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CD5 expression in *de novo* diffuse large B-cell lymphomas

Ennishi et al. [1] recently described *de novo* CD5-positive diffuse large B-cell lymphomas (CD5+ DLBCLs), which are now recognized in the new 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors as an immunohistochemical subgroup of DLBCL not otherwise specified. We looked for immunohistochemical CD5 expression in a previously well-characterized DLBCL tissue microarray [2] of patients treated with a combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like regimen without rituximab and found CD5 expression in 10 of 260 tumors (4%). Secondary transformed or preexisting DLBCLs were excluded.

In our cohort, 82 tumors were classified as primary extranodal, whereas 178 were nodal DLBCLs. All 10 *de novo* CD5+ DLBCLs showed BCL2 expression and eight showed MUM1/IRF4 expression (Table 1). MUM1/IRF4 indicates the possibility of a post-germinal-center-cell phenotype. The transcription factor BCL6 was expressed in 50% of these tumors; by FISH analysis trisomy 3 as origin of BCL6 deregulation was excluded. Although patients with *de novo* CD5+ DLBCL showed a tendency toward higher stages, there was no correlation of CD5 expression with Ann Arbor stage, sex, B symptoms, International Prognostic Index, lactate dehydrogenase or survival. We, therefore, agree with Ennishi et al. that large-scale prospective studies are required to further define the relevance of CD5 in DLBCL. In this context, future studies should address specifically the primary site, as the separation of primary nodal and extranodal lymphomas is emphasized by the 2008 WHO classification, which defines new site-specific large B-cell lymphomas, e.g. DLBCL of the central nervous system (CNS). Although at times it can be difficult to discriminate primary nodal from primary extranodal lymphomas with major nodal involvement, extranodal lymphomas may not equal to nodal counterparts. This matters especially in *de novo* CD5+ DLBCL, as the often CD5+ intravascular large B-cell lymphomas are now recognized as own subgroup of DLBCL. The concept of site-specific impact on tumor biology is strikingly challenged in *de novo* CD5+ DLBCLs: (i) several studies found a relation of prognosis and CD5 protein expression and (ii) they are often primary extranodal, but the primary site can be found in various organs. Of our 10 CD5+ DLBCLs, one was of testicular origin, while two of four nodal lymphomas showed extranodal involvement. In the study of Ennishi et al., 45% of the reported cases were primary extranodal lymphomas. CNS involvement in 13% of *de novo* CD5+ DLBCLs has been reported in the large study of Yamaguchi et al. [3], which is substantially higher than in conventional DLBCL.

The basis of this association of involvement of extranodal and immunoprivileged sites and biological behavior in *de novo* CD5+ DLBCLs still remains to be elucidated. Comprehension of physiological CD5+ B-cell homing properties may help to understand why in these lymphomas expression of CD5 is of higher relevance than primary site.

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Table 1. Features of *de novo* CD5+ diffuse large B-cell lymphoma. Percentages of immunohistochemically positive tumor cells are indicated

	Age/sex	CD10 (%)	BCL2 (%)	BCL6 (%)	MUM1 (%)	Stage	FU	DOD
1	n.a.	0	100	0	100	n.a.	n.a.	n.a.
2	79/M	80	90	80	50	n.a.	3	Yes
3	76/F	80	10	80	50	n.a.	72	Yes
4	83/F	0	90	50	30	III	6	No
5	n.a.	0	80	0	40	III	17	Yes
6	79/M	0	90	0	0	n.a.	n.a.	n.a.
7	81/F	20	90	50	25	III	16	No
8	80/M	0	70	n.a.	35	II	62	No
9	82/F	0	90	10	30	II	11	Yes
10	39/F	0	80	n.a.	0	IV	106	No

FU, follow-up in months; DOD, dead of disease; n.a., not available; M, male; F, female.

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