EUROPEAN HEMATOLOGY ASSOCIATION

Diffuse large B-cell lymphoma - Section 3

Primary cutaneous B-cell lymphomas

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In recent classifications three types of primary cutaneous B-cell lymphomas (CBCL) are recognized: primary cutaneous marginal zone lymphoma, primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL,LT). PCFCL may have a follicular (5%), follicular and diffuse (20%) or a diffuse growth pattern (75%). In previous classifications PCFCL with a diffuse growth pattern were classified as diffuse large B-cell lymphoma and their differentiation from PCDLBCL, LT was a matter of debate. Clinical, histological, immunophenotypical and genetic differences between PCFCL with a diffuse growth pattern and PCDLBCL, LT are presented in Table 1. Primary cutaneous marginal zone lymphoma will not be discussed.

Clinically, most patients with a PCFCL present with solitary or grouped plaques and tumors, preferentially located on the scalp or forehead or on the trunk. PCFCL have an indolent clinical course, uncommonly disseminate to extracutaneous sites (10%) and have an excellent prognosis with a 5-year-disease-specific survival of 95%. Radiotherapy (30 Gy) is the preferred treatment in patients with localized skin lesions. Cutaneous relapses do not indicate progressive disease and can be treated with low dose radiotherapy (4 Gy) as well. In patients with few scattered lesions both low-dose radiotherapy as well as a wait and see policy with treatment of only symptomatic lesions can be considered.

PCDLBCL, LT presents with generally rapidly growing red or bluish-red tumors on one or both (lower) legs, or in approximately 15% at sites other than the legs. They predominantly affect elderly patients, particularly females. Based on similarities in gene expression profile and cytogenetic alterations, including translocations and NF-kB activating mutations, PCDLBCL, LT is considered as a cutaneous counterpart of ABC-type DLBCL (Table 1). Compared to PCFCL, PCDLBCL, LT have a much more aggressive clinical behaviour (5-year- survival 50-60%), and R-CHOP is the first line of treatment.

Table 1. Characteristic features of PCFCL, diffuse type and PCDLBCL, leg type.

	PCFCL, diffuse type	**PCDLBCL, leg type**
Clinical presentation	Localized skin lesions on head or trunk; Multifocal lesions in rare cases.	Skin tumors on (lower) leg(s). Uncommonly, lesions at other sites than the leg (15%)
Histopathology		
Morphology tumor cells	Predominance of large centrocytes (large cleaved cells)	Predominance of centroblasts and/or immunoblastst (large noncleaved cells)
Immunohistochemistry		
B-cell lineage markers	CD20+, CD79a+, PAX5+IgM and IgD – (intracytoplasmic)	CD20+, CD79a+, PAX5+
Germinal center markers	BCL6+, BCL2-, CD10-	IgM+, IgD+/-; monotypic light chain expression
Post-germinal center markers	IRF4/MUM1-, FOXP1-negative	BCL6+/-, BCL2+, CD10-
MYC expression		IRF4/MUM1+, FOXP1+ positive
Molecular genetics		
Gene expression profile	GCB-type DLBCL	ABC-type DLBCL
Translocations *BCL6, MYC, IgH*	Absent	30-50%
Copy number variations	Amplification 2p16.1 region, deletion 14q11.2-q12 region	deletion 6q arm (BLIMP1;60%) deletion *CDKN2A*; 67%
(Array-based CGH; FISH)	not available	MYD88 (60%), CD79B (20%), CARD11 (10%),
NF-kB pathway mutations		*TNFAIP3/A20* (40%),
Cutaneous relapse	30%	65%
Nodal/visceral dissemination	10%	35%
5-year disease-specific survival	95%	50-60%

References

1. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.
*2. Senff NJ, Hoefnagel JJ, Jansen PM et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Cin Oncol 2007;25:1581-1587.

Validation of the WHO-EORTC classification with survival data of the different types of cutaneous B-cell lymphomas.

*3. Swerdlow SH, Quintanilla-Martinez L, Willemze R, Kinney MC. Cutaneous B-cell lymphoproliferative disorders: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop. Am J Clin Pathol 2013;139:515-535.

Excellent review on current status and current controversies in CBCL.

*4. Senff NJ, Noordijk EM, Kim YH et al. European Organization for Research and Treatment of Cancer (EORTC) and International Society for Cutaneous Lymphoma (ISCL) consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

This paper presents the consensus recommendations for the treatment of cutaneous B-cell lymphomas.

*5. Hoefnagel JJ, Dijkman R, Basso K et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671-3678.

Similarities between PCFCL and GCB-DLBCL and PCDLBCL, LT and ABC-DLBCL.

*6. Dijkman R, Tensen CP, Jordanova ES et al. Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. J Clin Oncol 2006;24:296-305.

Distinct genetic alterations in PCFCL and PCDLBCL, LT.

*7. Koens L, Zoutman WH, Ngarmlertsirichai P et al. Nuclear factor-kappaB pathway-activating gene aberrancies in primary cutaneous large B-cell lymphoma, leg type. J Invest Dermatol 2014;134:290-292.

NF-kB activating mutations in PCDLBCL, LT.

*8. Pham-Ledard A, Prochazkova-Carlotti M, Andrique L et al. Multiple genetic alterations in primary cutaneous large B-cell lymphoma, leg type support a common lymphomagenesis with activated B-cell-like diffuse large B-cell lymphoma. Mod Pathol 2014;27:402-411.

This paper describes similarities in gene expression profile and cytogenetic alterations between PCDLBCL, LT and ABC-type DLBCL.

*9. Grange F, Joly P, Barbe C et al. Improvement of survival in patients with primary cutaneous diffuse large B-cell lymphoma, leg type, in France. JAMA Dermatol 2014;150:535-541

This paper reports better survival of PCDLBCL, LT with R-CHOP than with CHOP alone.

*10. Pham-Ledard A, Beylot-Barry M, Barbe C et al. High Frequency and Clinical Prognostic Value of MYD88 L265P Mutation in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg-Type. JAMA Dermatol 2014;150:1173-1179.

Prognostic significance of MYD88 L265P mutations in PCDLBCL, LT.