City of Hope

International Society for Cutaneous Lymphomas ISCL

5TH World Congress of Cutaneous Lymphomas

Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Classification/Epidemiology/Prognostic Factors | #117

Clinical consequences of reclassifying low-grade malignant lymphomas as cutaneous lymphoproliferative disorders.

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

4th edition of the WHO classification (2008)

Cutaneous T-cell lymphomas

- Mycosis fungoides & variants of MF
  - Folliculotropic MF
  - Granulomatous slack skin
  - Pagetoid reticulosis
- Sezary syndrome
- Adult T-cell lymphoma/leukemia
- Spectrum cutaneous CD30+ LPD
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Hydroa vacciniforme-like lymphoma
- Primary cutaneous peripheral T-cell lymphoma, NOS + rare subtypes

- Primary cutaneous γ/δ T-cell lymphoma
- Aggressive cytotoxic epidermotropic CD8+ CTCL
- Primary cutaneous CD4+ small/medium T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma

Cutaneous B-cell lymphomas

- Extranodal marginal zone lymphoma (MALT) (Primary cutaneous marginal zone lymphoma)
- Primary cutaneous follicle center lymphoma
- Primary cutaneous DLBCL, leg type
- EBV-positive mucocutaneous ulcer
- Intravascular large B-cell lymphoma

5th edition of the WHO classification (2023)

Cutaneous T-cell lymphomas

- Mycosis fungoides & variants of MF
  - Folliculotropic MF
  - Granulomatous slack skin
  - Pagetoid reticulosis
- Sezary syndrome
- Adult T-cell lymphoma/leukemia
- Spectrum cutaneous CD30+ LPD (LyP – C-ALCL)
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma
- Hydroa vacciniforme-like LPD; mosquito bite allergy
- Primary cutaneous peripheral T-cell lymphoma, NOS + rare subtypes

  - Primary cutaneous γ/δ T-cell lymphoma
  - Aggressive cytotoxic epidermotropic CD8+ CTCL
  - Primary cutaneous CD4+ small/medium T-cell LPD
  - Primary cutaneous acral CD8+ T-cell LPD

Cutaneous B-cell lymphomas

- Primary cutaneous marginal zone lymphoma #
- Primary cutaneous follicle center lymphoma
- Primary cutaneous DLBCL, leg type
- EBV-positive mucocutaneous ulcer
- Intravascular large B-cell lymphoma

International consensus classification (ICC):

primary cutaneous marginal zone B-cell LPD

PCSM-TCLPD

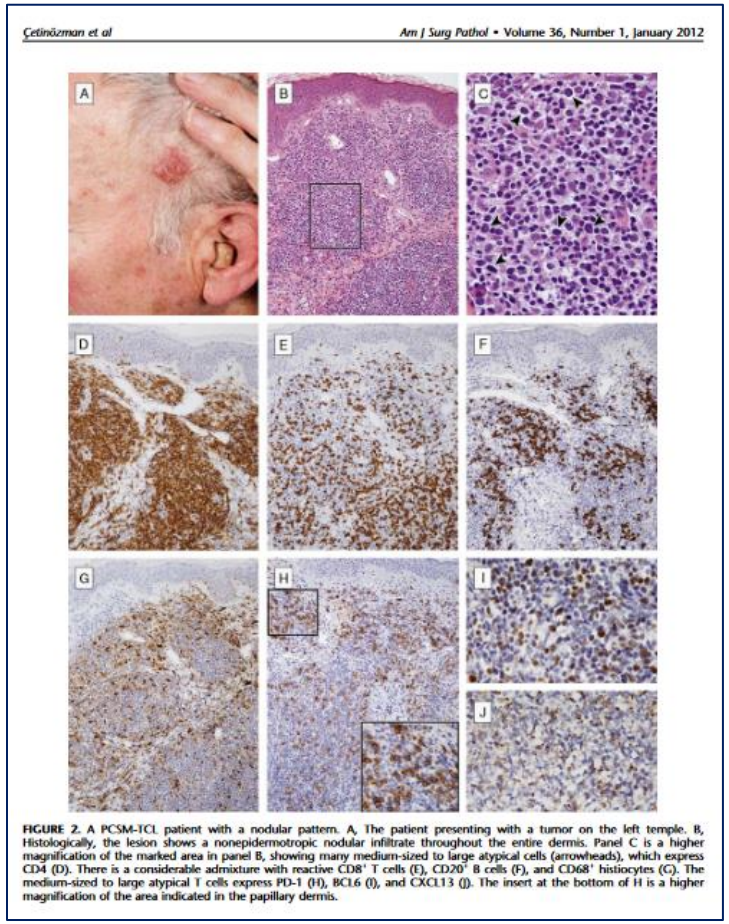


FIGURE 2. A PCSM-TCL patient with a nodular pattern. A, The patient presenting with a tumor on the left temple. B, Histologically, the lesion shows a nonepidermotropic nodular infiltrate throughout the entire dermis. Panel C is a higher magnification of the marked area in panel B, showing many medium-sized to large atypical cells (arrowheads), which express CD4 (D). There is a considerable admixture with reactive $CD8^+$ T cells (E), $CD20^+$ B cells (F), and $CD68^+$ histiocytes (G). The medium-sized to large atypical T cells express PD-1 (H), BCL6 (I), and CXCL13 (J). The insert at the bottom of H is a higher magnification of the area indicated in the papillary dermis.

Acral CD8+ TCLPD

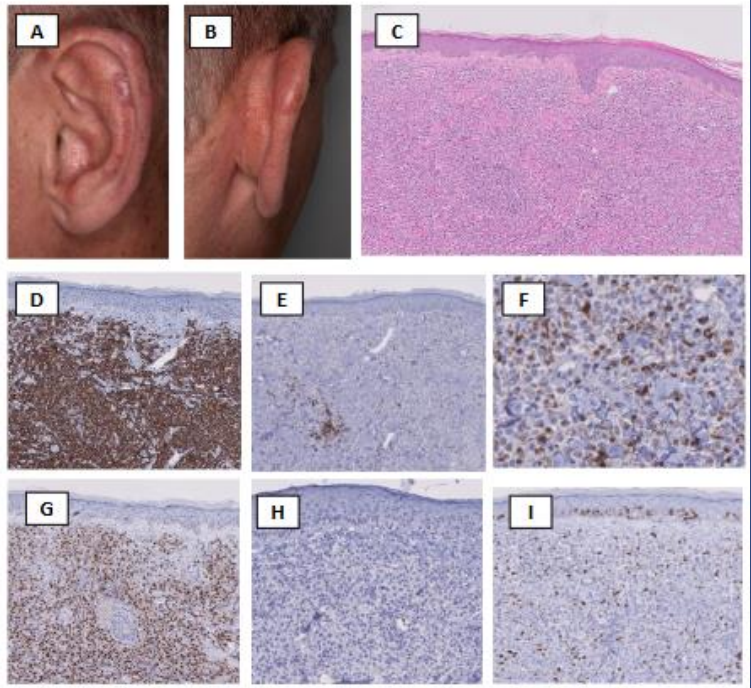


Figure 2. Primary cutaneous acral CD8-positive T-cell lymphoma. (A-B) clinical presentation with nodular lesions on both ears. (C) diffuse non-epidermotropic infiltrate throughout the whole dermis. (D) Atypical cells show strong expression of CD8, but (E) are completely negative for CD7. Note very low number of admixed reactive T cells. (F) atypical cells show dot-like staining for CD68, (G) are strongly positive for TIA-1, but (H) completely negative for granzyme B. (I) low prokiferation rate (Ki-67)

PCMZL(PD)

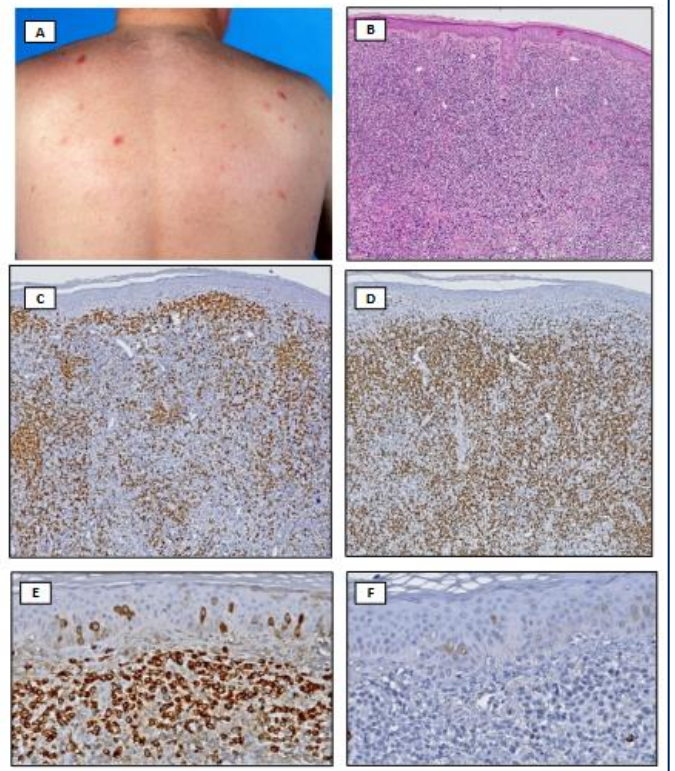


Figure 3. Primary cutaneous marginal zone lymphoma. (A) Typical clinical presentation with multiple nodules on the back. (B) Dense non-epidermotropic infiltrate throughout the dermis. (C) CD79a positive B cells and plasma cells. (D) CD3 staining shows many admixed reactive T cells. (E) Subepidermal plasma cells with positive staining for kappa light chains. (F) Negative staining for lambda light chains.

Willemze R. Cutaneous lymphoproliferative disorders: back to the future. J Cutan Pathol (in press)

What does the term LPD mean?

- Includes benign and malignant lymphoid proliferations and both LPD with an excellent and LPD with a poor prognosis
- Immunodficiency-associated LPD
  - Post-transplant lymphoproliferative disorders
  - iatrogenic immunodficiency-associated LPD
- Primary cutaneous CD30+ LPD
  - includes benign (LyP) and malignant (C-ALCL) conditions

Expected effects on clinical management:

In typical cases no (or less):

- staging
- aggressive treatment
- long-term follow-up

Questionnaire

Questionnaire to 30 cutaneous lymphoma centers

What does the term LPD mean to you?

Benign; indolent malignant; other, namely ……

- Benign without restriction: 12
- Benign with a caveat: 3
- Benign, but not PCMZL: 5
- Indolent malignant: 7
- Borderline/uncertain: 5

Questionnaire to 30 cutaneous lymphoma centers

What does the term LPD mean to you? **Benign; indolent malignant; other, namely ……** • Benign without restriction: 12 • Benign with a caveat: 3 • Benign, but not PCMZL: 5 • Indolent malignant: 7 • Borderline/uncertain: 5	**Effect on clinical management of any of the LPD in daily practise?** Change in clinical management: 19/30 - Less intense staging (no PET-CT): 10/30 - Less aggressive therapy (less RT): 6/30 - Less or shorter follow-up: 11/30 No change in clinical management: 11/30 Term LPD useful for patient reassurance

Questionnaire II

PCSM-TCLPD is	**A: benign condition/reactive process (not a cancer)** **B: indolent (low-grade) malignant lymphoma** **C: other: ……..**
PC acral CD8+ T-cell LPD is	A: benign condition/reactive process (not a cancer) B: indolent (low-grade) malignant lymphoma C: other: ……..
PCMZL(PD)	A: benign condition/reactive process (not a cancer) B: indolent (low-grade) malignant lymphoma C: other: ……..
Have you seen patients in your clinic with the characteristic clinicopathologic features[#] of a PCSM-TCLPD who	(A) developed extracutaneous disease: Yes/No. If so, how many? …… (B) died of lymphoma: Yes/No. If so, how many? ……
Have you seen patients in your clinic with an acral CD8+ T-cell LPD who	(A) developed extracutaneous disease: Yes/No. If so, how many? …… (B) died of lymphoma: Yes/No. If so, how many? ……
Have you seen patients in your clinic with a PCMZL(PD) who	(A) developed extracutaneous disease: Yes/No. If so, how many? …… (B) died of lymphoma: Yes/No. If so, how many? ……

Questionnaire II

	Benign	Malignant	Other	Change in clinical management		
				staging	treatment	FU policy
PCSM-TCLPD *	**24 (80%)**	3 (10%)	3 (10%)	7/30	4/30	7/30
Acral CD8+ TCLPD	**17 (57%)**	9 (30%)	4 (13%)	6/30	3/30	6/30
PCMZL(PD)	6 (20%)	**21 (70%)**	3 (10%)	4/30	3/30	6/30

* solitary lesion without prior or concurrent patches and/or plaques typical of MF

Extracutaneous dissemination

Have you seen patients in your clinic with the characteristic clinicopathologic features[#] of a PCSM-TCLPD / acral 8+ TCLPD / PCML(PD) who	(A) developed extracutaneous disease: Yes/No. If so, how many? …… (B) died of lymphoma: Yes/No. If so, how many? ……

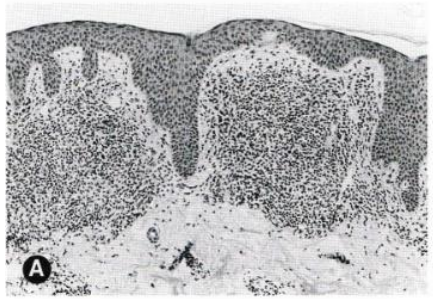
	Extracutaneous dissemination seen in	Cumulative number of patients	Died of LPD
PCSM-TCLPD *	3/30 centres	3	1
Acral CD8+ TCLPD	1/30 centres	1**	1 **
PCMZL(PD)	16/30 centres	ca. 50	ca. 5

* solitary lesion without prior or concurrent patches and/or plaques typical of MF

** Alberti-Violetti S, et al. Primary cutaneous acral CD8 positive T-cell lymphoma with extra-cutaneous involvement. J Cutan Pathol 2017; 44:964-8

Focus on PCSM-TCLPD

Pseudo-CTCL (nodular)



Pseudo-CTCL (band-like)

1980	Lymphomatoid reactions
1990	Pseudo-T-cell lymphomas (MF-plaque and nodular type)
1997	EORTC classification: CTCL, pleomorphic small/medium
2005	WHO-EORTC: Primary cutaneous CD4+ small/medium T-cell lymphoma
2008	WHO: Primary cutaneous CD4+ small/medium T-cell lymphoma
2016	Revised WHO: primary cutaneous CD4+ small/medium T-cell LPD
2018	Update WHO-EORTC: primary cutaneous CD4+ small/medium T-cell LPD
2022	5th edition WHO classification; ICC: unchanged

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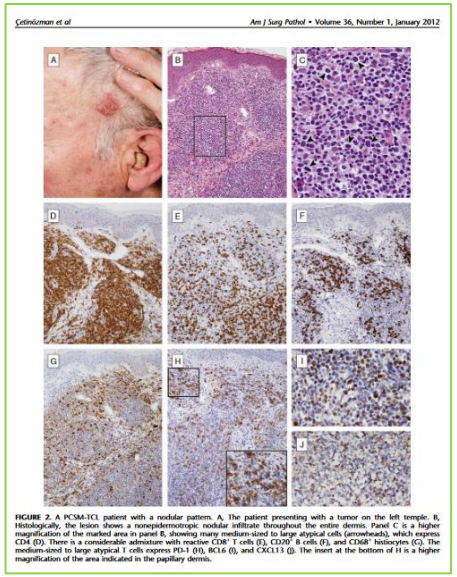
REVIEW

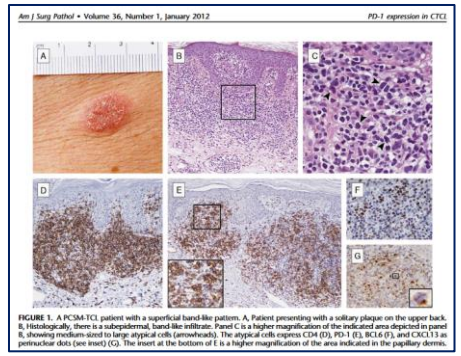
JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Cutaneous lymphoproliferative disorders: Back to the future

Rein Willemze MD



PCSM-TCLPD (nodular)



PCSM-TCLPD (band-like)

Rijlaarsdam JU et al. Seminars in Dermatology 1994;13:187-196; Cancer 1992;69:717-724

PCSM-TCLPD

- Second most common condition in consultation (>40/year)
- Considered as a benign condition by 80% of CL centers
- Extracutaneous dissemination exceedingly rare.

Literature	Number	Extracutaneous disease	Died of LPD
Beltramelli (2009)	136	0	0
Alberti-Violetti (2016)	62	0	0
Beltzung (2020)	60	0	0
Surmanowicz (2020)	160	0	0
Oschlies (2023)	177	0	0
LUMC (2019-2023)	200	0	0

PCSM-TCLPD

- Second most common condition in consultation (30-40/year)
- Considered as a benign condition by 80% of CL centers
- Extracutaneous dissemination exceedingly rare.

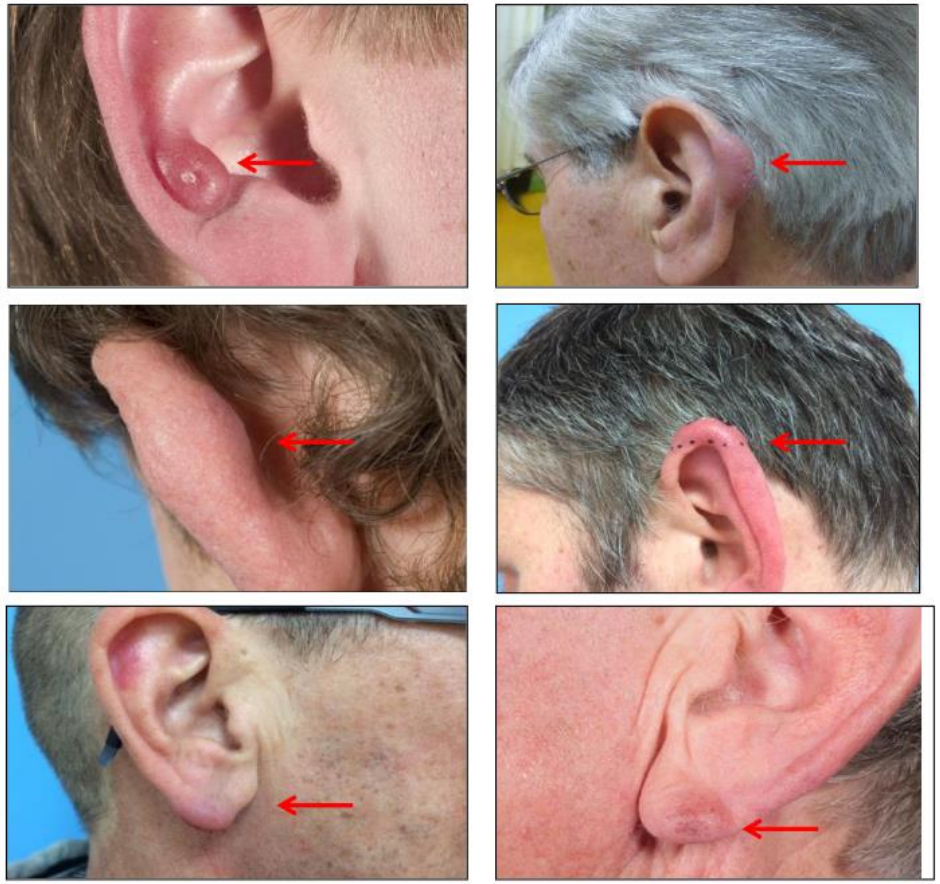
Literature	Number	Extracutaneous disease	Died of LPD
Beltramelli (2009)	136	0	0
Alberti-Violetti (2016)	62	0	0
Beltzung (2020)	60	0	0
Surmanowicz (2020)	160	0	0
Oschlies (2023)	177	0	0
LUMC (2019-2023)	150-200	0	0

- Clinical practise one would expect **In typical cases**:
  - no staging
  - no aggressive treatment
  - No long-term follow-up
- Current clinical practise:
  - Only 10 centers indicate staging not useful
  - No aggressive therapies proposed
  - FU ≥ 24 months: 16/30 centers

great need to develop uniform guidelines

for management and treatment

Acral CD8+ TCLPD



Biologically malignant – clinically benign

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Clinical, histopathological and prognostic features of primary cutaneous acral CD8$^+$ T-cell lymphoma and other dermal CD8$^+$ cutaneous lymphoproliferations: results of an EORTC Cutaneous Lymphoma Group workshop*

Werner Kempf,[1,2] Tony Petrella,[3] Rein Willemze,[4] Patty Jansen,[5] Emilio Berti,[6] Marco Santucci,[7] Eva Geissinger,[8] Lorenzo Cerroni,[9] Eve Maubec,[10] Maxime Battistella,[11] John Goodlad,[12] Emmanuella Guenova,[2,13] Katariina Lappalainen,[14] Annamari Ranki,[14] Paul Craig,[15] Eduardo Calonje,[16] Blanca Martin,[16] Sean Whittaker,[17] Ilske Oschlies,[18] Ulrike Wehkamp,[19] Jan P. Nicolay,[20] Marion Wobser,[21] Julia Scarisbruck,[22] Nicola Pimpinelli,[23] Rudi Stadler,[24] Katrin Kerl French,[25] Pietro Quaglino,[26] Jinran Lin,[27] Lianjun Chen,[27] Michaela Beer,[1] Patrick Emanuel,[28,29] Stephane Dalle[30] and Alistair Robson[31,32]

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biopsy. [16,20] For nonregressing lesions, surgical excision and/or radiotherapy were efficient therapeutic modalities and resulted in complete remission with an overall low rate of relapses. [3,18] There was consensus in the workshop that staging examinations are not mandatory in the context of typical clinical and histological findings, in the absence of immunodeficiency, as suggested in the updated WHO-EORTC classification for primary cutaneous lymphomas.[3]

PCMZL/PCMZLPD

- Considered as a indolent lymphoma by 70% of CL centers
- Reluctance to accept the term PCMZLPD
- Large series: extracutaneous dissemination: 4-8%
- Dutch CL registry: extracutaneous dissemination: 10/391 (2.5%)
- Experience with extracutaneous dissemination: 16/30 centres with in total > 50 patients

Which patients are at risk to develop extracutaneous disease?

EORTC CLG meeting

Lausanne

Summary and conclusions

- Downgrading of low-grade malignant lymphomas to LPD: most important change in cutaneous lymphoma classifications over the last 15 years
- Term LPD widely accepted, but interpreted in different ways and often not followed by changes in clinical management.
- Current clinical practise very heterogeneous.
- Need to develop uniform guidelines for typical cases.
- For philosophers: How to define malignant: biologically or clinically ?

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Patty Jansen

Ellen Kim

Youn Kim

Marjolein Koldijk

Marta Marschalko

Christine Mitteldorf

Montserrat Molgo

Elise Olsen

Pablo Ortiz

Lia Papadavid

Nicola Pimpinelli

Melissa Pulitzer

Pietro Quaglino

Christiane Querfeld

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Thank you!

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