Advances in cutaneous B-cell lymphomas

Werner Kempf

Dept. of Dermatology
University Zürich

Kempf and Pfaltz
Histological Diagnostics
Zürich
Cutaneous B-cell lymphomas

- Clinicopathological variants of MZL and FCL
- Prognostic factors
- EBV- and MTX-associated B-cell LPD
- Post-transplant CBCL
Primary cutaneous B-cell lymphomas (CBCL) account for 25-35% of all primary cutaneous lymphomas.
Primary cutaneous B-cell lymphomas account for 30% of cutaneous lymphomas.

- Marginal zone B-cell lymphoma (MZL): 50-55%
- Follicle center lymphoma (FCL): 35-40%
- Diffuse large B-cell lymphoma, leg type: 10-15%
Primary cutaneous follicle center lymphoma

Follicular pattern

Mixed

Diffuse pattern

Centrocyte-like cells of variable size with cleaved nuclei.
Primary cutaneous follicle center lymphoma

bcl-6 +  bcl-2 -

Bcl-2 negative and lack of underlying translocation
Primary cutaneous follicle center lymphoma

Mean age: 59 years (20-80 years)

Solitary nodule, surrounding plaques
Predilection sites: head and neck, upper trunk

T-stage at diagnosis:
- T1 (solitary) 38%
- T2 (regional) 62%
- T3 (dissemin) 0%

Golling et al. Leuk Lymphoma 2008
Multiple erythematous, firm papules resembling millet seeds or arranged in small clusters.

Head and neck region (80% pat.)
Disseminated (head and neck, trunk) (20% pat.)

Fig 1. Miliary primary cutaneous follicle center lymphoma (case 9). A, Disseminated erythematous papules simulating clinical picture of lupus miliaris disseminatus faciei or of papular rosacea; in this patient similar lesions were located also on back (B) and upper extremities (C). D, Papule detail.
The initial diagnosis was never cutaneous lymphoma, but rosacea, lupus miliaris disseminatus faciei, and persistent arthropod bite reaction.

Microscopic examination confirmed the diagnosis of PCFCL in all patients.

Miliarial FCL with follicular mucinosis

Figure 1. A Case of Primary Cutaneous Follicle Center Lymphoma With a Very Unusual Miliary Clinical Presentation

Primary cutaneous follicle center lymphoma with follicular mucinosis.
Garrido MC1, Riveiro-Falkenbach E1, Rodriguez-Peralto JL1.

Figure 2. Histologic Specimens From Primary Cutaneous Follicle Center Lymphoma With Follicular Mucinosis

CD20
Cutaneous follicle center lymphoma - spindle cell variant

Fascicular pattern, spindle cells
CD20+, bcl-6+, bcl-2 +/- CD10+
CD21+ FDC

Cutaneous spindle-cell B-cell lymphoma

Primary cutaneous spindle cell follicular center lymphoma with extracutaneous spread to the liver after 27 months

Rozati et al. J Cutan Pathol 2013
Primary Cutaneous Spindle Cell B-Cell Lymphoma of Follicle Origin Mimicking Acne Rosacea.

Garrido MC1, Rios JJ, Riveiro-Falkenbach E, Escamez PJ, Ronco MA, Rodríguez-Peralto JL.
Primary cutaneous follicle center lymphoma with Hodgkin and Reed-Sternberg-like cells: a new histopathologic variant.

Marie D, Houba BR, Béatrice V, Matthieu F, Louis T, Olivier N, Marie BR, Audrey G, Jean-Philippe M, Marie P.
**PCFCL with Hodgkin and Reed-Sternberg-like cells**

**Hodgkin-like cells:** CD30+, CD15+, PAX5+, OCT2+, BOB1+, MUM1+, Ki67+, Bcl6+ and focally CD20+ and CD10-. EBER-

**Medium-sized cells:** CD20+, CD79a+, Bcl2+, Bcl6+ and CD10+ in a network of CD21-positive follicular dendritic cells.
CD30+ cutaneous follicle center lymphoma
CD30+ cutaneous follicle center lymphoma

Three men and one woman
No immunosuppression

Tumors on the scalp and trunk
Indolent course.

Mixed, diffuse, and follicular growth pattern
Centrocyte-like tumor cells
CD20+, bcl-6+, bcl-2-, CD10-

Expression of CD30 by 70-90% of the tumor cells

All cases EBER negative.

# B-cell clonality

<table>
<thead>
<tr>
<th></th>
<th>SB/PCR - IgH</th>
<th>IHC - k / l</th>
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<tbody>
<tr>
<td>Follicle center lymphoma</td>
<td>58-80%</td>
<td>39%</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>50-80%</td>
<td>38-82%</td>
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</table>
Clonality and flow cytometry

**FCI analysis possible in 88% of cases -> clonality in 68% of CBCLs**

**Molecular studies for IgH clonality possible in 74% -> % clonality in 39%**

**ICH/ISH results interpretable in 84% of cases -> 55% clonality**

**FCI is feasible and more reliable than molecular studies or IHC/in situ hybridization for detecting clonality in CBCLs**

**Exception: Cases with plasmacytic differentiation such as marginal zone lymphoma -> IHC might be a superior tool.**

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**Clonality assessment of cutaneous B-cell lymphoid proliferations: a comparison of flow cytometry immunophenotyping, molecular studies, and immunohistochemistry/in situ hybridization and review of the literature.**

Schafernak KT¹, Variakojis D, Goolsby CL, Tucker RM, Martinez-Escala ME, Smith FA, Dittman D, Chenn A, Guitart J.
Cutaneous marginal zone lymphoma (MALT lymphoma)

Lymphoplasmacytoid cells
Plasma cells
Monocytoid B-cells

Nodular and confluent infiltrates
Cutaneous marginal zone lymphoma

Tumor cells:
CD20+
bcl-2 +, bcl-6 -

Infiltration of germinal centers by bcl-2 + neoplastic B-cells and T-cells
Primary cutaneous marginal zone lymphoma
(extranodal MALT lymphoma)

Clinical features

Median age: 39 years (30 – 50y)

Trunk, extremities (arms >> legs)

Multifocal (50-72%)


Golling et al. Leuk Lymphoma 2008
Prognosis in B-cell lymphomas

95% (5 year-survival rate)

50% (5 year-survival rate)

Fig 1 C; Senff et al. J Clin Oncol 2007
Primary cutaneous marginal zone B-cell lymphoma: Response to treatment and disease-free survival in a series of 137 patients

Octavio Servitje, MD, Cristina Municsa, MD, Yolanda Benavente, PhD, Verónica Monsálvez, MD, M. Pilar García-Muret, MD, Fernando Gallardo, MD, Eva Domingo-Domench, MD, Anna Lucas, MD, Fina Climent, MD, Jose L. Rodríguez-Peralto, MD, Pablo L. Ortiz-Romero, MD, Juan Sandoval, PhD, Ramon M. Pujol, MD, and M. Teresa Estrach, MD, PhD

Barcelona and Madrid, Spain

Background: Primary cutaneous marginal zone B-cell lymphomas are low-grade lymphomas running an indolent course. Skin relapses have been frequently reported but little information about disease-free survival (DFS) is available.

Objective: We sought to evaluate relapse rate and DFS in patients with primary cutaneous marginal zone B-cell lymphomas.

Methods: Clinical features, European Organization for Research and Treatment of Cancer/International Society for Cutaneous Lymphomas stage, light chain restriction, clonality, treatments, skin relapses, DFS, stage progression, extracutaneous disease, and outcome are analyzed in a series of 137 patients.

Results: Patients were classified as solitary lesion (T1) (n = 70; 51%), regional skin involvement (T2) (n = 40; 29%), and generalized skin lesions (T3) (n = 27; 20%). Surgical excision, local radiotherapy, or a combination were the initial treatment in 118 patients (86%). In 121 of 137 patients (88%) a complete remission was observed after initial treatment, including 99 of 106 patients (93%) with solitary or localized disease and 22 of 31 patients (71%) with multifocal lesions. Cutaneous relapses were observed in 53 patients (44%). Median DFS was 47 months. Patients with multifocal lesions or T3 disease showed higher relapse rate and shorter DFS. No significant differences were observed between surgery and radiotherapy, but surgery alone was associated with more recurrences at initial site. Overall survival at 5 and 10 years was 93%. Six patients (4%) developed extracutaneous disease during follow-up.

Limitations: This was a case series retrospective study.

Conclusion: Our results support long-term follow-up in patients with primary cutaneous marginal zone B-cell lymphomas. Disseminated skin lesions have higher relapse rate and shorter DFS suggesting further investigation on systemic therapies in such a group of patients. (J Am Acad Dermatol 2013;69:357-65.)
<table>
<thead>
<tr>
<th>Extension of skin lesions</th>
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<tr>
<td>Solitary</td>
<td>70 (51%)</td>
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<tr>
<td>Localized</td>
<td>36 (26%)</td>
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<td>Multifocal</td>
<td>31 (23%)</td>
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<th>Complete response after initial therapy</th>
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<tr>
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<td>121 (88%)</td>
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<th>Relapse rate</th>
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<td>≥2 Relapses</td>
<td>53/121 (44%)</td>
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<td>18/121 (15%)</td>
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<td>6 (4%)</td>
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<td>54 (12-165)</td>
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<td>Died, other cause</td>
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**Surgical excision and/or radiotherapy**

**5y and 10 year DSS: 93%**
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| Complete response after initial therapy | 121 (88%) |
| Relapse rate                         | 53/121 (44%) |
| ≥ 2 Relapses                         | 18/121 (15%) |
| Extracutaneous involvement           | 6 (4%)  |

Follow-up, mo, median (range) 54 (12-165)

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Surgical excision and/or radiotherapy

5y and 10 year DSS: 93%
6 / 137 patients (4%) with extracutaneous involvement (3 T1a; 1 T2a; 2 T3a)

Mean time to systemic disease: 24 months (range 5-44)

**Extracutaneous sites:** Lymph nodes
GI tract
Bone marrow
Lung

In half of the patients simultaneous skin relapse

**Outcome**
CR in all but one patient after chemotherapy and rituximab

Large-cell transformation in marginal zone lymphoma
Large-cell transformation in marginal zone lymphoma
Large-cell transformation in marginal zone lymphoma

Large cell transformation preceded systemic involvement.

Large cell transformation and/or systemic involvement exclusively in patients with disease greater than stage T2b (regional disease).

Gerami et al. JAAD 2008
Nonclass-switched MZL (group 2)(6 cases)

Large nodules with diffuse proliferation of CD20+ B-cells

Predominance of B-cells with only moderately numerous T-cells

IgM+ reactive follicles

CXCR3+ B-cells (2/5 cases)

Extracutaneous involvement (3/6 cases)
Primary cutaneous marginalzone lymphoma

Excellent prognosis: 93-98% 5-year-survival rate

Tx: Surgical excision / radiotherapy

Relapses: 40-50%

Extracutaneous spread (4%)

Large cell transformation
Nonclass-switched pattern

-> Multiagent chemotherapy and rituximab
Class-switched MZL (group 1; 23 cases) [IgG, IgA, or IgE + plasma cells]

Perivascular/periadnexal infiltrate with small to medium-sized nodules

Numerous T-cells (>90% cases)

IgD+ reactive follicles

Lack of CXCR3

No extracutaneous involvement
In lymphocytoma cutis, but not in MZL:

Confluence of follicles
Lack of polarization
CD10+ and/or bcl-6+ interfollicular clusters

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Lymphocytoma Cutis (%)</th>
<th>Follicle Center Cell Lymphoma (%)</th>
<th>Marginal Zone Lymphoma (%)</th>
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<tbody>
<tr>
<td>Mantle zone absent</td>
<td>11/12 (91.6)</td>
<td>25/29 (86.2)</td>
<td>0/6 (0)</td>
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<tr>
<td>Tingible body macrophages absent</td>
<td>0/12 (0)</td>
<td>23/29 (79.3)</td>
<td>0/6 (0)</td>
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<tr>
<td>Confluence of follicles</td>
<td>5/12 (41.6)</td>
<td>12/29 (41.3)</td>
<td>0/6 (0)</td>
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<tr>
<td>Lack of polarization</td>
<td>10/12 (83.3)</td>
<td>28/29 (96.5)</td>
<td>0/6 (0)</td>
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<tr>
<td>Lack of polarization (MIB-1)</td>
<td>6/12 (50)</td>
<td>25/29 (86.2)</td>
<td>0/6 (0)</td>
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<tr>
<td>CD10+ and/or Bcl-6+ interfollicular clusters</td>
<td>3/12 (25)</td>
<td>19/29 (65.5)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Bcl-2+ on follicular cells</td>
<td>0/12 (0)</td>
<td>8/29 (28.6)*</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Reduced proliferation rate</td>
<td>1/12 (8.3)</td>
<td>23/29 (79.3)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Monoclonoality by PCR</td>
<td>1/10 (10)</td>
<td>14/27 (51.9)</td>
<td>2/4 (50)</td>
</tr>
</tbody>
</table>

Leinweber et al. Am J Dermatopathol 2004
Cutaneous marginal zone lymphoma

Plasma cells
Often in sheets

Monoclonal expression of Ig light chains kappa or lambda

Monoclonal = ratio > 5:1 or 10:1

CD79a
Ig kappa
Ig lambda
Cutaneous marginal zone lymphoma
Cutaneous marginal zone lymphoma

Ig kappa

Ig lambda
Light chain restriction confined to lower portions of cutaneous lymphocytic proliferations: a potential diagnostic pitfall.
MZL and B-cells

Pax 5
IgG4 and skin diseases

Cutaneous pseudolymphomas and marginal zone lymphoma

IgG4+ count: 342 to 425 cells per HPF

IgG4 / IgG ratio >68 and 100%

Cutaneous MZL and IgG4

169 marginal zone lymphomas of various primary sites -> +: IgG4:IgG 70%

19 of 49 (39%) primary cutaneous MZL: IgG4+
No evidence of a preexisting systemic IgG4-related disease. 16 IgG4+ cases were kappa+

Only 1 out of 120 noncutaneous marginal zone lymphomas (ocular adnexae) expressed IgG4

IgG4-positive and IgG4-negative PCMZL
No differences in architecture or composition of the reactive T-cell infiltrate.

PCMZL: localized immunologic IgG4-driven pathogenetic process at early stages of the disease.

Brenner et al. Mod Pathol 2013

from: Fig. 2 Brenner et al. Mod Pathol 2013
PD-1, S-100 and CD1a expression in pseudolymphomatous folliculitis, primary cutaneous marginal zone B-cell lymphoma (MALT lymphoma) and cutaneous lymphoid hyperplasia.

Goyal A1, Moore JB, Gimbel D, Carter JB, Kroshinsky D, Ferry JA, Harris NL, Duncan LM.
MZL vs. pseudolymphoma

PD1+ cells
Significant increase in PD-1+ T cells in pseudolymphoma compared with MALT lymphoma (p < 0.0001).

CD1a staining pattern
Peripheral concentration of CD1a+ dendritic cells around lymphoid nodules more common in MZL than in pseudolymphoma CLH (p < 0.05).

Interstitial distribution of CD1a+ cells more often in PSL than in MZL (p < 0.04).
Follicular helper T-cells

Follicular helper T-cells (T<sub>FH</sub>)
- CD4
- PD-1
- CXCL-13
- Bcl-6
- CD10
- ICOS

Germinal center associated T-cells
- Inhibition of T-cell activity
- Induction of peripheral tolerance

Activated T-cells
- PD-1
PD-1 cells in follicular lymphoma

High Numbers of Tumor-Infiltrating Programmed Cell Death 1–Positive Regulatory Lymphocytes Are Associated With Improved Overall Survival in Follicular Lymphoma

Joaquin Carreras, Armando Lopez-Guillermo, Giovanna Roncador, Neus Villamor, Lluis Colomo, Antonio Martinez, Rijat Hamoudi, William J. Howat, Emili Montserrat, and Elias Campo

ABSTRACT

Purpose
Tumor microenvironment influences the behavior of follicular lymphoma (FL), although the specific cell subsets involved are not well known. The aim of this study was to determine the impact of programmed cell death 1 (PD-1)–positive inhibitory immunoregulatory lymphoid cells in the clinicobiologic features and outcome of patients with FL.

Patients and Methods
We examined samples from 100 patients (63 men and 47 women; median age, 54 years) at diagnosis, as well as in 32 patients at first relapse, with a recently generated monoclonal antibody against PD-1. The cells were quantified using computerized image analysis. Additional analysis consisted of double immunofluorescence and flow cytometry.

Results
PD-1 expression was alternative to FOXP3 in lymphoid cells from both reactive tonsils and FL. At diagnosis, the median percentage of PD-1–positive cells was 14% (range, 0.1% to 74%). Patients with grade 3 FL, poor performance status, and high serum lactate dehydrogenase showed lower numbers of PD-1–positive cells. After a median follow-up of 6.2 years, patients with PD-1–positive cells ≤ 5% (n = 25), 6% to 33% (n = 50), and more than 33% (n = 25) had a 5-year progression-free survival rate of 20%, 46%, and 48% (P = .038) and overall survival (OS) of 50%, 77%, and 96% (P = .004), respectively. PD-1 and FL International Prognostic Index maintained prognostic value for OS in multivariate analysis. Patients with PD-1–positive cells ≤ 5% showed a higher risk of histologic transformation. At that time, transformed diffuse large B-cell lymphomas had lower percentage of PD-1–positive cells than FL.

Conclusion
A high content of PD-1–positive cells predicted favorable outcome of FL patients, whereas a marked reduction is observed in transformation.

J Clin Oncol 27:1470-1476. © 2009 by American Society of Clinical Oncology
Expression of programmed death-1 (CD279) in primary cutaneous B-cell lymphomas with correlation to lymphoma entities and biological behaviour

C. Mitteldorf,1 M. Bleri,2 N. Wey,2 K. Kerl,2 J. Kamarachev,3 M. Pfaltz,4,5 H. Kutzner,6 G. Roncador,7 D. Tomasini8 and W. Kempf1,5

1Department of Dermatology, Klinikum Hildesheim GmbH, Hildesheim, Germany
2Department of Pathology, 3Department of Dermatology, 4Department of Psychiatry and Psychotherapy, University Hospital Zürich, Zürich, Switzerland
5Kempf and Pfaltz, Histologische Diagnostik, Research Unit, Sempierstrasse 1, CH-8044 Zürich, Switzerland
6Dermatoscopic Freiburg, Friedenshoehe, Germany
8Cenro Nacional de Investigaciones Biologicas, Madrid, Spain

Summary

Background Programmed death-1 (PD-1/CD279) is a cell-surface protein expressed in activated T cells and a subset of T lymphocytes including follicular helper T cells (THF). The interaction between PD-1 and its ligands plays a role in immune response and evasion of malignancies. In nodal follicular lymphoma, the number of intratumoral PD-1-positive lymphocytes is associated with overall survival.

Objective To investigate 28 cases of primary cutaneous B-cell lymphoma, including the subtypes PCCL (n = 10), PCMZL (n = 10) and DLBCL-LT (n = 8) for the number and density of PD-1-positive cells.

Methods Immunohistochemical staining and a computerized morphometric analysis for evaluation were applied. The results were correlated with the clinical outcome. To distinguish between activated T cells and THF we performed PD-1/bcl-6 double staining and compared these results with CXCL-13 staining. Double staining for PD-1 and PAX-5 was used to investigate whether tumour cells were positive for PD-1.

Results The PD-1-positive cells represented tumour-infiltrating T cells (TILs). Only a minor subset was represented by THF. Patients with DLBCL-LT had a significantly lower number of PD-1-positive TILs than those with PCMZL (P = 0.012) and PCCL (P = 0.002) or both (P = 0.001). The difference between PCMZL and PCCL did not reach significance (P = 0.074). The tumour cells were negative for PD-1.

Conclusions A higher number of PD-1-expressing cells was found in indolent PCMZL and PCCL than in high-malignant DLBCL-LT. The PD-1-positive cells represented not only THF, but also other activated T cells as a part of the tumour microenvironment. The tumour cells in all investigated types of PCCL did not show aberrant PD-1 expression.
PD-1 positive $T_{FH}$ cells in cutaneous follicle center lymphoma

Numerous scattered PD-1 positive T-cells mostly in the neoplastic follicles.
PD-1 positive $T_{FH}$ cells in cutaneous B-cell lymphomas

Marginal zone lymphoma (MZL)  Follicle centre lymphoma (FCL)  Diffuse large B-cell lymphoma (DLBL)
Prognosis in B-cell lymphomas

Fig 1 C; Senff et al. J Clin Oncol 2007

95% (5 year-survival rate)

50% (5 year-survival rate)
Colon disorders, including irritable bowel syndrome and inflammatory bowel disease (20 vs 7 in the CG, P = .01).

Autoimmunity was reported in 20.0% of participants (16 vs 6 in the CG, P = .03).

- Sicca syndrome (10), Hashimoto thyroiditis (8), lupus erythematosus (2),
- Sjögren syndrome (1), positive antinuclear antibody (3)
Primary cutaneous B-cell lymphomas

Primary cutaneous B-cell lymphomas account for 30% of cutaneous lymphomas.

- Marginal zone B-cell lymphoma (MZL) - 50-55%
- Follicle center lymphoma (FCL) - 35-40%
- Diffuse large B-cell lymphoma, leg type - 10-15%
Primary cutaneous diffuse large B-cell lymphoma, leg type

Elderly women > men
Median age: 78 years (50-95y)

Most commonly on the lower legs
Solitary or multiple nodules
Rapid growth
Primary cutaneous diffuse large B-cell lymphoma, leg type

Definition
Large B-cell lymphoma with a predominance or confluent sheets of centroblast-like and immunoblast-like cells, characteristically presenting with skin lesions on the (lower) legs.

Uncommonly, skin lesions with a similar morphology and phenotype can arise at sites other than the legs.
Primary cutaneous diffuse large B-cell lymphoma, leg type

Grenzzone
Diffuse infiltrates

Centroblast and immunoblast-like large cells with round nuclei and prominent nucleoli
DLBL, leg type – morphological spectrum

- epidermotropic
- angiocentric
- anaplastic
- spindle cell

Plaza et al. Am J Dermatopathol 2011
Primary cutaneous diffuse large B-cell lymphoma, leg type

Tumor cells

CD20+ or CD79a+
CD10-/+  

**bcl-2+++**

**bcl-6 +/-**

MUM-1 / IRF-4 ++

Monotypic slg/clg
**Differential Diagnosis**

**Follicle center lymphoma, diffuse growth pattern**

- Centrocyte-like cells with cleaved nuclei
- $bcl-6^+ \quad IgM^- \quad bcl-2^-$

**Diffuse large B-cell lymphoma, leg type**

- Centroblast-like cells with round nuclei
- $Bcl-2^+ \quad IgM^+ \quad MUM-1$

Centroblast-like cells with round nuclei
DLBL and FDC

Follicular dendritic cells (FDCs): CD21, CD35

All 82 cases were classified as pcDLBCL

- 53 cases DLBCL, leg type,
- 29 cases DLBCL “NOS/others”

In 15/82 cases (18%) CD21/CD35+ networks within the tumor

FDC networks as remnants of residual germinal center suggesting the possibility of a transformed low-grade B-cell lymphoma from FCL to DLBL.

Plaza et al. Am J Dermatopathol 2014
Prognosis in B-cell lymphomas

95% (5 year-survival rate)

50% (5 year-survival rate)

Fig 1 C; Senff et al. J Clin Oncol 2007
**DLBCL, leg type – prognostic markers**

### Factors

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<th>Localisation and number of lesions</th>
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<tbody>
<tr>
<td><strong>Solitary lesion:</strong> 100%</td>
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<td><strong>Multiple lesions:</strong> 45% (one leg), 36% (both legs)</td>
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Grange et al. J Clin Oncol 2001

### Apoptosis profile

<table>
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<th>AAC: activation of NFkB pathway</th>
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<td>-&gt; Inhibition of anti-apoptosis proteins</td>
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Van Galen et al. J Pathol 2008

### Deletion of 9p21 and/or p16 expression

<table>
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<tr>
<th>FISH 9p21 negative -&gt; poor prognosis</th>
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<tr>
<td>p16 negative -&gt; poor prognosis</td>
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Senff et al. JID 2009
Spectrum of EBV-associated lymphomas

- Cutaneous marginal zone lymphoma
  - Cutaneous immunocytoma (Borr, HCV)
  - Cutaneous plasmacytoma
- EBV-associated diffuse large B-cell lymphoma of the elderly
- Plasmablastic lymphoma (EBV, HHV-8)
- Burkitt lymphoma (EBV)
- Post-transplant B-cell LPD (EBV)
- Plasma cell myeloma
- Extraosseous plasmacytoma (EBV, HSV)

Plasmacellular or plasmablastic differentiation
Definition

EBV positive clonal B-cell lymphoid neoplasm in patients > 50 years and without any known immunodeficiency or prior lymphoma

Probably related to immunological deterioration or senescence in immunity as part of the aging process.

Extranodal (70% of patients), most commonly skin, lung, tonsil, stomach

Aggressive course, median survival 2 years.

Hoeller et al. Hum Pathol 2010

Courtesy by Dr. B. Zelger and Dr. H. Müller, Innsbruck
EBV positive diffuse large B-cell lymphoma of the elderly

Immunoblast-like cells
Plasmablast-like cells
Hodgkin / Reed-Sternberg-like cells

EBER
EBV positive mucocutaneous ulcer

**Histology**
Polymorphous infiltrate
atypical large B-cell blasts
often with HRS cell-like
morphology.

**Phenotype**
B-cells:
CD20 +/- CD30++; EBER ++

Background of abundant T cells
and eosinophils

Isolated, sharply demarcated ulceration

Oropharynx > skin > GI tract

Drug-related immunosuppression (35% of the pat.)
Complete remission after withdrawal of immunosuppression

45% spontaneous regression
15% Recurrence
Complete remission in all patients
Methotrexate-associated B-cell LPD

61-year-old man with rheumatoid arthritis. MTX since 5 years.

Images: Dr. R. Litvik (CZ)

Case: Dr. D. V. Kazakov, Pilsen
Methotrexate-associated B-cell LPD

Perivascular and perieccrine infiltrates
Methotrexate-associated B-cell LPD

bcl-2

bcl-6

MUM1

CD30 / bcl-6
Methotrexate-associated B-cell LPD

10 patients with MTX-associated B-LPD first presenting in the skin

EBV status: 5 EBV+ and 5 EBV- cases

Ulcerating and/or generalized skin lesions

Abrogation of MTX therapy resulted in a complete response in 4 cases and a partial response in 2 patients.

5-year disease specific survival: 90%.
MTX B-cell LPD - histology

Histology
Infiltrate composed of centroblasts and immunoblasts rather than large centrocytes.

Phenotype
B-cell markers with reduced staining for CD79a MUM1 (80%) and FOXP1 (70%) in most cases. Bcl-2 (80%), bcl-6 (70%) CD30 (60%), EBER (50%)

Admixture of T-cells
**Post-transplant lymphoproliferative disorders (PTLD)**

**Definition (WHO 2008)**

PTLD are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ, bone marrow, or stem cell allograft.

**Epidemiology**

PTLD account for 1-10% of all neoplasms in OTR.

The rate of PTLD higher in first year after TPL.

Higher risk in cardiac and liver TR than in renal TR.

Opelz et al. 1993; Caillard et al. 2000

Majority of PTLD are **EBV-associated B-cell lymphomas**.

Trappe et al. 2006

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Primary cutaneous lymphomas after TPL are rare with less than 100 cases published until 2013.
Aim
To assess the spectrum of PCL and to characterize the clinico-pathologic features of primary cutaneous lymphomas in OTR.

Method
Retrospective multicenter study (SCOPE members)
• Clinical data on presentation and disease course
• Histologic, phenotypic and genotypic features
• Virologic studies


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<table>
<thead>
<tr>
<th>Table 1. Categories of PTLD (WHO 2008)</th>
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</thead>
<tbody>
<tr>
<td>1. Early lesions</td>
</tr>
<tr>
<td>a Reactive plasmacytic hyperplasia</td>
</tr>
<tr>
<td>b Infectious mononucleosis-like lesions</td>
</tr>
<tr>
<td>2. Polymorphic PTLD</td>
</tr>
<tr>
<td>3. Monomorphic PTLD</td>
</tr>
<tr>
<td>B cell neoplasms</td>
</tr>
<tr>
<td>a Diffuse large B cell lymphoma</td>
</tr>
<tr>
<td>b Burkitt’s lymphoma</td>
</tr>
<tr>
<td>c Plasma cell myeloma</td>
</tr>
<tr>
<td>d Plasmacytoma-like lesions</td>
</tr>
<tr>
<td>e Others</td>
</tr>
<tr>
<td>T cell neoplasms</td>
</tr>
<tr>
<td>a Peripheral T cell lymphoma not otherwise specified</td>
</tr>
<tr>
<td>b Hepatosplenic T cell lymphoma</td>
</tr>
<tr>
<td>c Others</td>
</tr>
<tr>
<td>4. Classical Hodgkin’s lymphoma-type and Hodgkin’s lymphoma-like PTLD</td>
</tr>
</tbody>
</table>
SCOPE cutaneous lymphoma study

Retrospective, multicenter study on 35 cases

24 / 35 (69%) primary cutaneous T cell lymphoma (CTCL)
  Mycosis fungoides (MF) (50%)
  CD30+ LPD
  ATLL

11 / 35 (31.4%) primary cutaneous B cell PTLD
  EBV-associated B-PTLD (91%)

Death due to lymphoma
  16 / 35 (46%) patients died after a median follow-up of 19.5 months

Seckin et al. Am J Transplantation 2013
### Primary cutaneous lymphomas in OTR

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>SCOPE CL study</th>
<th>CL registries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous B-cell lymphoma</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>0</td>
<td>14%</td>
</tr>
<tr>
<td>Follicle center lymphoma</td>
<td>0</td>
<td>14%</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>10%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>B-cell lymphomas, NOS</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Cutaneous B-cell lymphomas in OTR

Study group 11 cases (SCOPE centers)

Epidemiology
Median age: 55 years (range: 22-75) at diagnosis
M : F = 10:1

Heart (44%), kidney (34%), kidney + pancreas (22%) TPL

Interval TPL - diagnosis: 8 years (range: 0-15)

Presentation
TNM Stage: T1 or T2
Solitary or multiple nodules and plaques

SCOPE study Case 6, Paris
B-PTLD – Histological subgroups in SCOPE series

Early lesions (10%)
Plasma-cell hyperplasia (n=1) EBV+

Polymorphic B-cell lymphoproliferation

Monomorphic lymphoma (90%)

Diffuse large-cell lymphoma (n=9)
  immunoblastic (EBV+) (n=3)
  centroblastic (EBV+) (n=5)
  anaplastic / Hodgkin type (EBV+) (n=1)

Burkitt/Burkitt-like lymphoma

Plasma cell myeloma

Plasmacytoma-like lymphoma (EBV-) (n=1)
Cutaneous B-cell lymphomas in OTR

Histology

- Nodular dermal and subcutaneous infiltrates
- Monomorphous
- Centroblastic or immunoblastic morphology
B-PTLD

Diffuse cohesive infiltrates
Immunoblastic or plasmablastic differentiated tumor cells

Mitoses, apoptotic tumor cells

CD79a+, CD138+, MUM1/IRF4+
EMA, CD30, MIB-1 (>90%)

EBER (10/11 cases)
### Table 1. Categories of PTLD (WHO 2008)

1. Early lesions
   - a Reactive plasmacytic hyperplasia
   - b Infectious mononucleosis-like lesions

2. Polymorphic PTLD

3. Monomorphic PTLD
   - B cell neoplasms
     - a Diffuse large B cell lymphoma
     - b Burkitt’s lymphoma
     - c Plasma cell myeloma
     - d Plasmacytoma-like lesions
     - e Others
   - T cell neoplasms
     - a Peripheral T cell lymphoma not otherwise specified
     - b Hepatosplenic T cell lymphoma
     - c Others

4. Classical Hodgkin’s lymphoma-type and Hodgkin’s lymphoma-like PTLD
B-PTLD - Course

**Treatment**
- Reduction of ISS (8/11)
- Multiagent chemotherapy (CHOP or PMitCEBO) (6/11)
- Rituximab in combination with chemotherapy (5/11)
- Surgical excision (5/11)
- Radiotherapy (2/11)

**Outcome**
- Death 5/11 -> Mortality rate 45%
  (3 pat. disease progression – 2 pat. sepsis)

**Follow-up (median 112 months)**
- Alive without disease: 1/11
- Alive without disease: 5/11