New prognostic relevant factors in primary cutaneous diffuse large B-cell lymphomas

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Background: There is a growing body of literature that has enhanced our understanding of the biology of primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) including in the context of gene profiling studies. Recent studies have demonstrated an activated proliferation profile associated with leg type lymphoma including overexpression of proto-oncogenes PIM1, PIM2, and cMYC, and the transcription factors MUM1 and OCT2. Although gene profiling is very useful in understanding the molecular basis of diffuse large B-cell lymphoma (LBCL), it is not practical from a routine diagnostic perspective. In this regard, the purpose of the study was to further define an armamentarium of easily applied immunohistochemical stains to accurately prognosticate PCDLBCL.

Methods: In all, 35 patients with PCDLBCL, 14 of follicle center and 21 of leg type, were analyzed using antibodies against CD5, CD138, BCL2, BCL6, OCT2, MUM1, FOXP1, and cMYC. Findings were correlated with clinical data.

Results: All cases stained negative for CD5 and CD138. Both subtypes differed in distinct staining patterns for BCL6, BCL2, OCT2, MUM1, and FOXP1. Staining for BCL2, OCT2, and/or MUM1 was associated with poor, and BCL6 with a favorable prognosis. Expression of cMYC was irrespective of prognosis or subtype, whereas ulceration or primary manifestation on the leg or multiple lesions was indicative for worse prognosis.

Limitations: Case number was a limitation.

Conclusion: Discriminating PCDLBCL supports the validity of the World Health Organization/European Organization for Research and Treatment of Cancer classification. To identify risk factors in patients with PCDLBCL we recommend thorough evaluation of clinical presentation and exploratory staining pattern for BCL2, BCL6, MUM1 and OCT2. (J Am Acad Dermatol 2007;56:588-97.)

The group of primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) is heterogeneous. According to the World Health Organization (WHO)/European Organization for Research and Treatment of Cancer (EORTC) classification, they are divided into large B-cell lymphoma (LBCL) leg type (LBCL-L), LBCLs as a variant of primary cutaneous follicle center lymphoma (LFCL), and a third group including all LBCLs that do not fulfill the criteria of the first two groups.[1,2]

Abbreviations used:

ABC:	activated B cell
DSS:	disease-specific survival
EORTC:	European Organization for Research and Treatment of Cancer
GC:	germinal center
LBCL:	large B-cell lymphoma
LBCL-L:	large B-cell lymphoma, leg type
LFCL:	follicle center lymphoma
OS:	overall survival
PCDLBCL:	primary cutaneous diffuse large B-cell lymphoma
WHO:	World Health Organization

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This grouping mirrors not only the different clinical behavior of both main entities; moreover, it also correlates differences in cytogenetic aberrations and different gene expression profiles.[3-8]

Although it is a well-known fact that PCDLBCL-L has a poorer outcome compared with LFCL, the reason for this is still a matter of debate. It seems likely that not the location but the differences in morphology and gene expressions are reasons for the different behavior. For this reason the WHO/EORTC classification chose the term "leg type" and not the former designation "large B-cell lymphoma of the leg" as proposed by the EORTC in 1997.[9]

Using microarray techniques it is possible to distinguish 3 different groups of nodal diffuse LBCLs. They are characterized by different gene expression profiles: the germinal center (GC) profile, the activated B cell (ABC)-like profile, and a third group that does not fulfill the criteria of the first two groups.[10] The GC subtype is defined by the expression of a panel of genes characteristic for normal GC cells. The ABC subtype is defined by the expression of genes characteristic for activated blood lymphocytes. The ABC subtype has a poorer outcome compared with the GC subtype.[10] Microarray analyses in PCDLBCLs confirm the relevance of grouping into LFCL and LBCL-L. Both show profiles similar to that of GC type and ABC type, respectively. Several marker genes have been identified that express significantly differently in both groups.[8]

Although gene profiling is very useful in understanding the molecular basis of diffuse LBCL, it is not practical from a routine diagnostic perspective. In this regard, the purpose of the study was to further define an armamentarium of easily applied immunohistochemical stains to accurately prognosticate diffuse LBCL of the skin.

METHODS

Patients and samples

For examination we used formalin-fixed skin biopsy specimens from patients with LBCL-L and LFCL. An informed consent was obtained from each patient before biopsy. All biopsy specimens were taken for diagnostic reasons. For inclusion into our study the lymphoma had to be restricted to the skin at the time of diagnosis. This was confirmed by appropriate staging procedures. Patients with immunosuppression have been excluded from the study. We only included cases composed of diffuse arranged lymphoid cells resembling large centrocyts, centroblasts, immunoblasts, or a combination of these. For inclusion into the study, the number of large cells had to be at least 50% of the B cells. As defined by Anagnostopoulos and Stein,[11] a lymphoma cell is considered large if it is at least twice as big as a normal lymphocyte (bystander cell).

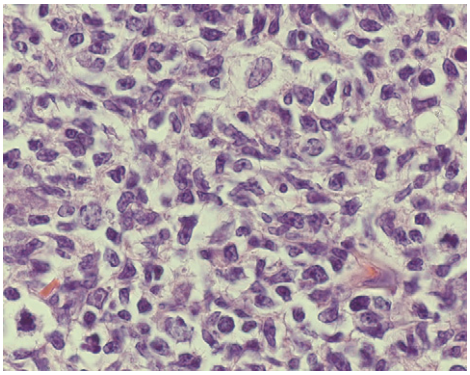

Fig 1. Biopsy specimen of representative lesion from patient with follicle center lymphoma (case 25). Mixture of large cleaved cells resembling centrocytes and some centroblasts not arranged in sheets. (Hematoxylin-eosin stain; original magnification: ×1000.)

The diagnoses were made using the criteria published in the WHO/EORTC classification.[1] LFCL was defined as a lymphoid neoplasia composed of diffuse lesions with predominantly large cleaved cells (resembling large centrocytes) with a variable infiltrate of centroblasts, which were not arranged in confluent sheets (Fig 1). LBCL-L was defined as a lymphoid neoplasia with predominance of large noncleaved round cells (resembling centroblasts and immunoblasts) arranged in confluent sheets with a diffuse growth pattern (Fig 2, *A*).

Cases with an exclusively follicular growth pattern were excluded. Because of its heterogeneity and its ill definition, patients with the diagnosis "PCDLBCL, other" were also excluded from the study.

Clinical parameters

The following regions of the body were defined: head and neck; arm; trunk; and leg. The therapeutic response was classified into 4 categories (complete remission, partial remission, stable disease, and progression).

Methods

A tumor biopsy specimen was fixed in formalin, embedded in paraffin, and cut into 2- to 4-μm sections. In addition to hematoxylin-eosin and Giemsa staining, immunohistochemistry was performed using standard immunoperoxidase techniques. The sections were dewaxed in xylol (Merck, Darmstadt, Germany) and rehydrated in serial dilutions of ethanol. The used antibodies are listed in Table I. An autostainer was used in combination with a detection kit (Chem-Mate LSAB-KIT, DAKO, Glostrup, Denmark). All biopsy specimens were reviewed

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