Current Concepts in Hematopathology

Updates in Cutaneous Lymphoma

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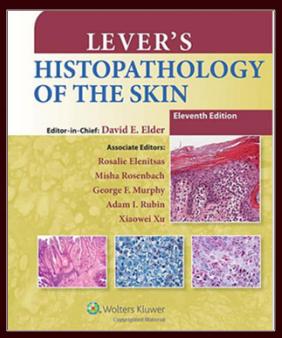
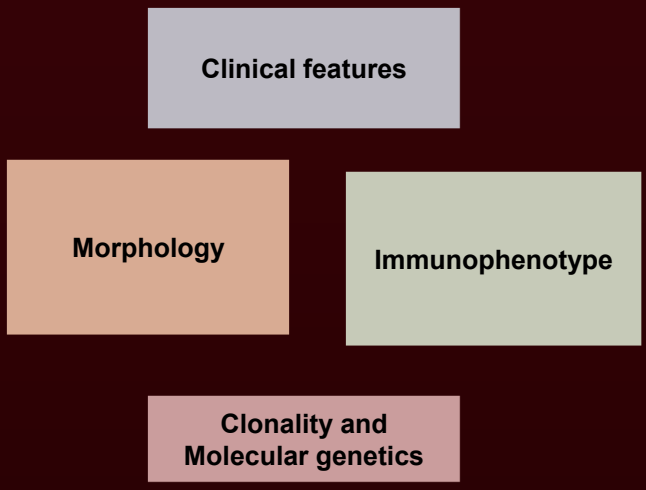
Classification of Primary Lymphomas of Skin

Mature B-cell lineage
Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
EBV+ mucocutaneous ulcer
Mature T-/NK-cell lineage
Mycosis fungoides including variants/subtypes
Sézary syndrome
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder
Hydroa vacciniforme-like lymphoproliferative disorder



Revised WHO classification 2017
Updated WHO-EORTC classification for CL 2018

Integrated Diagnostic Approach is Essential



B-cell lineage

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Primary Cutaneous Marginal Zone Lymphoma

Technically WHO places in greater category of MALT lymphomas
WHO/EORTC classification designates PCMZL

~9% primary cutaneous lymphomas

Single or multiple, clustered erythematous or violaceous papules, plaques, or nodules
most common on **trunk / upper extremities**, or less commonly head and neck region
H&N lesions in older patients may reflect underlying nodal MZL → systemic investigation

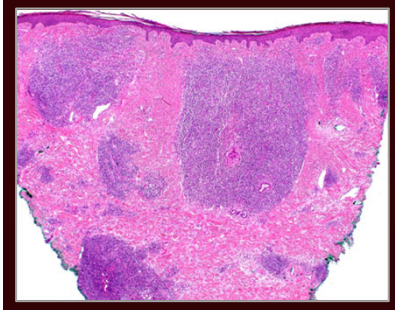
M:F ~2:1, median age 55

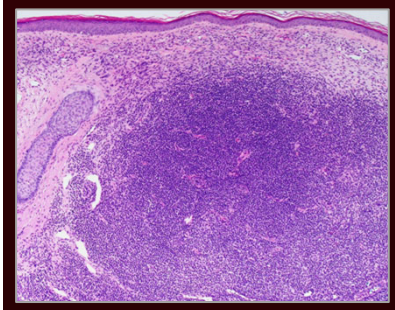
Very indolent, 5-year survival close to 100%. **Spontaneous regression or localized therapy**
Recurrence at same site or distant site in 40% patients. Very rare reports of transformation to DLBCL

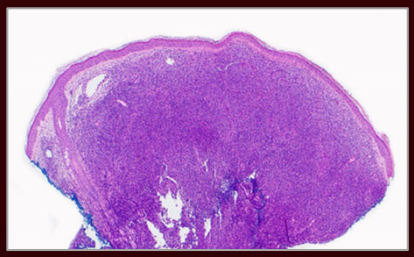
Gerami P, et al. JAmAcadDermatol. 2010

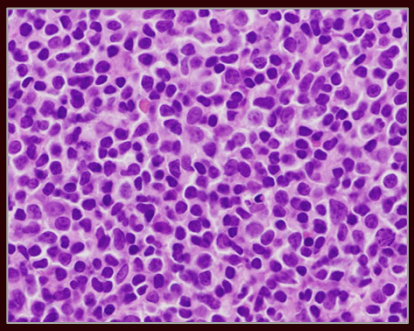
PCMZL

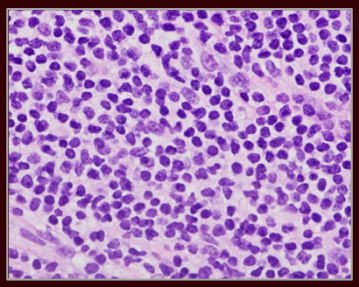
Nodular or diffuse

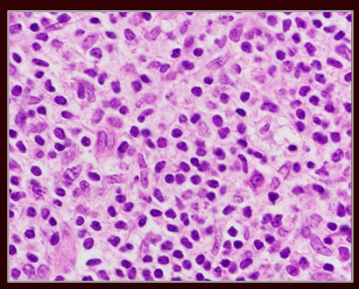








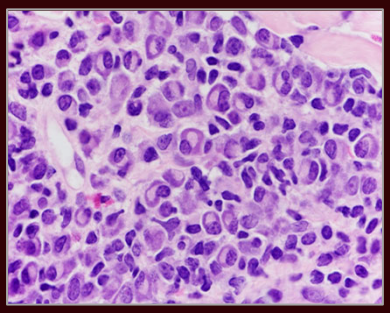


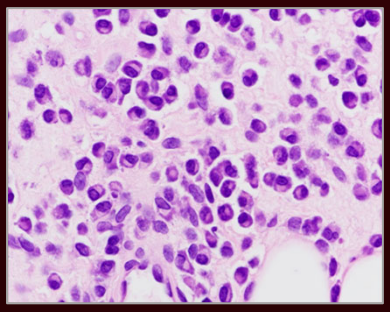


Monocytoid appearance

PCMZL

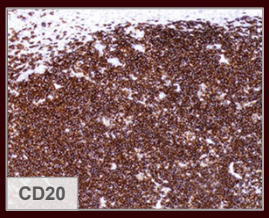
Plasmacytic differentiation

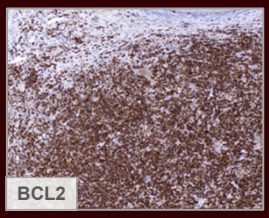


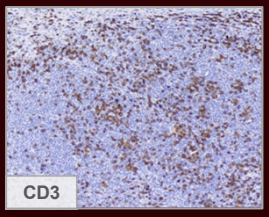


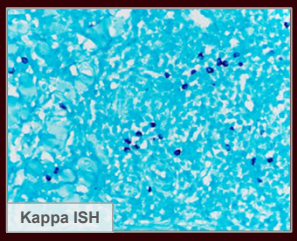
- **Plasma cell–rich variants previously designated:**
  - primary cutaneous immunocytoma
  - follicular lymphoid hyperplasia with monotypic plasma cells
  - extramedullary plasmacytoma
- **commonly associated with older patients and lower-extremity lesions**
- **In endemic areas, may be associated with the tick-associated spirochete Borrelia burgdorferi**

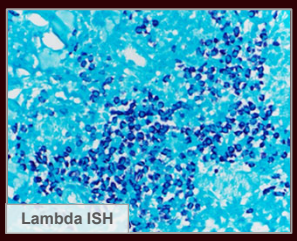
PCMZL







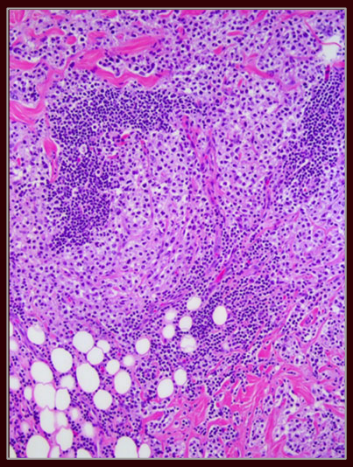




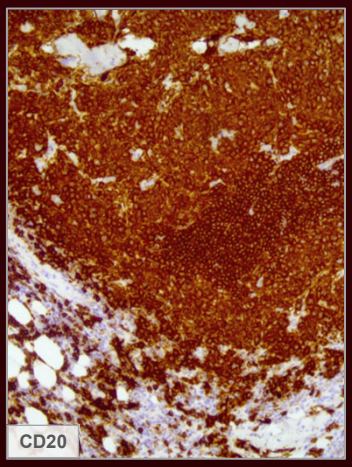
- **B cells positive for BCL2, negative for CD5, CD10, BCL6**
- **Dense population of B cells very helpful clue**
- **No specific marker or immunophenotypic aberrancy (e.g., CD43 not common)**
- **ISH helpful in detecting monotypic plasma cells / plasmacytoid cells**

PCMZL

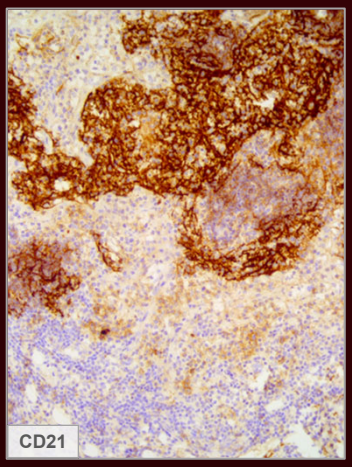
CD21/CD23 can highlight disrupted FDC meshworks



Monocytoid appearance



Dense B-cell population



Expanded/disrupted FDC meshworks

PCMZL : Genetics and new subtypes

- ❑ ~85% **clonal IGH rearrangements**; up to 35% also have **clonal TCR rearrangements**
- ❑ Minority show (not skin specific):
  t(14;18) : includes translocations between *IGH@* and *MALT1* as well as *IGH@* and *BCL2*
  t(3;14) : *FOXP1* on chromosome 3 partners with *IGH@*
  t(11;18)(q21;q21)

Recent studies have suggested that there are two distinct subtypes of PCMZL

IgH class-switched (more common) : IgG >IgA

- ❑ half show IgG4 heavy chain restriction
- ❑ T cell-predominant background enriched for TFH type 2-like cytokines; lack CXCR3 expression
- ❑ Monotypic plasma cells at the periphery of the infiltrate

IgM+ B-cell predominant (less common) :

- ❑ expresses IgM and often CXCR3
- ❑ more likely to involve the subcutis, with plasma cells diffusely scattered, and uniformly show follicular colonization
- ❑ IgM+ cases share features with non-cutaneous MZLs and often associated with extracutaneous disease

Edinger JT, et al. Am J Surg Pathol. 2010
van Maldegem F, et al. Blood. 2008
Carlsen ED, et al. Am J Surg Pathol. 2019

PCMZL – Differential Dx.

overlapping features with both neoplastic and non-neoplastic cutaneous B-cell infiltrates

PCFCL:

- ❑ If there is colonization of follicles and increased centroblasts in PCMZL
- ❑ Expression of BCL6 and CD10 outside of follicles would favor PCFCL

Benign reactive infiltrate:

- ❑ Secondary to antigens (e.g., arthropod bite) or drug; close clinical correlation required
- ❑ Clonal IGH rearrangements can be seen in both
- ❑ Dense / infiltrative B-cell growth and clonal plasma cells favor PCMZL, otherwise often no antigenic aberrancy

PCSM-TLPD:

- ❑ Marked CD4 predominance
- ❑ TFH markers

Primary Cutaneous Follicle Center Lymphoma

Cutaneous lymphoma derived from follicular center B cells including centrocytes and centroblasts

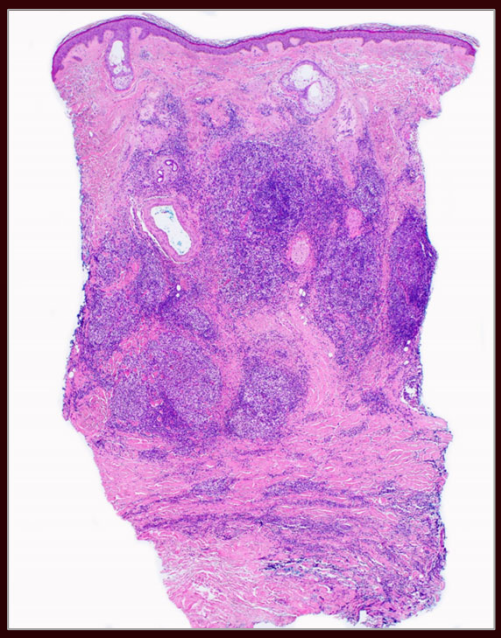
~10% primary cutaneous lymphomas

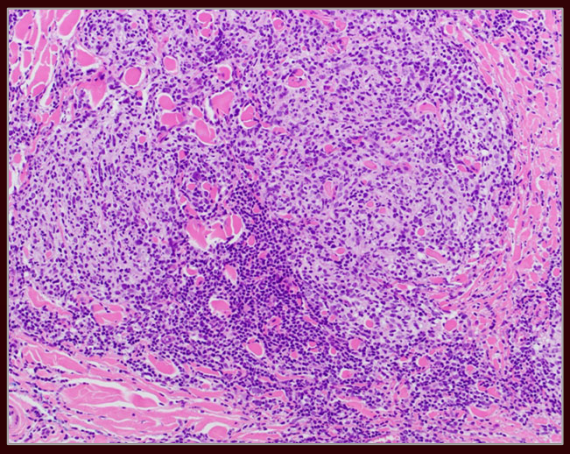
Typically one to several red- to plum-colored plaques or nodules/tumors, often on **head or trunk**

Indolent course
Solitary/localized lesions treated with radiation therapy or excision
Tend to remain localized in skin, though relapse in ~30% cases
5-year survival >95% despite variations in clinical/morphologic features (localized vs. multifocal; follicular or diffuse growth; number of centroblasts)

Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias".
Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.
Courtesy of Cecilia Larocca, MD. Dana-Farber Cancer Institute, Boston, MA

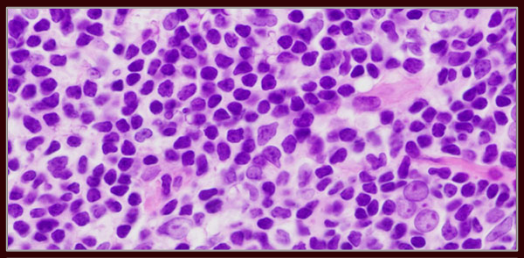
PCFCL

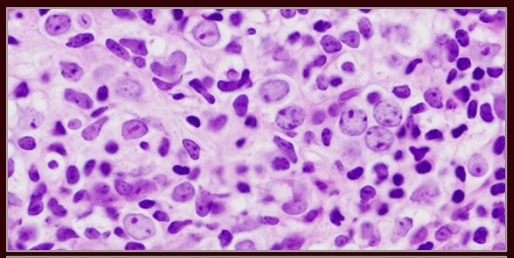


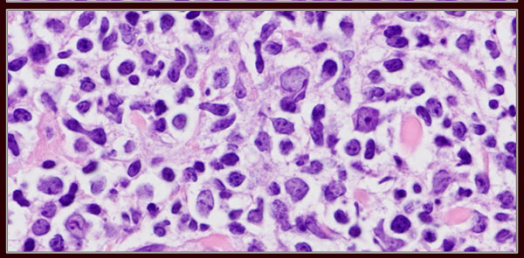


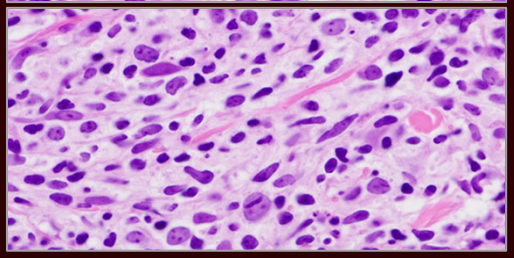
- Dermal nodular aggregates, diffuse pattern, or combination
- Follicles are depolarized, often devoid of mantle zones, and do not contain tingible-body macrophages
- Diffuse areas may splay dermal fibers and demonstrate sclerosis

PCFCL







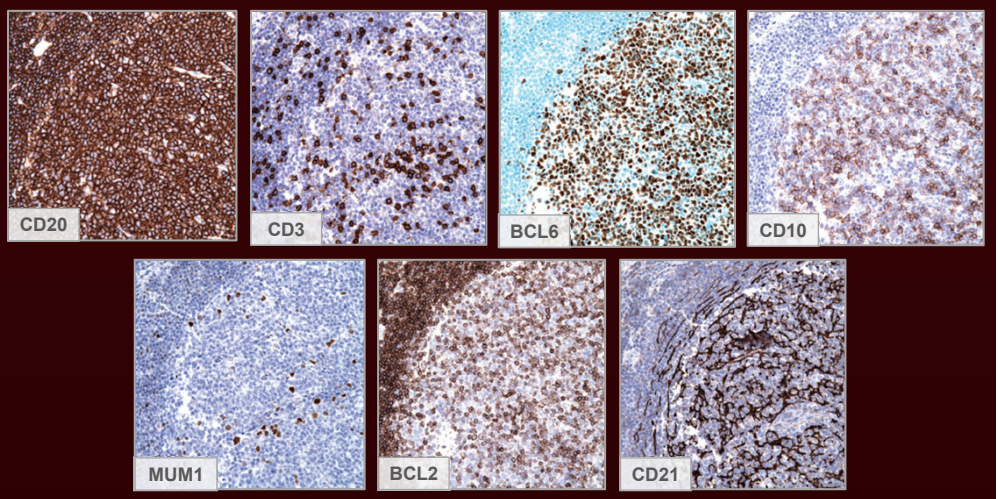


- Medium- to large-sized centrocytes, and admixed centroblasts (can sometimes predominate); occasional spindled morphology

Histologic grading not performed, as the growth pattern and number of centroblasts do not have prognostic relevance in the skin

monotonous sheets of centroblasts or immunoblasts may be PCLBCL-LT

PCFCL



- positive for CD20, CD19, CD79a
- BCL6 positive
- +/-CD10 more common with follicular architecture
- BCL2 often weak to negative
- FDC markers (CD21/CD23) highlight follicular pattern

- Ki67 proliferation can be high

Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

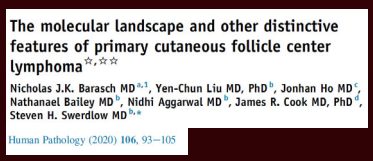
PCFCL : Genetics

- ❑ Germinal center–derived B cells; **clonal IGH** often detected
- ❑ **t(14;18) in a subset** of cases
  more often with FISH compared to PCR
- ❑ BCL2 protein ICH can be detected in cases without t(14;18)

Kim BK, et al. Am J Surg Pathol. 2005
Vergier B, et al. Am J Surg Pathol. 2004
Streubel B, et al. Am J Surg Pathol. 2006

PCFCL : Genetics

increasing recent evidence showing PCFCL harbor a distinctive genetic profile compared to systemic FL

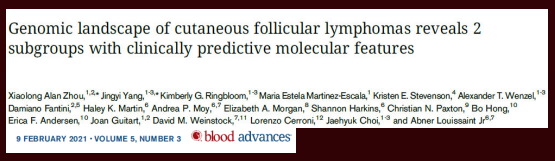

The molecular landscape and other distinctive features of primary cutaneous follicle center lymphoma☆,☆☆

Nicholas J.K. Barasch MD[a,1], Yen-Chun Liu MD, PhD[b], Jonhan Ho MD[c], Nathanael Bailey MD[b], Nidhi Aggarwal MD[b], James R. Cook MD, PhD[d], Steven H. Swerdlow MD[b,*]

Human Pathology (2020) 106, 93–105

- most common somatic mutation *TNFRSF14* (40%, plus 10% with 1p36 deletions)

Small subset with *CREBBP* (25%)


Genomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features

Xiaolong Alan Zhou,[1,2,*] Jingyi Yang,[1-3,*] Kimberly G. Ringbloom,[1-3] Maria Estela Martinez-Escala,[1] Kristen E. Stevenson,[4] Alexander T. Wenzel,[1-3] Damiano Fantini,[2,5] Haley K. Martin,[6] Andrea P. Moy,[6,7] Elizabeth A. Morgan,[8] Shannon Harkins,[6] Christian N. Paxton,[9] Bo Hong,[10] Erica F. Andersen,[10] Joan Guitart,[1,2] David M. Weinstock,[7,11] Lorenzo Cerroni,[12] Jaehyuk Choi,[1-3] and Abner Louissaint Jr[6,7]

9 FEBRUARY 2021 • VOLUME 5, NUMBER 3 blood advances

- Frequent *TNFRSF14* mutations (LOF) and chromosome 1p36 copy number loss
- Skin-restricted PCFCL lacked chromatin-modifying genes *CREBBP* or *KMT2D*

Barasch NJK, et al. Hum Pathol. 2020
Zhou XA, et al. Blood Adv. 2021

PCFCL – Differential Dx.

Reactive (B-cell cutaneous lymphoid hyperplasia) :

- ❑ Well-formed mantle zones, polarized germinal centers with tingible-body macrophages, and numerous mitotic figures versus the monomorphous follicles of PCFCL
- ❑ IGH clonality studies –exceptions exist

Nodal FL, secondarily involving skin :

- ❑ no absolute morphologic or immunophenotypic features
- ❑ If **strong BCL2 and CD10, and/or t(14;18)** raise possibility of systemic FL
- ❑ If lacking staging information, a differential diagnosis should be provided

PCMZL :

- ❑ If follicular colonization or with reactive follicles; immunophenotype of interfollicular cells helpful (negative for CD10 and BCL6 in PCMZL)

PCFCL

Genomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features

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9 FEBRUARY 2021 · VOLUME 5, NUMBER 3 blood advances

A

Proposed Prognostic Criteria for Systemic Spread
Positivity for ≥ 2 of the following criteria favors systemic spread. **Negativity for ≥ 2** of the following criteria favors skin restriction.
Mutations in ≥ 2 of the following genes: *CREBBP, KMT2D, EZH2, EP300*
BCL2 gene rearrangement
Low proliferation index (Ki-67 < 30%)

B

	SCFL									
	SC01	SC02	SC03	SC04	SC05	SC06	SC07	SC08	SC09	SC10
Mutations in ≥ 2: *CREBBP (C), KMT2D (K), EZH2 (Z), EP300 (P)*	3 CKP	3 CKZ	2 CZ	1 C	2 CK	1 P	ND	ND	ND	ND
BCL2 Rearrangement	+	+	ND	+	+	+	+	+	+	+
Ki-67 < 30%	30%	10%	10%	20%	20%	20%	20%	70%	10%	20%
Number of Criteria Met	+2	+3	+2	+2	+3	+2	+2	N	+2	+2

	PCFCL, Systemic			
	PS01	PS02	PS03	PS04
Mutations in ≥ 2: *CREBBP (C), KMT2D (K), EZH2 (Z), EP300 (P)*	2 CK	1 Z	ND	ND
BCL2 Rearrangement	+	+	–	–
Ki-67 < 30%	20%	20%	10%	20%
Number of Criteria Met	+3	+2	N	+2

	PCFCL, Skin Restricted																								
	PR01	PR02	PR03	PR04	PR05	PR06	PR07	PR08	PR09	PR10	PR11	PR12	PR13	PR14	PR15	PR16	PR17	PR18	PR19	PR20	PR21	PR22	PR23	PR24	PR25	PR26
Mutations in ≥ 2: *CREBBP (C), KMT2D (K), EZH2 (Z), EP300 (P)*	0 –	1 K	0 –	1 K	0 –	2 CK	0 –	0 –	1 C	0 –	0 –	1 Z	0 –	1 P	0 –	0 –	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
BCL2 Rearrangement	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ki-67 < 30%	40%	50%	50%	ND	50%	60%	ND	50%	ND	70%	50%	50%	60%	60%	60%	50%	ND	50%	60%	40%	50%	5%	10%	50%	ND	ND
Number of Criteria Met	-2	-2	-2	-2	-2	-2	-2	-3	-2	-3	-3	-3	-2	-3	-3	-3	N	-2	-2	-2	-2	N	N	-2	N	N

Cases marked as N are indeterminate as one of the criteria was not available and only 1 of 2 remaining criteria were fulfilled

Predict systemic spread

Predict PCFCL with skin restriction

Zhou XA, et al. Blood Adv. 2021

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

PCLBCL-LT: **aggressive primary cutaneous large B-cell lymphoma** with a diffuse, cutaneous infiltrate of immunoblasts or centroblasts, and strong expression of MUM1 and BCL2

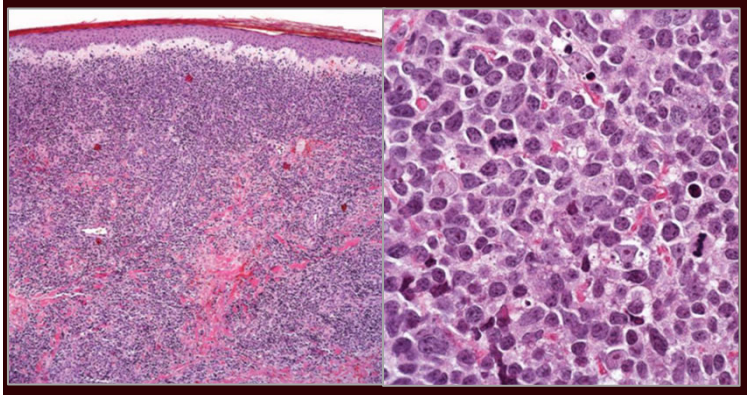
Solitary or multiple localized reddish-brown tumors or plaques
typically presents on the leg, though can arise at any cutaneous site

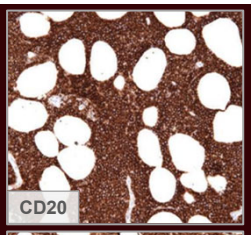
Usually **elderly, with a female predominance**

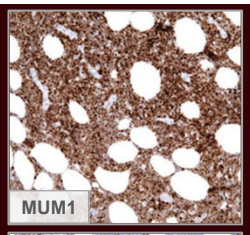
Overall prognosis is intermediate to poor; 5-year survival 55%
with tendency to disseminate to extracutaneous sites
Ulceration or multiple lesions at presentation have adverse prognosis

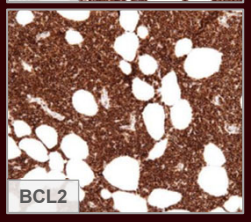
Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias". Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.
Courtesy of Nicole R. LeBoeuf, MD, MPH. Dana-Farber Cancer Institute, Boston, MA

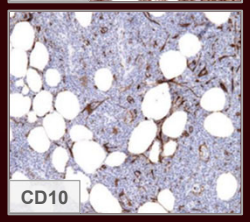
PCLBCL-LT

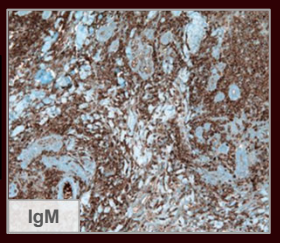












- Dense, monotonous infiltrate of predominantly medium- to large-sized cells with round nuclei and prominent nucleoli
- Frequent mitotic figures and few background lymphocytes
- Diffuse involvement of dermis, with adnexal structures effaced; can have focal epidermotropism

- Positive: MUM1, BCL2, +/- BCL6
- Negative CD10
- Express IgM or less common IgD
- Strong FoxP1 expression
- Ki67 proliferation typically high

Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

PCLBCL-LT : Genetics

- ❑ differentiation profile of **post–GC (activated) B cells**
- ❑ Molecular signature distinct from other cutaneous B-cell lymphomas
  most similar to ABC subtype of systemic DLBCL, resembling pCNS lymphoma
- ❑ t(14;18) is not found
- ❑ frequent translocations similar to systemic DLBCL involving ***IGH@*, *MYC*, and *BCL6* loci**, as well as presence of ***MYD88* L265P mutation**, or mutations in other **genes activating the NF-kB pathway**
- ❑ ~75% exhibit **inactivation of 9p21.3/*CDKN2A*** via deletion or promoter hypermethylation
  poor prognostic indicator

PCLBCL-LT – Differential Dx.

PCFCL, diffuse type :

- ❑ Distinction can be histologically difficult when there is admixture of centrocytes and centroblasts or predominance of centroblasts
- ❑ IHC essential: **MUM1, BCL2, IgM**

systemic DLBCL secondarily involving skin :

- ❑ Clinical/radiologic correlation

EBV-Positive Mucocutaneous Ulcer

EBV+ MCU newly recognized **immunodeficiency-associated** B-cell LPD
localized cutaneous or mucosal ulcerated lesions, typically with an **indolent course**

Setting of advanced age-related immunosenescence or iatrogenic immunosuppression

Isolated well-demarcated ulcerative lesion involving the skin, oropharyngeal mucosa or GI tract

When age-related, median age >70 years

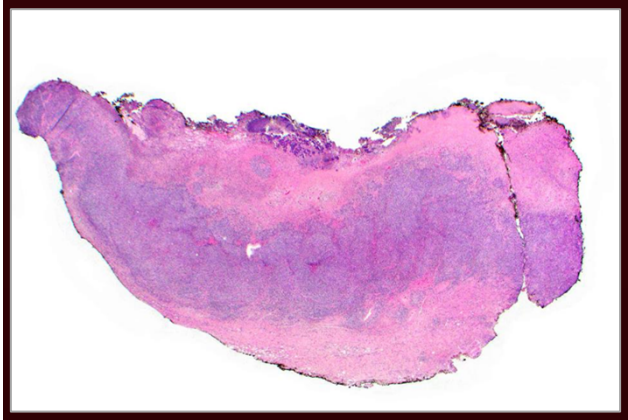
No systemic LAD, hepatosplenomegaly, or BM involvement

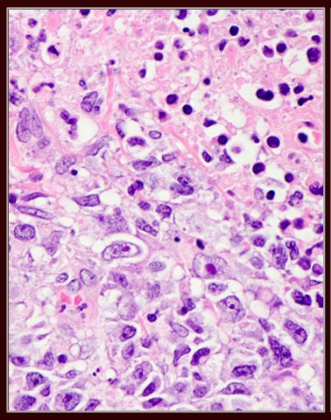
Indolent course, may wax and wane but do not show systemic progression; may resolved with reduction of immunosuppression

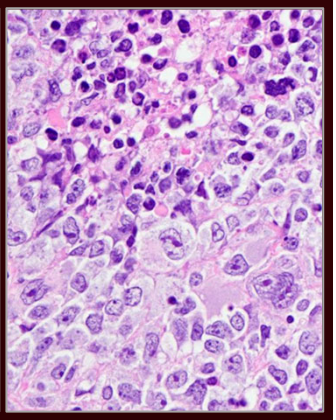
EBV implicated in pathogenesis; immunosuppression or localized lapse in immunosurveillance, with altered T-cell response or diminished T-cell repertoire; **monoclonal or oligoclonal TCR gene rearrangement**

A subset of cases have clonal IHG rearrangements

EBV+ MCU



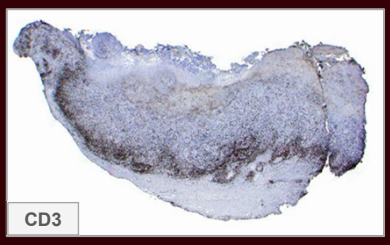


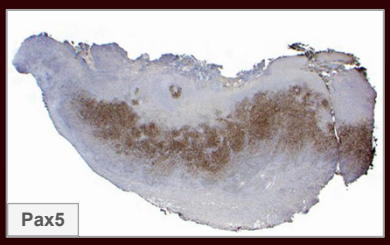


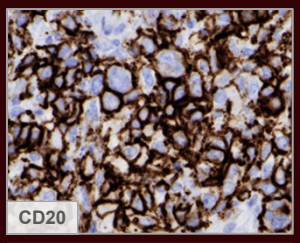
- Sharply circumscribed lesions
- polymorphous infiltrate including variably dense atypical large cells, with either immunoblastic or HRS-like features
- Frequent apoptotic bodies, admixed histiocytes, plasma cells, eosinophils
- Can involve vessel walls
- Often rim of small lymphocytes at the base of the lesion, accentuating the sharp delineation

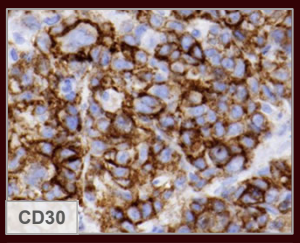
Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias".
Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.

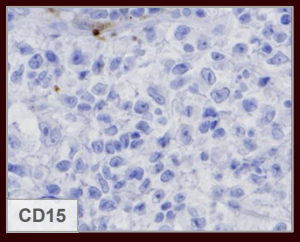
EBV+ MCU

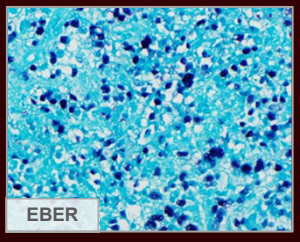












- Usually positive for Pax5, variable CD20, MUM1
- Typically CD30+
- Subset can express CD15
- Negative CD10, BCL6
- Most cases positive for CD45, Bob-1, Oct-2

Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias".
Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.

EBV+ MCU – Differential Dx.

EBV+ DLBCL : Histology overlaps. Helpful clues are:

- ❑ very well-demarcated and isolated nature of lesions in EBV+ MCU, and the frequent finding of a band of reactive lymphocytes at the periphery
- ❑ Clinical/radiologic correlation to assess other sites of disease

classic Hodgkin lymphoma :

- ❑ Characteristic presentation of EBV+ MCU as an isolated, sharply demarcated and ulcerated lesion, and the exceptional rarity of primary presentation of CHL in the skin or mucosa
- ❑ atypical large cells in EBV+ MCU often CD45+ with more fully retained B-cell antigenic profile, with more polymorphous spectrum of EBV+ cells

T-/NK-cell lineage

Mature B-cell lineage
Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
EBV+ mucocutaneous ulcer
Mature T-/NK-cell lineage
Mycosis fungoides including variants/subtypes
Sézary syndrome
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder
Hydroa vacciniforme-like lymphoproliferative disorder

Mycosis Fungoides

prototype and most common CTCL (nearly 50%)

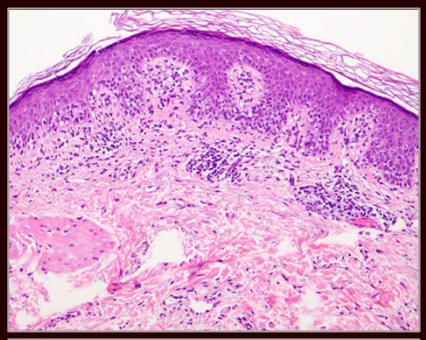
Predominantly adults, M:F 2:1

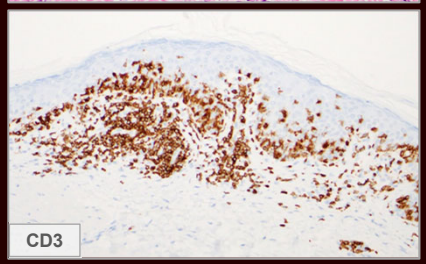
Typically begins as:

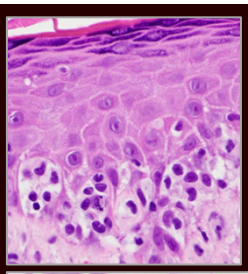
slowly progressive erythematous patches (**Patch stage**) and more infiltrated plaques (**Plaque stage**) in a subset evolving to nodules or large tumors (**Tumor stage**)

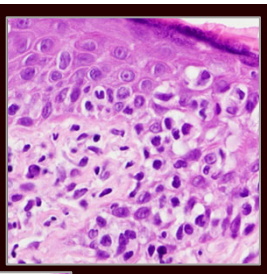
Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

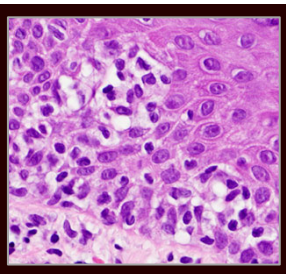
MF –earlier stages

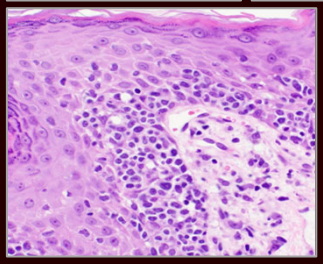








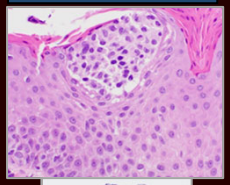


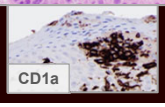


Tagging and pagetoid epidermotropism
Pautrier micro-collections:
frequently in plaque-stage

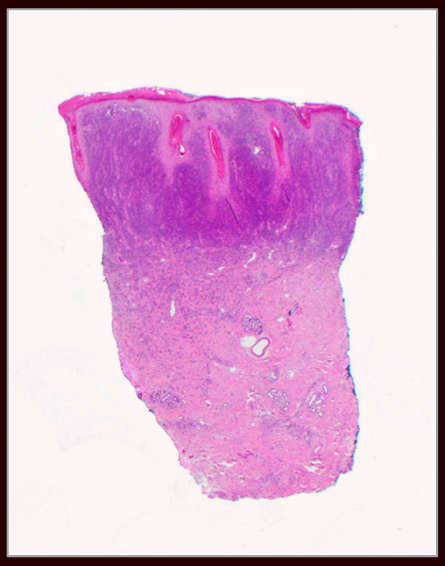
- CD3+ CD4+ CD5+ and CD8−
- C7 loss common
- Loss of CD3/CD2/CD5 very helpful for diagnosis
  ** may be only in epidermotropic component
- Cytotoxic markers negative in early stage but subset+ in tumor stage

Distinguish from:
LC aggregates

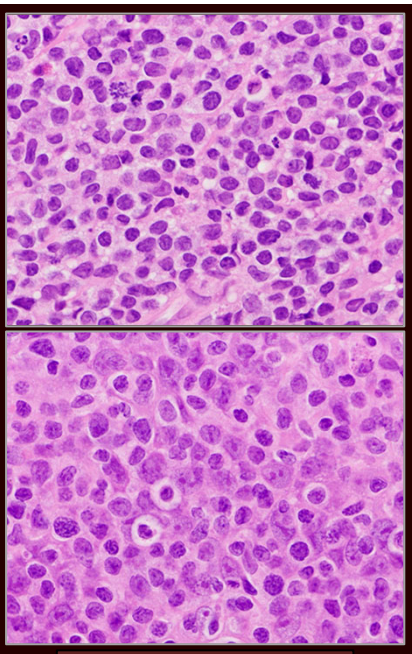




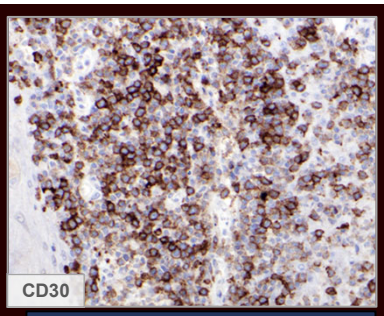
MF –advanced stages



Nodular/diffuse infiltrate with loss of epidermotropism



Large cell transformation:
25% or more of the dermal infiltrate or forming microscopic nodules



- **Tumor-stage / LCT may show CD30 ** not perquisite for LCT**
- **CD30+ LCT may portend a better prognosis than CD30- cases**

(Benner MF, et al. Blood. 2012)

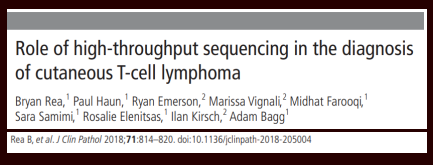
LCT seen in >50% of tumor-stage MF, usually aggressive course

MF –clonality testing

TCR gene rearrangement PCR analysis

Clonal TCR rearrangements may or may not be present in MF
Reactive conditions may also show clonal TCR rearrangements
** **demonstration of identical clones at different anatomic sites or over time supports MF**

NGS analysis
New study assessed both clonality and T-cell fractions in skin biopsies
→ more specific than TRG PCR in distinguishing definitive CTCL from reactive samples
→ Identically sized peaks by PCR (usually interpreted as clonally related), are not always identical by sequencing



Role of high-throughput sequencing in the diagnosis of cutaneous T-cell lymphoma

Bryan Rea,[1] Paul Haun,[1] Ryan Emerson,[2] Marissa Vignali,[2] Midhat Farooqi,[1] Sara Samimi,[1] Rosalie Elenitsas,[1] Ilan Kirsch,[2] Adam Bagg[1]

Rea B, *et al. J Clin Pathol* 2018;**71**:814–820. doi:10.1136/jclinpath-2018-205004

Rea B, et al. J Clin Pathol. 2018.

MF –diagnostic challenges

Favors MF:

Significant epidermotropism
Cytologic atypia
Marked CD4>>CD8
Pronounced loss of pan-T antigens (CD2/CD3/CD5 >>CD7)

**** TCR clonality by PCR and recently NGS**

Vs. lymphoid exocytosis / spongiosis / LC microgranulomas

Integrate: clinical features / histology / immunohistochemistry / TCR clonality

+/- repeat biopsy over time and across sites/lesions

ISCL/EORTC revision to the classification of MF and SS

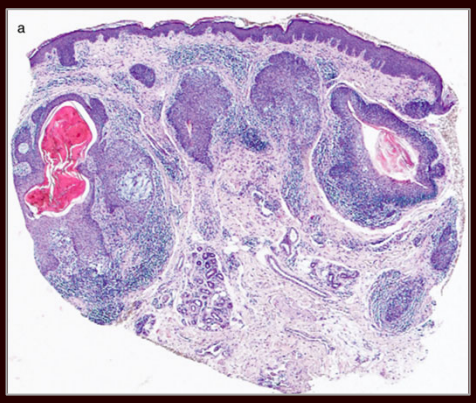
TNMB classification	
Skin	
T_1	Limited patches,* papules, and/or plaques† covering <10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors‡ (≥1-cm diameter).
T_4	Confluence of erythema covering ≥80% BSA.
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required.
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}.
N_{1a}	Clone negative.‖
N_{1b}	Clone positive.‖
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3.
N_{2a}	Clone negative.‖
N_{2b}	Clone positive.‖
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative.
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation.
Visceral	
M_0	No visceral organ involvement.
M_1	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.#
B_{0a}	Clone negative.‖
B_{0b}	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.
B_{1a}	Clone negative.‖
B_{1b}	Clone positive.‖
B2	High blood tumor burden: ≥1000/μL Sézary cells# with positive clone.‖

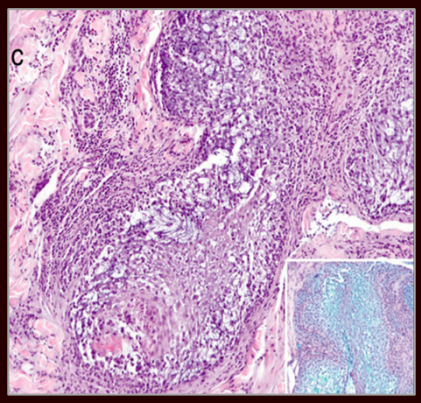
	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1,2	1,2	0	0,1
IIB*	3	0-2	0	0,1
III*	4	0-2	0	0,1
IIIA*	4	0-2	0	0
IIIB*	4	0-2	0	1
IVA_1*	1-4	0-2	0	2
IVA_2*	1-4	3	0	0-2
IVB*	1-4	0-3	1	0-2

Olsen, et al. Blood. 2007
Tables from: Whittaker, et al. Blood. 2016

Folliculotropic MF

Folliculotropic MF (FMF) is a distinct variant ~ 10% of all MF
Atypical lymphocytes in the hair follicle epithelium -> alopecic patches and plaques





Images from:
Mitteldorf, et al.
J Dtsch Dermatol Ges. 2018

Sézary syndrome

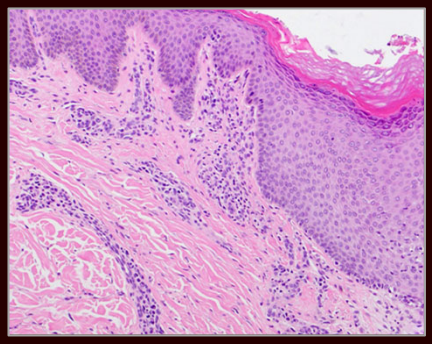
Rare, aggressive form of CTCL with triad of:

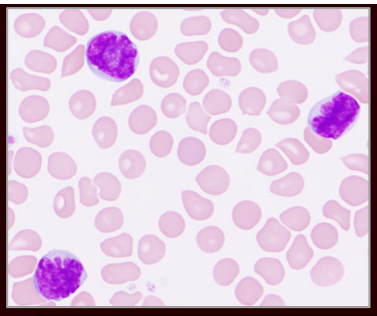
- Generalized redness and scaling of the skin (**erythroderma**)
- **Lymphadenopathy**
- **clonally- related neoplastic T cells** in the skin, lymph nodes, and peripheral blood

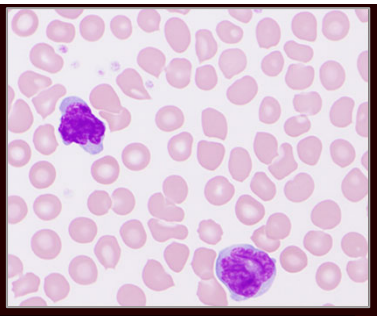
Peripheral blood involvement requires ≥1,000/µL Sézary cells, a CD4:CD8 ratio ≥ 10:1, or atypical CD4+ cells in the blood (CD4+CD7− cells ≥40% or CD4+CD26− cells ≥30%).

MF and SS are distinct entities with different presumptive cells of origin and genetics
The term Sézary syndrome should be used in cases without preceding MF
if prior established diagnosis of MF, should be "**erythrodermic MF**" or secondary erythrodermic CTCL
if MF without erythroderma meets hematologic criteria for SS, "**MF with leukemic involvement**"

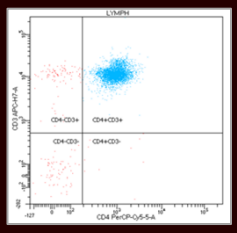
SS

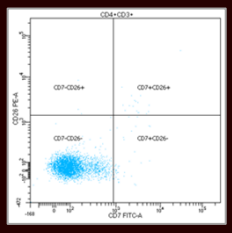






- Blood: atypical lymphocytes with cerebriform nuclei (Lutzner cells and larger Sézary cells)
- CD4+ w/ loss of CD7 or occasionally other pan-T markers (CD2, CD3, CD5)

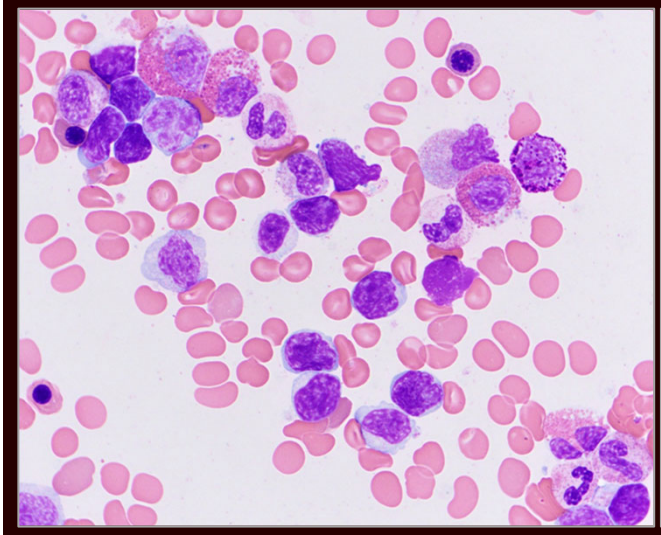


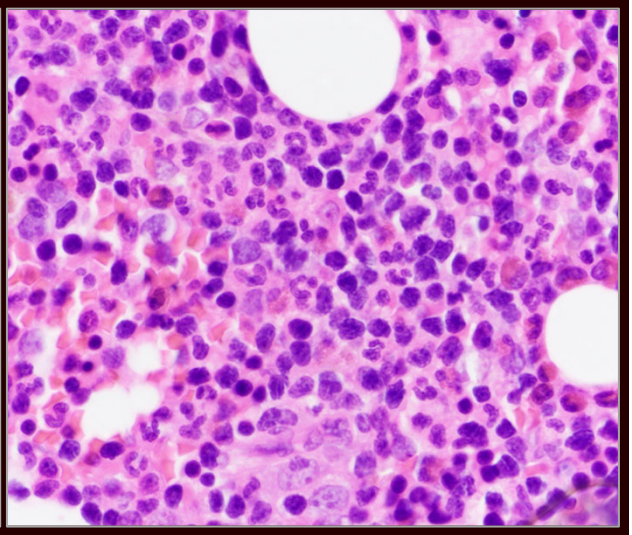


Skin findings can be similar to early MF, though often infiltrate is more sparse with less epidermotropism

Involved LNs typically have effaced architecture

SS





Bone marrow involvement

SS –Differential Dx.

Other circulating T-cell lymphomas: typically distinguished by respective immunophenotype and unique constellation of features in SS
ATLL: can have PB and skin involvement; “flower-like” cells, skin lesions tend to be nodules, HTLV-1 related

Erythrodermic inflammatory dermatoses
(e.g., psoriasis, atopic dermatitis, drug rash, pityriasis rubra pilaris, contact dermatitis)

absence of circulating clonally related T cells and close clinical correlation


CLINICAL AND LABORATORY INVESTIGATIONS

British Journal of Dermatology

Histopathological and immunophenotypical criteria for the diagnosis of Sézary syndrome in differentiation from other erythrodermic skin diseases: a European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Study of 97 cases

C.D. Klemke,[1] N. Booken,[1] C. Weiss,[2] J.P. Nicolay,[1] S. Goerdt,[1] M. Felcht,[1] C. Géraud,[1] W. Kempf,[3] C. Assaf,[4] N. Ortonne,[5] M. Battistella,[6] M. Bagot,[7] R. Knobler,[8] P. Quaglino,[9] B. Arheiliger,[10] M. Santucci,[11] P. Jansen,[12] M.H. Vermeer[13] and R. Willemze[13]

British Journal of Dermatology (2015) **173**, pp93–105

Atypical intraepidermal lymphocytes + Pautrier microabscesses
Expression of **PD-1** and **MUM1**

→ strongly favors SS versus dermatitis

Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

second most common group of CTCL (25%)

spectrum of disease characterized by **indolent course** and **CD30 expression**
good prognosis despite recurrences (5-year survival 90%)

cALCL – LyP **: (and occasional borderline lesions)**

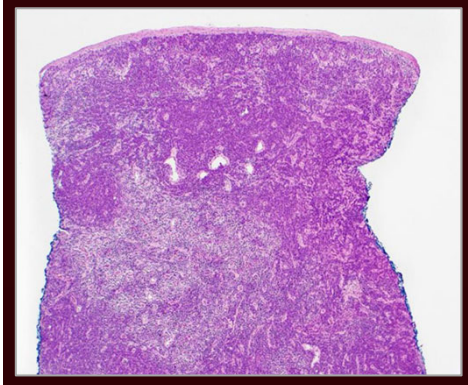
Overlapping histology – requires close clinical correlation

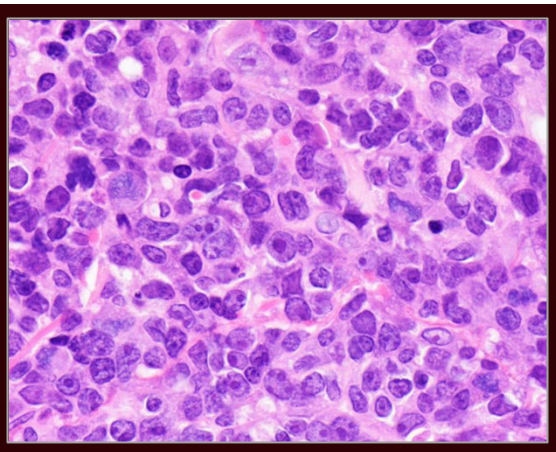
Primary Cutaneous Anaplastic Large Cell Lymphoma (cALCL)

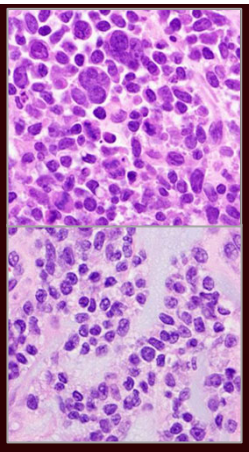
- Localized, solitary or grouped, **rapidly growing** nodules/tumors, with **frequent ulceration**
- There can be partial regression, but complete untreated resolution (as seen in LyP) is unusual
- 5-year survival >90%
- Extra-cutaneous dissemination can occur in ~10% patients

Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias". Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.
Courtesy of Cecilia Larocca, MD. Dana-Farber Cancer Institute, Boston, MA

cALCL

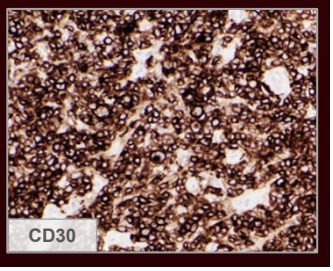






- **Dense diffuse infiltrate of large anaplastic cells in dermis +/- subcutis**
- **background of secondary inflammation may be observed, occasional prominent eosinophils**
- **Some cases with areas of mucinous or myxoid-appearing stroma**

- **>75% of infiltrate is CD30+**
- **CD4+ (can be CD8); often cytotoxic (granzyme B, TIA-1)**
- **Can lose CD2, CD3, CD5, CD7**
- **EMA and ALK1 are negative**



Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias". Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.

cALCL – Molecular genetic features

Most cases show **clonal rearrangement of TCR genes**

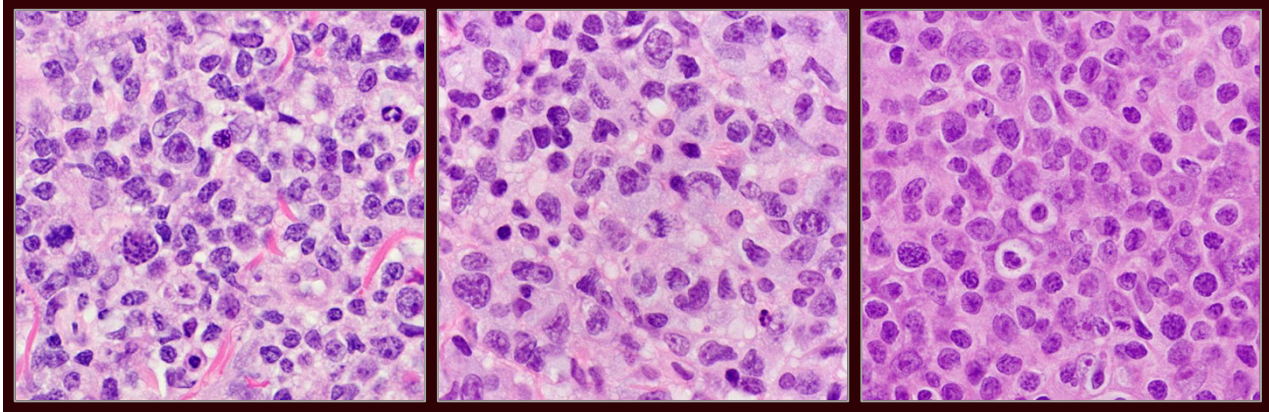
ALK (anaplastic lymphoma kinase) gene translocations are not detected
ALK1 expression strongly suggests secondary involvement by systemic ALCL, ALK+
very rare cases of ALK1+ IHC or *ALK* translocations described in CD30+ skin tumors without evidence of systemic disease → **staging studies essential**

IRF4/DUSP22 rearrangements at 6p25.3 found in ~25% of cases
can also be in PTCL and small subset of LyP

Novel recurrent ***NPM1-TYK2*** gene fusion, leading to STAT signaling activation, in a subset of cALCL and LyP

Pham-Ledard A, et al. J Invest Dermatol. 2010.
Wada DA, et al. Mod Pathol. 2011.
Velusamy T, et al. Blood. 2014.

cALCL | LyP type C | LCT of MF



- **LCT of MF**
  documented history of MF, other bx sites or areas with more typical patch/plaque-stage MF features
- **LyP type C**
  can have fully overlapping histology; distinguished by clinical features
- Secondary cutaneous involvement by ALK– systemic ALCL and other CD30+ large-cell lymphomas

Lymphomatoid Papulosis (LyP)

Chronic disease w/ lesions at different stages

Typically develops as **grouped or generalized papules** and small nodules on the trunk and extremities that **spontaneously regress within weeks to months**

Most frequently in middle-aged adults; M:F 2-3:1

5-10% can involve regional draining lymph nodes

** Up to 20% of cases can have concurrent MF, cALCL, systemic ALCL, or CHL

Considered "clinically benign" despite a subset showing clonality; 10-year survival rate near 100%

Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias". Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.
Courtesy of Cecilia Larocca, MD. Dana-Farber Cancer Institute, Boston, MA

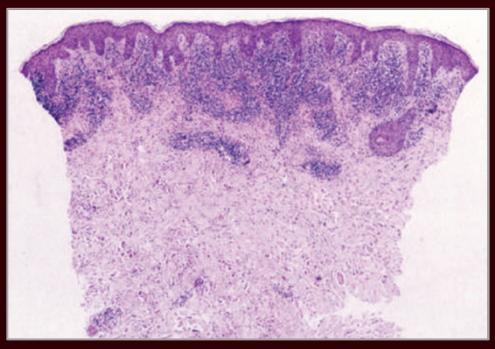
LyP – extremely broad histologic spectrum
5 subtypes (type A–E) and a recent molecularly-defined subtype

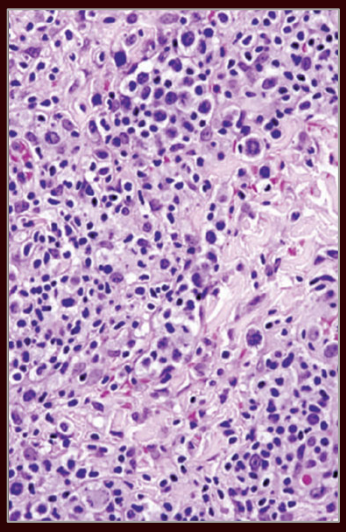
Subtype	Main features	Relative Frequency	Predominant Phenotype	Main DDx
Type A	**Prototypical pattern; wedge-shaped infiltrate** extending from superficial into mid/deep dermis; marked inflammatory cells (lymphocytes, histiocytes, neutrophils, eosinophils), admixed minority atypical large cells, can be Reed–Sternberg–like	**> 80%**	CD4+	**Reactive/self-resolving** Arthropod bites / viral / drug **Hodgkin lymphoma**
Type B	**Mimics mycosis fungoides**; superficial dermal and epidermotropic	< 5%	CD4+	**Plaque-stage MF**
Type C	**Monotonous population of large cells**, with sparse or minimal inflammatory component and diffuse CD30 expression; mimic cALCL, behave like LyP		CD4+	**cALCL** **LCT of MF**
Type D	**Striking epidermotropism**, similar to pagetoid reticulosis **Cytotoxic** (CD8+ TCR βF1+ and TIA-1+ and/or granzyme B+); strong CD30	< 5%	**CD8+**	**CD8+ aggressive epidermotropic TCL**
Type E	**Angioinvasive**, ulcerative/necrotic lesions due to underlying angiocentric and angiodestructive infiltrate of small- to medium-sized atypical lymphocytes	< 5%	**CD8+**	**Extranodal NK/TCL**
***IRF4/DUSP22* rearranged**	rearrangements of the *IRF4/DUSP22* locus on chromosome 6p25.3	< 5%	CD8+ or CD4− CD8−	

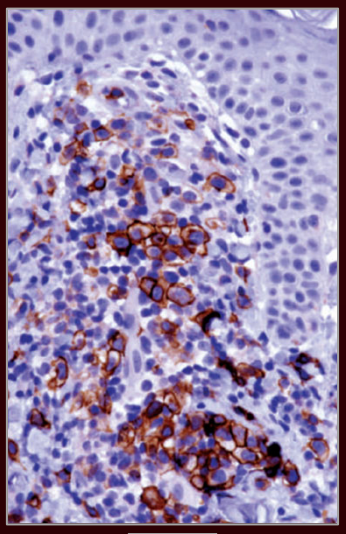
- LyP can have variable loss of CD2, CD3, or CD5, although pronounced loss of multiple pan-T antigens would be unusual
- TCR gene rearrangements are detected in approximately 60% of LyP

Adapted from WHO, 2017.

LyP – type A





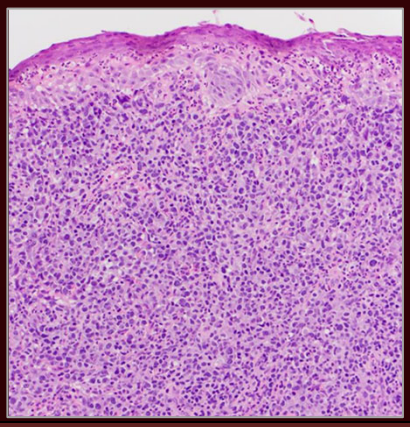


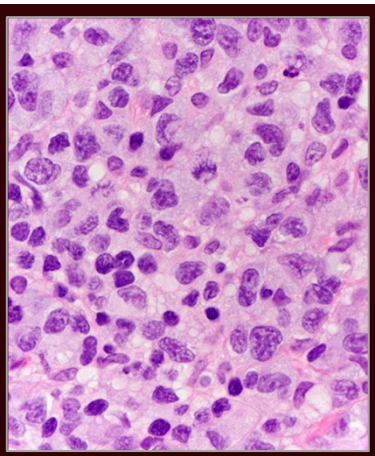
CD30

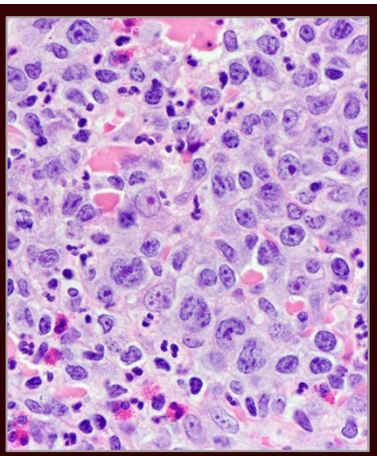
- Superficial and mid-dermal infiltrate becoming a wedge-shaped architecture
- Variably atypical scattered and clustered larger cells
- Marked inflammatory component (small lymphocytes, histiocytes, neutrophils, and eosinophils)

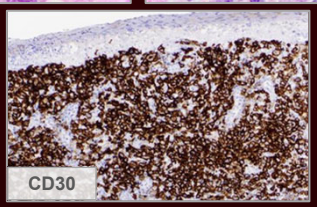
Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

LyP – type C









CD30

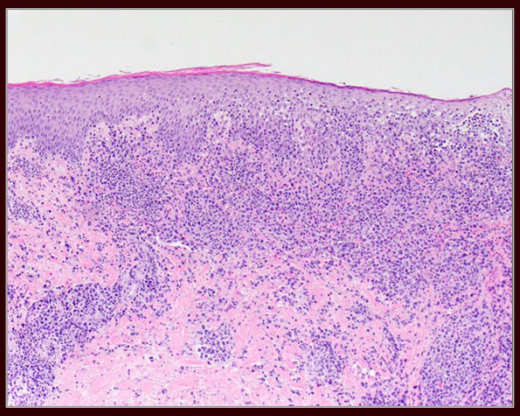
- Dense, diffuse dermal infiltrate of large cells
- Diffuse positivity for CD30
- Can have few background inflammatory cells

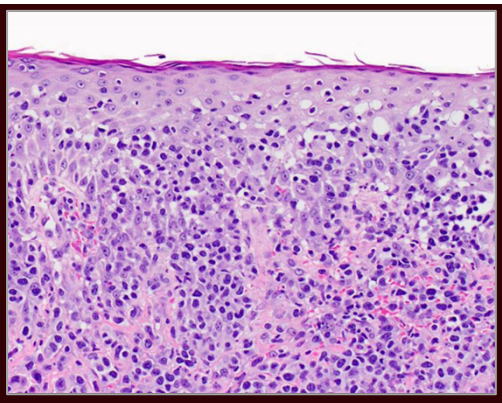
Histologically indistinguishable from cALCL

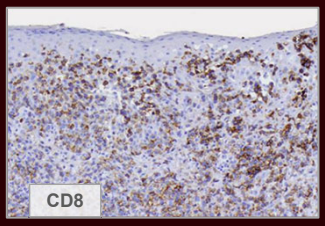
In absence of clinical data, may be designated "cutaneous CD30+ T-LPD, in the spectrum of cALCL versus LyP, type C"

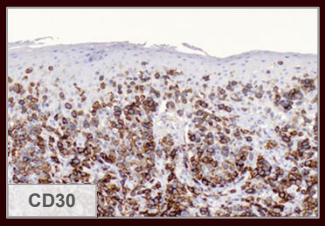
Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias". Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.

LyP – type D









- Superficial infiltrate with marked epidermotropism
- Predominance of CD8
- Strong, diffuse positivity for CD30

overlaps with:
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

Clinical course and behavior fits with LyP

Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias".
Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.

LyP – Molecular subtype – *IRF4/DUSP22* rearrangement

Harbor rearrangements of the *IRF4/DUSP22* locus on chromosome 6p25.3

Less than 5% of LyP cases

Do not fit nicely into any of the 5 histologic subtypes but have **strong CD30 expression** and are **self resolving**

25% of cALCL

further evidence that entities within category of indolent primary cutaneous CD30+ T-LPDs are related spectrum of diseases

Karai LJ, et al. Am J Surg Pathol. 2013.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

Rare cytotoxic T-cell lymphoma that primarily infiltrates subcutaneous adipose tissue

TCR alpha/beta phenotype (distinguishes from gamma/delta T-cell lymphoma)

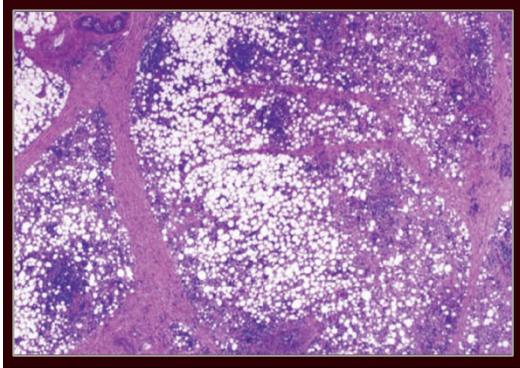
Mainly adults, but childhood cases reported; solitary or generalized deep, erythematous subcutaneous nodules, involving extremities and/or trunk

60% have systemic symptoms (fever, fatigue, weight loss), 20% associated with **hemophagocytic syndrome**

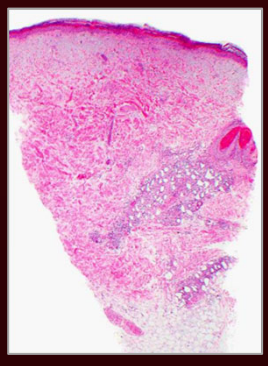
Relationship with systemic lupus erythematosus, and has overlapping features with lupus panniculitis

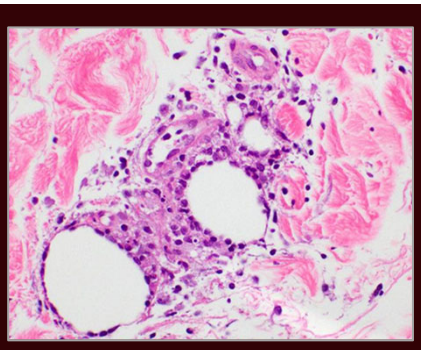
Protracted indolent course **(5-year survival >80%)**; **unless HLH is present (survival 40%)**

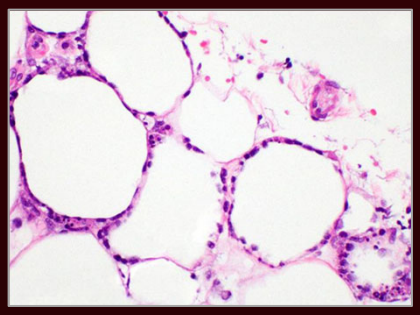
SPTCL



Lobular and septal pattern of subcutaneous infiltration



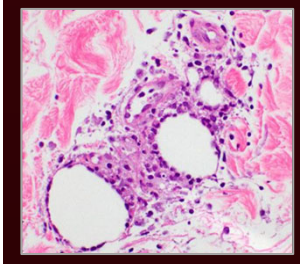


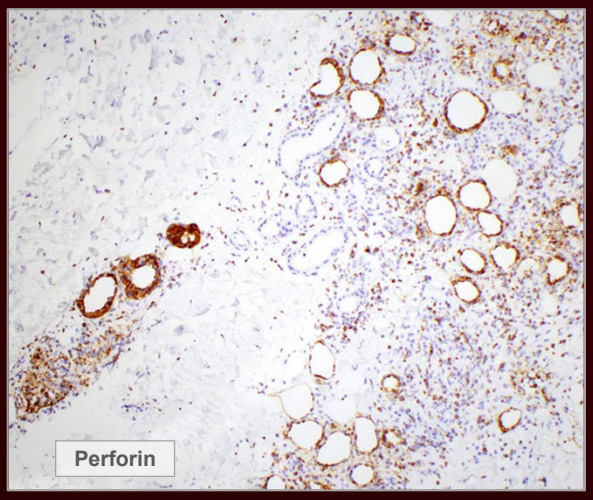


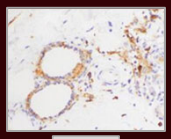
hyperchromatic cells; adipocyte rimming; Fat necrosis/ karyorrhectic debris/ histiocytes

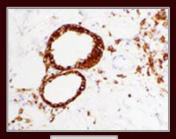
Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

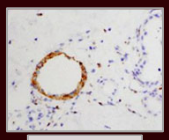
SPTCL

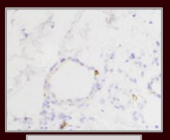








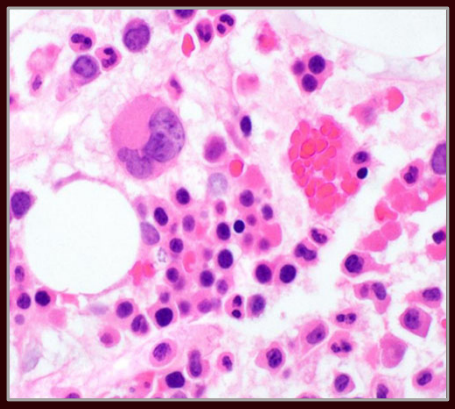


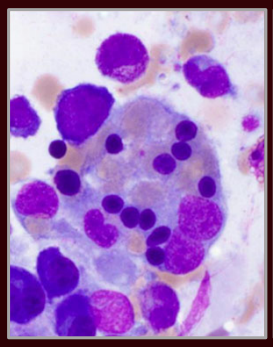


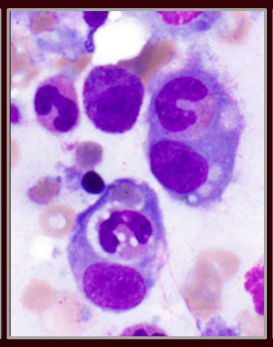
Cytotoxic: granzyme B, perforin, TIA-1

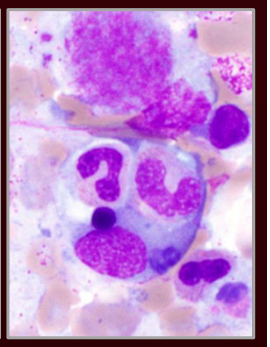
Negative: CD56, CD30, EBER

SPTCL –associated with Hemophagocytic Syndrome (20% cases)









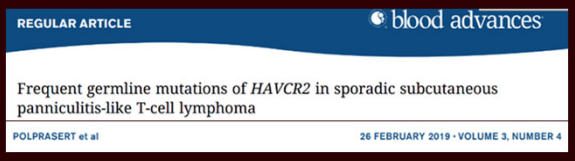
60M with SPTCL and pancytopenia
BMbx: MTH and no evidence of lymphoma, but extensive hemophagocytosis

SPTCL

- Clonal TCR gene rearrangements

  Underlying mechanism for association with hemophagocytic syndrome not yet fully determined

- Biallelic germline mutations in ***HAVCR2*** (gene encoding TIM-3, an immune inhibitory receptor expressed on CD8+ T cells), confers high susceptibility to developing primary SPTCL
- Cases also harbored somatic mutations in genes ~ **epigenetic regulation and signal transduction**


REGULAR ARTICLE

blood advances

Frequent germline mutations of *HAVCR2* in sporadic subcutaneous panniculitis-like T-cell lymphoma

POLPRASERT et al

26 FEBRUARY 2019 · VOLUME 3, NUMBER 4

Primary Cutaneous Gamma-Delta T-Cell Lymphoma

Typically aggressive cutaneous cytotoxic T-cell lymphoma with **TCR gamma/delta** phenotype

Disseminated indurated plaques and ulcerated nodules/tumors, commonly on extremities and trunk

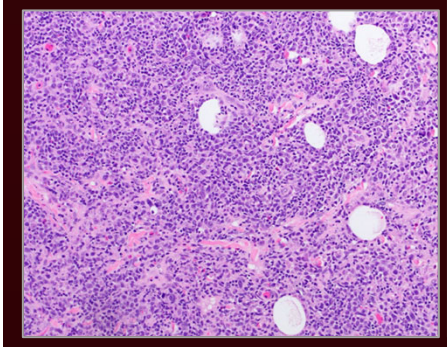
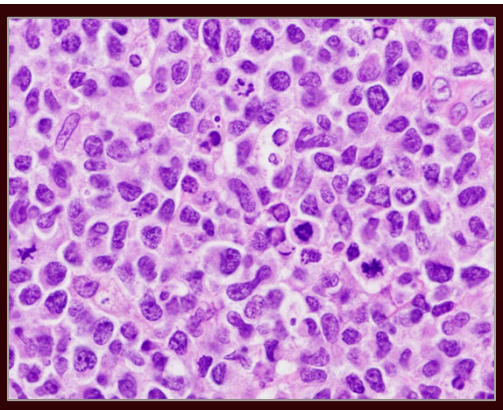
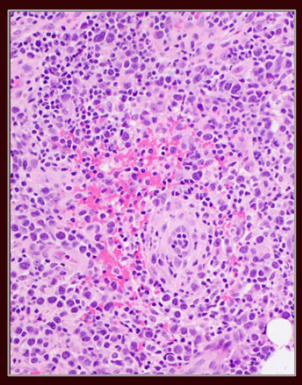
Systemic involvement of mucosa and extranodal sites common

~50% associated with HLH

Overall 5-year survival low (11%)

Photo courtesy of: Cecilia Larocca, MD. Dana-Farber Cancer Institute, Boston, MA

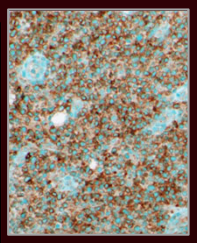
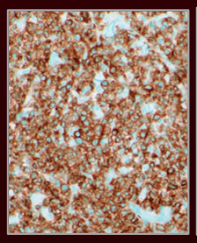
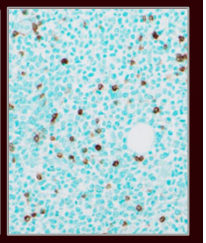
PCGD-TCL

- Variable pattern:
  epidermotropic, diffusely dermal, panniculitic
- variably sized, with irregular to pleomorphic nuclei and coarse chromatin
- Angioinvasion is common (usually without extensive necrosis)

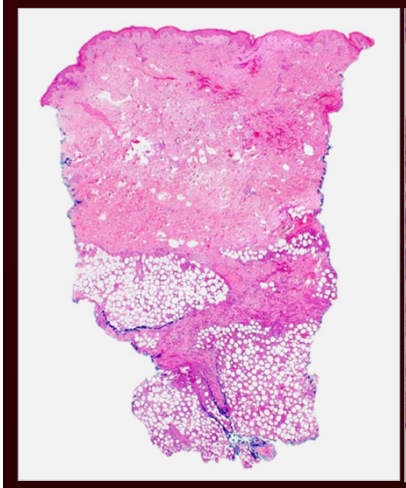
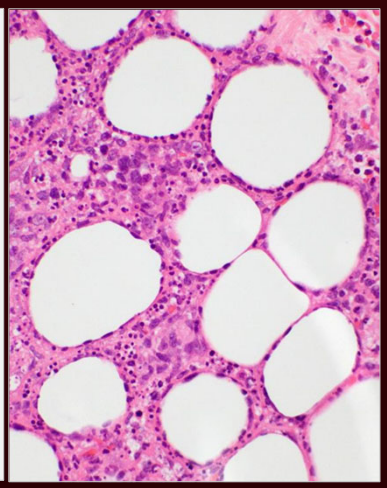
- $CD3^{+}$ $CD2^{+}$ $CD4^{-}$ $CD8^{-/+}$ $CD7^{+/-}$ cytotoxic (TIA-1, granzyme B, and perforin)
- γδ phenotype: IHC for TCR gamma chain or TCR delta chain
- CD56+ ; negative for EBER

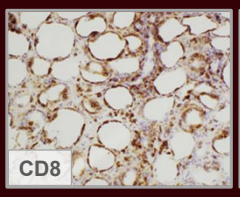
- Clonal TCR gene rearrangement

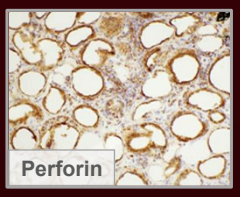




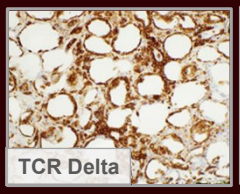
TCR gamma | TCR delta | TCR βF1

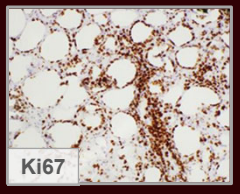
PCGD-TCL histology can overlap with SPTCL









SPTCL

DDx with lupus panniculitis may be challenging

- reactive lymphoid follicles, plasma cells, myxoid changes, CD123+ PDCs, eosinophilic acellular hyaline necrosis of fat lobules ("honeycomb-like"), lack of TCR clonality

Disease	Clinical features	CD3	CD4	CD8	Cytotoxic	CD56	EBV	TCR	Lineage
SPTCL	Tumors (ext. / trunk)	+	-	+	+	-	-	Ò	T
PCGD-TCL	Tumors, plaques, ulcerated nodules	+	-	-/+	+	+	-	âx	T
Extranodal NK/TCL	Nodules, tumors	+ cCD3e	-	-/+	+	+	+	-	NK/T

PCGD-TCL

- includes cases previously called SPTCL with γδ phenotype
- γδ T-cell lymphomas presenting primarily in mucosal sites (mucocutaneous GD-TCL) belong to other site-dependent peripheral T-cell lymphomas
- ENKTCL are EBV+ with prominent angiodestruction/necrosis; TCR in germline configuration
- rare cases of MF and LyP can have γδ TCR phenotype : requires clinical correlation; these have similar indolent course as their counterparts with an alpha beta phenotype

Primary Cutaneous CD8-Positive Aggressive Epidermotropic Cytotoxic T-cell Lymphoma

(Provisional Entity)

PCCD8AC-TCL

proliferation of epidermotropic CD8+ cytotoxic T cells and aggressive clinical course

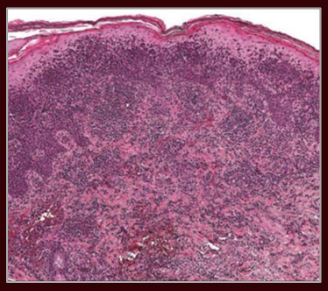
Median age 54 years; M:F 1.5:1

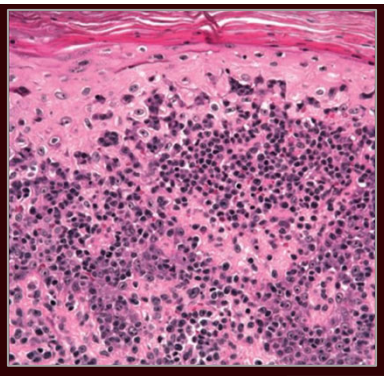
Localized or disseminated eruptive papules, nodules, or tumors with central ulceration and necrosis or hyperkeratotic patches and plaques

Spread to other visceral sites can occur but nodal involvement is unusual

Rapid progression with median survival 12 months

PCCD8AC-TCL

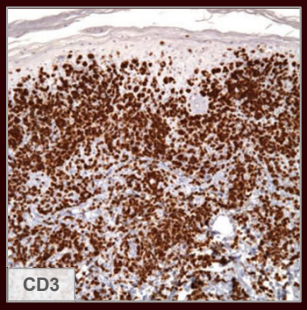


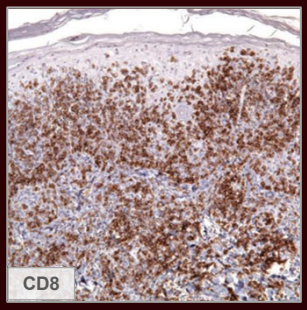


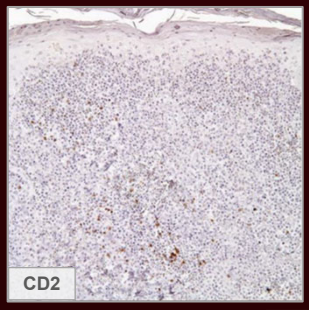
- Variable pattern: lichenoid, nodular, or diffuse
- Epidermis may be acanthotic or atrophic
- Marked epidermotropism (may be less if advanced)
- Pleomorphic atypical cells
- Ulceration, necrosis, or blister formation

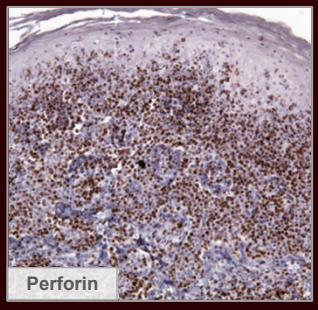
- $CD3^+$ $CD4^-$ $CD8^+$ $CD7^{-/+}$ cytotoxic T-cells, αβ phenotype
- CD2/CD5 often lost; negative for CD30, CD56, EBER
- Ki67 proliferation very high

- Cases with similar clinical/histologic features, but lacking CD8 or αβ TCR reported









Morgan EA and Murphy GF. Cutaneous Lymphomas and Leukemias in Lever's Histopathology of the Skin, 11th ed. 2015.

Primary Cutaneous Acral CD8-Positive T-Cell Lymphoma

(Provisional Entity)

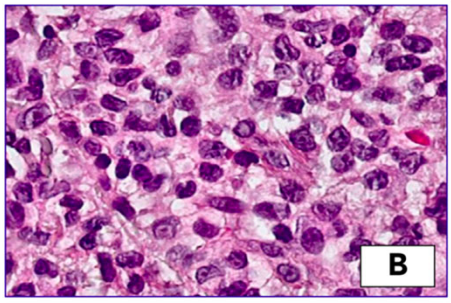
Newly described in most recent WHO/EORTC classification

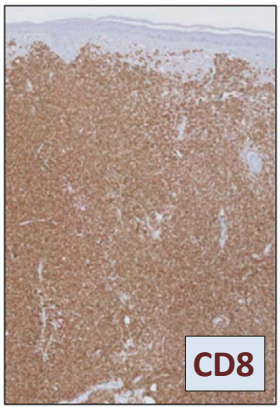
Very rare; initially reported as clinically indolent clonal proliferations of small to medium-sized, nonactivated cytotoxic CD8+ T cells of the ear/face or at acral sites

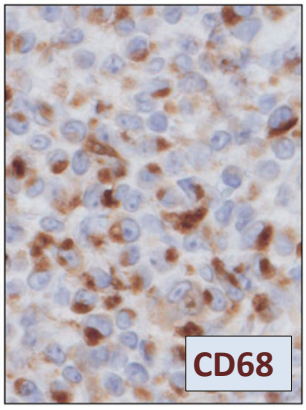
Isolated slow-growing nodules or papules; usually solitary, but bilateral or multifocal presentations can occur

Benign course: typically resolve following excision or radiotherapy with only rare local recurrences
- staging probably not necessary in cases with characteristic presentation and histology

CD8+ATCL







- Dense dermal infiltrate of small to medium-sized atypical lymphocytes
- No epidermotropism (vs. CD8+MF and CD8+AECTCL)
- CD3+ CD8+ TIA-1+
- (absence of other cytotoxic markers granzyme-B and perforin)
- CD68 shows characteristic perinuclear Golgi dot-like pattern
- Ki67 proliferation typically low (<15%)

Images from: Willemze, et al. Blood 2019

CD8+ATCL versus PCCD8AC-TCL

- share histologic and immunophenotypic features
- CD8+ ATCL follows an indolent course and lacks the marked epidermotropism, frequent ulceration, and high Ki67 proliferation of PCCD8AC-TCL

other epidermotropic CTCLs expressing a CD8+ cytotoxic T-cell phenotype

LyP type D – distinct clinical presentation and disease course; CD30+

CD8+ MF – characteristic clinical presentation, skin lesions and disease course

PCGD-TCL – distinguished by γδ T-cell phenotype

Primary Cutaneous CD4-Positive Small/Medium T-Cell Lymphoproliferative Disorder (Provisional Entity)

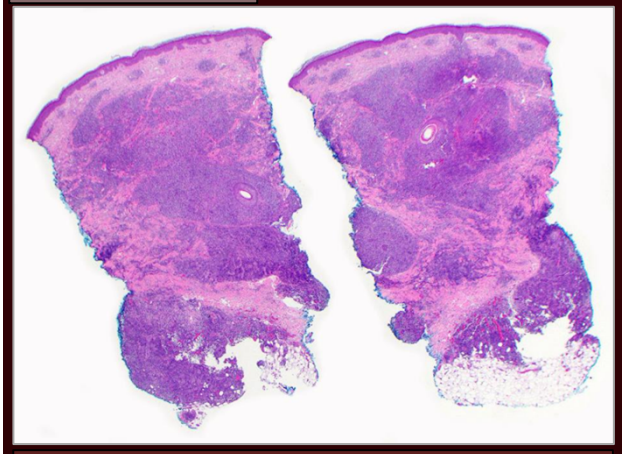
Clonal small/medium CD4+ pleomorphic T cells, with robust inflammatory component

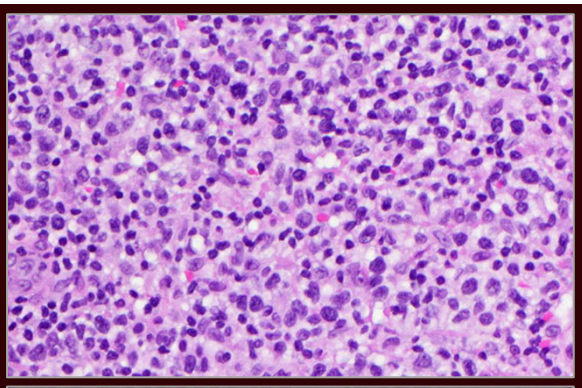
Terminology revised to "lymphoproliferative disorder" in 2016 WHO revision, in place of the prior "lymphoma" designation

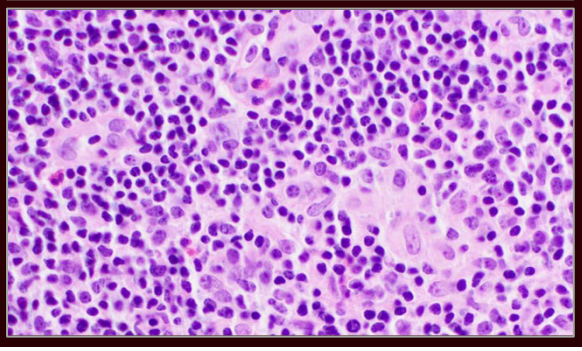
Adult patients; typically solitary plaque/nodule or reddish papule on head/ neck or upper body

Excellent prognosis; may regress spontaneously or with localized therapy

PCSM-TLPD



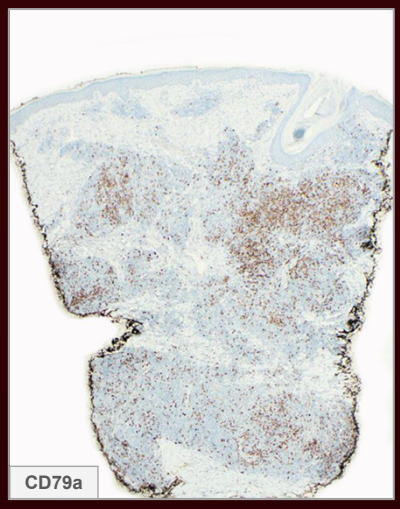


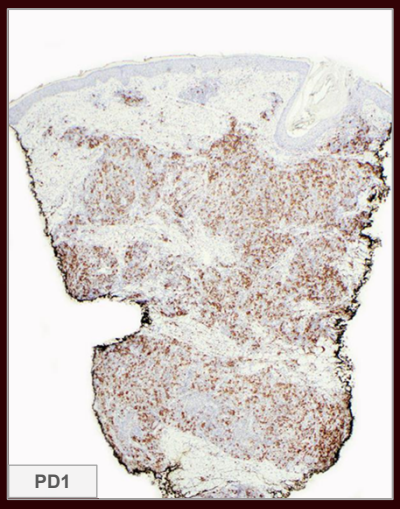


- Dense, diffuse, or nodular
- Dermis, extending into the upper subcutis
- Small- to medium-sized pleomorphic T cells (<30% large cells)
- Can have focal epidemotropism
- Multinucleated giant cells and/or granulomatous changes, infiltration of adnexal structures

- Abundant, small reactive B cells and CD8+ T cells, histiocytes, plasma cells

PCSM-TLPD





- $CD3^+$ $CD4^+$ αβ phenotype
- Negative for CD8, TIA-1, granzyme B, CD30
- Express follicular T-cell markers PD-1, BCL6, CXCL13, not CD10
- Proliferation index <20-30%

PCSM-TLPD – Differential Dx.

MF – needs to be excluded by clinical history

PTCL, NOS

Rapid growth or disseminated lesions; 30% large pleomorphic cells with high proliferation

prominent B-cell infiltrate
+ admixed plasma cells

PCMZL

- Density of B cells
- Follicular colonization / disrupted FDCs
- Monotypic plasma cells

Marked increase CD4 and Follicular T-cell marker expression favor PCSM-TLPD

Reactive / pseudo-T-cell lymphoma

- Solitary lesions with nodular or diffuse architecture
- Can have clonal TCR
- Excellent prognosis

IGH and TCR clonality studies

caveats both ways

Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorders

A Clinical, Pathologic, and Molecular Study of 60 Cases Presenting With a Single Lesion: A Multicenter Study of the French Cutaneous Lymphoma Study Group

Beltzung et al | Am J Surg Pathol • Volume 44, Number 7, July 2020

60 patients with PCSM-TLPD

- Single cutaneous lesion (45% nodule on head/neck)
- **All had indolent course (31% spontaneous regression)**

- Pattern 1: nodular/diffuse dermal (78%) vs. Pattern 2: subepidermal bandlike
- TFH lineage markers; substantial B-cell infiltrate

- **Clonal TCR rearrangement in 68%**
- **Clonal IGH rearrangement in 26%**

- Only one case harbored mutation in *DNMT3A*

Hydroa Vacciniforme–Like Lymphoproliferative Disorder (HV-LPD)

Rare, chronic EBV+ cutaneous lymphoproliferative disorder of childhood
most commonly Asia, Mexico, Central America, and South America

Terminology revised to "lymphoproliferative disorder" in 2016 WHO revision, in place of the prior "lymphoma" designation

Encompasses a broad spectrum of **HV-like skin lesions** with a highly variable clinical course

cutaneous manifestations of chronic active EBV infection of T- and NK-cells

HV-LPD spectrum

Hypersensitivity reactions w/ "severe mosquito bite allergy"

Classic HV: ultraviolet-light hypersensitivity condition with papulovesicular eruptions leading to scarring, and often with spontaneous remission

Severe HV: cutaneous lesions may also manifest as indurated plaques or large tumors, often developing ulceration; involving both sun exposed and sun-protected areas

+/- fever, weight loss, LAD, hepatosplenomegaly

→ progression to systemic lymphoma

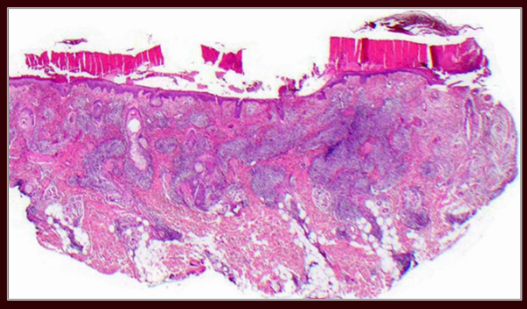
HV-LPD

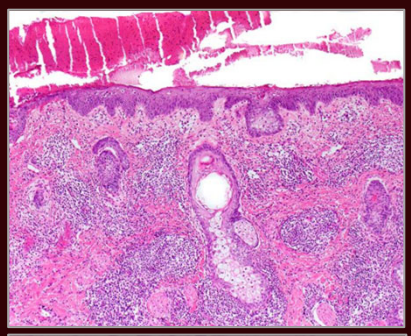
Papulovesicular eruptions on sun-exposed region

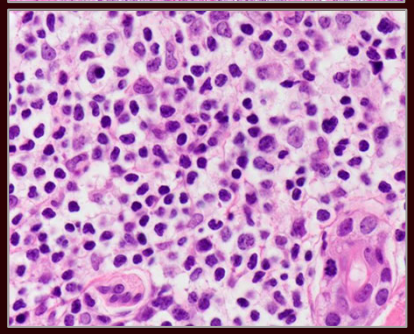
severe case with indurated, necrotic ulcerating lesions

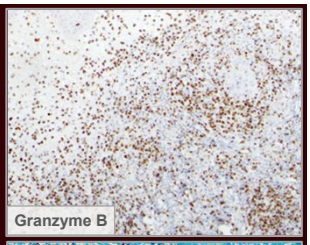
Sadigh S, Murphy GF and Morgan EA. "Cutaneous Lymphomas and Leukemias".
Elder, Lever's Dermatopathology: Histopathology of the Skin, 12e. 2023. Wolters Kluwer, in press.
Courtesy of Dr. John O'Malley, Dana-Farber Cancer Institute, Boston, MA

HV-LPD

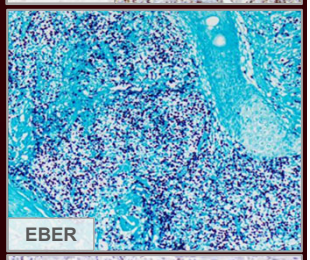




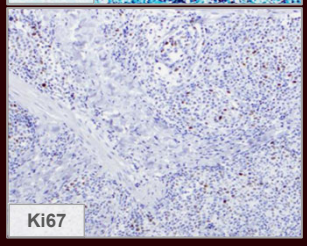




Granzyme B



EBER

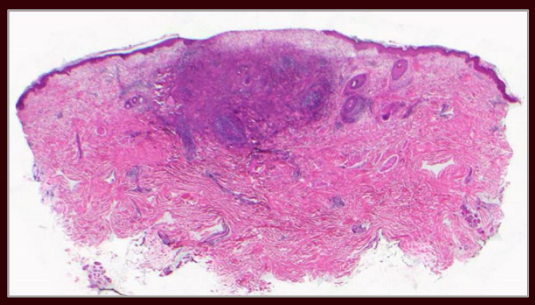


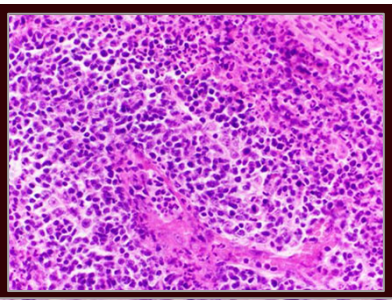
Ki67

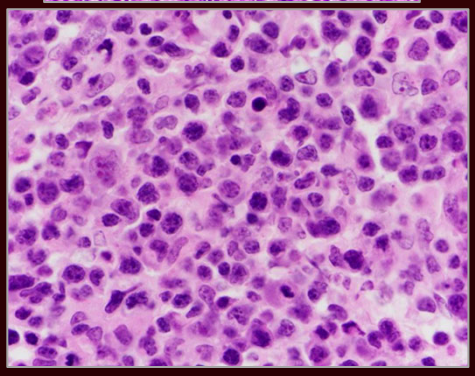
- blister-like papular lesion with a hemorrhagic crust
- dermal infiltrate with peri-adnexal and peri-neural accentuation, extending to the subcutis
- small to medium-sized lymphocytes with mild atypia

- αβ or γδ T or, less commonly, NK cells
- CD2+ CD3+ CD8+/− with cytotoxic markers
- CD30 often positive; CD56 detected in NK-cell cases
- EBER is positive

HV-LPD





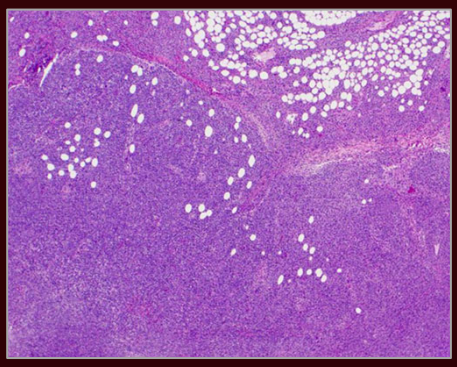


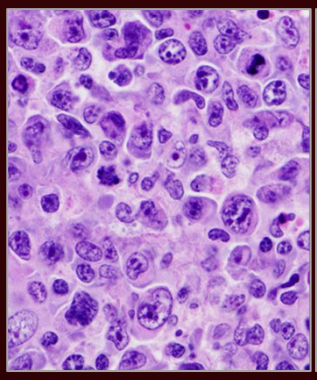
- more severe case exhibits ulceration and angiocentricity
- larger, highly atypical and mitotically active neoplastic lymphocytes

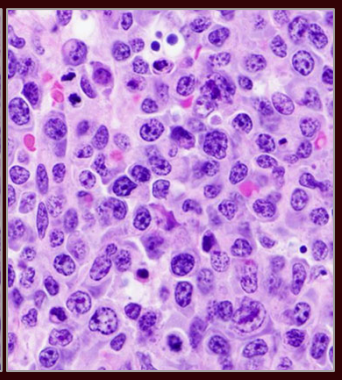
→ this patient developed systemic lymphoma

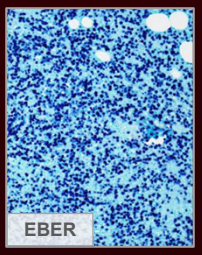
** however, there are no good (clinical / morphologic / molecular) predictors of systemic progression

HV-LPD → progression to aggressive systemic T-cell lymphoma









HV-LPD

blood Regular Article

LYMPHOID NEOPLASIA

Hydroa vacciniforme–like lymphoproliferative disorder: an EBV disease with a low risk of systemic illness in whites

Jeffrey I. Cohen,[1] Irini Manoli,[2] Kennichi Dowdell,[1] Tammy A. Krogmann,[1] Deborah Tamura,[1] Pierce Radecki,[1] Wei Bu,[1] Siu-Ping Turk,[4] Kelly Liepshutz,[1] Ronald L. Hornung,[5] Hiva Fassihi,[6] Robert P. Sarkany,[6] Lori L. Bonnycastle,[2] Peter S. Chines,[2] Amy J. Swift,[2] Timothy G. Myers,[7] Melissa A. Levoska,[3] John J. DiGiovanna,[3] Francis S. Collins,[2,8] Kenneth H. Kraemer,[3] Stefania Pittaluga,[6] and Elaine S. Jaffe[9]

COHEN et al | blood® 27 JUNE 2019 | VOLUME 133, NUMBER 26

Recent study of HV-LPD among Caucasian populations showed:

- very rare incidence
- earlier-onset disease
- very indolent clinical course and less systemic disease
- Less likely to have T-cell clones in PB
- Lower EBV DNA and normal NK-cell numbers in PB

- Did not find germline mutations in genes previously associated with severe EBV disease or UV damage

Thank you

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