Combined loss of HLA I and HLA II expression is more common in the non-GCB type of diffuse large B-cell lymphoma

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CORRESPONDENCE

Combined loss of HLA I and HLA II expression is more common in the non-GCB type of diffuse large B-cell lymphoma

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As an immune escape mechanism tumor cells may downregulate expression of Human Leukocyte Antigens (HLA). Loss of HLA class I and class II has been described in various subtypes of diffuse large B cell lymphoma (DLBCL), including the not otherwise specified (NOS) subgroup. [1,2] We analyzed HLA class I and class II expression in DLBCL not otherwise specified (NOS) to investigate whether there is an association between HLA expression, cell of origin (COO) and the recently reported FOXP1 expression in non-GCB DLBCL. [3]

Seventy-seven cases of DLBCL-NOS with an almost exclusively nodal presentation were classified for COO by immunohistochemistry (IHC) according to the Hans algorithm as germinal center B (GCB) cell type (N=42) or non-GCB type (N=35). (Table 1). Clinical data available from 67 cases indicated a histologically confirmed preexistent or concurrent indolent lymphoma in 16 patients, i.e. 13 follicular lymphoma, 2 marginal zone lymphoma and 1 chronic lymphocytic leukemia. Expression of HLA and FOXP1 was assessed by IHC, methods are described in the supplementary data.

Significant differences ($p<0.01$) in HLA loss were observed between the COO categories in the total group. Loss of HLA class I in 51% of non-GCB versus 21% of GCB, loss of HLA class II in 37% of non-GCB versus 10% of GCB and combined loss in 34% of non-GCB versus 5% of GCB (Figure 1a).

In the total group, 35% of the cases showed loss of HLA class I expression, 22% showed loss of HLA class II and 18% showed loss of both, whereas 25% retained expression of both HLA class I and class II. Two lymphomas with partial loss of HLA class I and two other lymphomas with partial loss of HLA class II were considered HLA negative.

In 51 de novo cases loss of HLA class I was observed in 21 (41%) and loss of HLA class II in 16 (31%) cases. In 16 transformed cases, expression of HLA class I was lost in 5 (31%; Figure S2) of which 2 cases showed additional loss of class II (13%). Since transformation from follicular lymphoma is associated with the GCB type, we separately studied GCB type DLBCL and found loss of HLA class I in

5/14 of transformed cases (36%) versus 4/28 de-novo GCB cases (14%) (p=0.13). In consequence, the differences for HLA class I between the COO subtypes were even more pronounced after exclusion of transformed cases: 55% of non-GCB versus 14% of GCB cases showed loss of expression (p=<0.01). Thus, these results were not influenced by inclusion of 16 cases with a history of follicular lymphoma or other types of indolent lymphoma, which in line with the literature, were almost exclusively of GCB type.

Brown et al. suggested that FOXP1, a protein associated with non-GCB type DLBCL, is inversely related with HLA class II expression. [4] A high expression of FOXP1 with a low expression of HLA class II expression was observed in normal pre-plasma cells and non-GCB type DLBCL maturing to plasmablasts. [5] This is in line with data from the group of Rimsza et al. suggesting that loss of HLA class II is seen in DLBCL cases maturing into plasmablastic lymphoma. [2,6] We studied the correlation between FOXP1 expression and HLA class II expression in 61 DLBCL cases (Figures S1 and S3). FOXP1 expression was not significantly associated with non-GCB type DLBCL (Table 1; p=0.08). We did not find an association between FOXP1 and HLA class II expression: loss of HLA class II was very weakly associated with FOXP1 expression in both non-GCB and GCB type DLBCL. However, the majority of cases retained HLA class II expression while expressing high FOXP1 levels in both categories and vice versa not all cases with low HLA class II showed high FOXP1 expression (Figure 1b, c). Of note, high expression of FOXP1 and HLA class II expression were excluded from analysis in the original study. [4] Furthermore, while most FOXP1 positive cases showed homogeneous staining of the tumor cells and only few cases showed partial loss of HLA class II expression, a qualitative (intensity of staining) analysis of both proteins is not easily accomplished by immunohistochemistry.

In conclusion, we show that loss of HLA class I and / or HLA class II, in particular the double negative signature is much more common in non-GCB type DLBCL than in GCB type DLBCL. Our data support previous reports, focusing on class II expression. [6] The preferential loss of HLA class II expression in non-GCB type DLBCL cannot be explained by a higher expression of FOXP1 alone.

Contributions of Authors

LM designed the study, collected cases, scored the immunohistochemical stainings, performed statistical analysis and wrote the manuscript. LV designed the study, collected cases, performed statistical analysis and wrote the manuscript. AD scored the immunohistochemical stainings and wrote the manuscript. MN collected clinical information on the cases and wrote the manuscript. AB designed the study, supervised and wrote the manuscript. PK designed the study, scored the immunohistochemical stainings and wrote the manuscript.

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Conflict of interest

The authors declare that they have no conflict of (financial) interest.

List of abbreviations

HLA: human leukocyte antigen

DLBCL-NOS: diffuse large B-cell lymphoma - not otherwise specified

COO: cell of origin

GCB: germinal center B-cell

ABC: activated B-cell

B2M: beta-2-microgobulin

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FIGURE LEGENDS MAIN DOCUMENT

Table 1. Features of DLBCL-NOS cases

Figure 1. Difference in loss of HLA class I and HLA class II between non-GCB and GCB DLBCL

1a. Percentage of HLA class I and II negative cases in non-GCB and GCB DLBCL and double negative cases, **1b.** Percentage of FoxP1 positive and negative cases in HLA class II negative and positive non-GCB DLBCL cases, **1c.** Percentage of FoxP1 positive and negative cases in HLA class II negative and positive GCB type DLBCL.

FIGURE LEGENDS OF SUPPLEMENTARY DATA

Figure S1. Percentage of FOXP1 positive cells. A cut-off of ≥80% was used as in the literature [13], since most cases were below 20% or 80% and higher.

Figure S2. HLA class I expression in a single case with DLBCL and co-existent follicular lymphoma (FL). The DLBCL shows loss of expression while the FL shows retained expression. A: overview; B: detail of DLBCL.

Figure S3. FoxP1 expression. A: case with 90% expression; B: case with 10% expression.

Table 1. Features of DLBCL-NOS cases

Characteristic	**non-GCB (35)**	**GCB (42)**	**p-value**
male (%)	23 (66)	24 (57)	
median age (range)	66 (9-85)	56 (14-77)	
Ann Arbor Stage			
I/II (%)	6 (17)	18 (43)	
III/IV (%)	26 (74)	18 (43)	
unknown (%)	3 (9)	6 (14)	
IPI			
0-1 (%)	5 (14)	13 (31)	
2-3 (%)	19 (55)	18 (43)	
4-5 (%)	7 (20)	1 (2)	
unknown (%)	4 (11)	10 (24)	
Transformation* (%)	2 (6)	14 (33)	<0.01
HLA class I + (%)	17 (49)	33 (79)	<0.01
HLA class I - (%)	17 (49)	8 (19)	
partial loss HLA class I (%)	1 (2)	1 (2)	
HLA class II + (%)	22 (63)	38 (91)	<0.01
HLA class II - (%)	12 (34)	3 (7)	
partial loss HLA class II (%)	1 (3)	1 (2)	
double negative (%)	12 (34)	2 (5)	<0.01
FOXP1 ≥80% + / evaluable cases (%)	18/26 (69)	16/35 (46)	0.08

*: transformation from a preexistent or concurrent indolent lymphoma, see text.