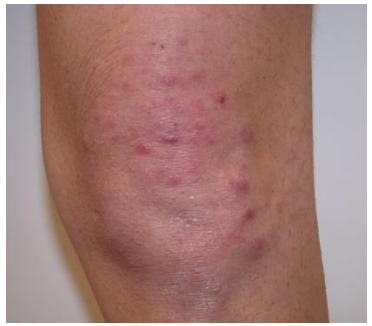
Mycosis fungoides

Patches – plaques

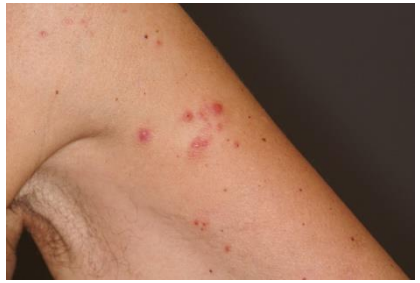


Lymphomatoid papulosis

Papulo-nodular lesions
Spontaneous regression



LyP - therapeutic management

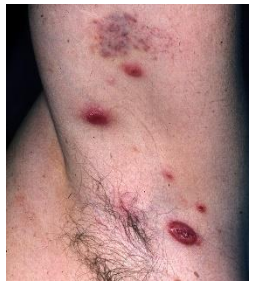


Limited to few lesions

Expectant observation («wait-and-see»)

UV light: Psoralen-UVA
UVB narrow band

Topical steroids (children)

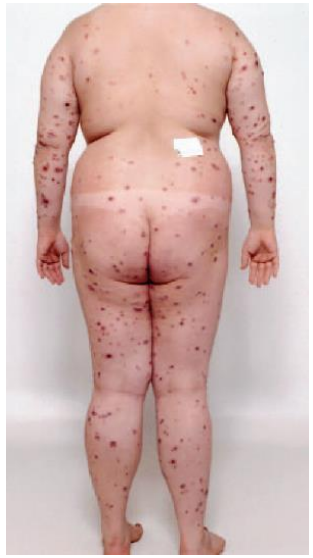


Larger lesions
> 2cm
> 12 weeks

Excision
Radiotherapy

Kempf et al. Blood 2011
Willemze et al. Ann Oncol 2018

Therapeutic strategy in LyP



Generalized or stigmatising lesions

↓

UV light tx: Psoralen-UVA
UVB narrow band

Low-dose methotrexate

Alternatives: retinoids, interferon

Evidence level:
IV A

MTX: 7,5-10mg once a week combined with folic acid 5mg on the following day.
Titration in steps of 2,5 mg per visit.

Bruijn et al. Br J Dermatol 2015

Kempf et al. Blood 2011

Newland et al. JAAD 2015

Willemze et al. Ann Oncol 2018

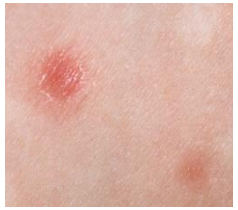
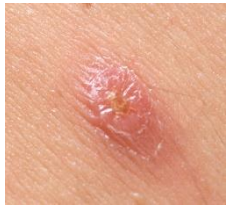
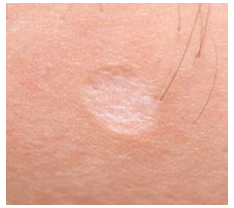
LyP - treatment

Treatment	RR	Relapse	SR
Psoralen-UVA	75%	60-94%	18%
Methotrexate	91-100%	89%	32%
Topical NH2	90%	n.a.	6%
Topical steroids	22%	n.a.	
Observation			45-55%

RR: Response rate; SR: Sustained remission

Note: Short-term benefits should be weighed against potential harmful effects.

LyP - course and prognosis

LyP

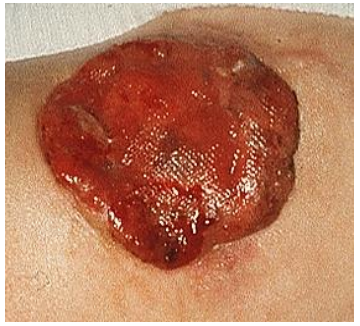
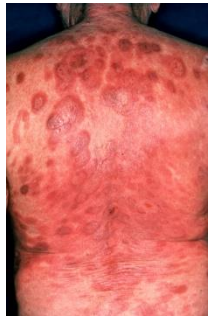
80-85% — **LyP (months, years); Survival rate: 100%**

15-20%

Mycosis fungoides

CD30+ ALCL (cutaneous, nodal)

Other neoplasms (B-cell, myeloid, epithelial)

Beljaards et al. 1993
Kadin et al. 1989
Bekkenk et al. 2000
Boccara et al. 2012
Melchers et al. 2019

LyP – associated hematologic neoplasms

Reference	Associated lymphoma
Thomsen et al. 1987	7/30 (23%)
Wang et al. 1992	16/57 (28%)
Christensen et al. 1994	6/41 (15%)
Bekkenk et al. 2000	23/118 (19%)
Kunishige et al. 2009	34/84 (40%)
Boccara et al. 2012	0/24 (0)
Melchers et al. 2019	78/504 (15.5%)

Increased risk in pat. with LyP to develop second neoplasm.

11.5% of patients died due to second hematologic neoplasm, mostly due to extracutaneous spread of ALCL.

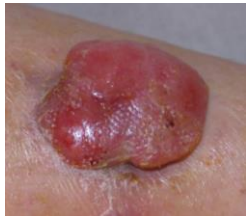
Melchers et al. JEADV 2019

No unambiguous prognostic factors identified in larger studies.

Summary

C-ALCL

1. Solitary > multiple large tumor(s), mostly on head and neck or limbs

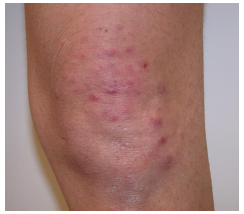


2. Excellent prognosis, but impaired in patients with extensive limb disease or extracutaneous spread beyond loco-regional lymph nodes

3. Excision and radiation are first-line therapies for most PC-ALCL.
For multifocal PC-ALCL methrotrexate or brentuximab vedotin as therapeutic options.

LyP

1. Typical clinical presentation with recurrent papulo-nodular skin lesions undergoing spontaneous regression.



2. Broad histological spectrum - no prognostic impact.

3. Risk of second lymphoid neoplasms - > life-long follow-up.

4. First line modalities for LyP are „wait-and-see“, UV light and MTX low-dose.

Clinico-pathological correlation is crucial for diagnosis and distinction from other cutaneous or systemic T-cell lymphomas.