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## 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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Sir: As an immune escape mechanism, tumour cells may down-regulate expression of human leucocyte antigens (HLA). Loss of HLA classes I and II has been described in various subtypes of diffuse large B cell lymphoma (DLBCL), including the not otherwise specified (NOS) subgroup.<sup>1,2</sup> We analysed HLA classes I and II expression in DLBCL-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.<sup>3</sup>

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 centre B (GCB) cell-type ( $n = 42$ ) or non-GCB-type ( $n = 35$ ) (Table 1). Clinical data available from 67 cases indicated a histologically confirmed pre-existent or concurrent indolent lymphoma in 16 patients, i.e. 13 follicular lymphoma, two marginal zone lymphoma and one chronic lymphocytic leukaemia. Expression of HLA and FoxP1 was assessed by IHC; methods are described in the Supporting Information.

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, 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 classes I and 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), two cases

**Table 1.** Features of DLBCL-NOS cases

Characteristic	Non-GCB (35)	GCB (42)	<i>P</i> -value
Male (%)	23 (66)	24 (57)	
Median age (years; 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 <sup>+</sup> (%)	17 (49)	33 (79)	<0.01
HLA class I <sup>−</sup> (%)	17 (49)	8 (19)	
Partial loss HLA class I (%)	1 (2)	1 (2)	
HLA class II <sup>+</sup> (%)	22 (63)	38 (91)	<0.01
HLA class II <sup>−</sup> (%)	12 (34)	3 (7)	
Partial loss HLA class II (%)	1 (3)	1 (2)	
Double-negative (%)	12 (34)	2 (5)	<0.01
FoxP1 ≥ 80% <sup>+/</sup> evaluable cases (%)	18/26 (69)	16/35 (46)	0.08

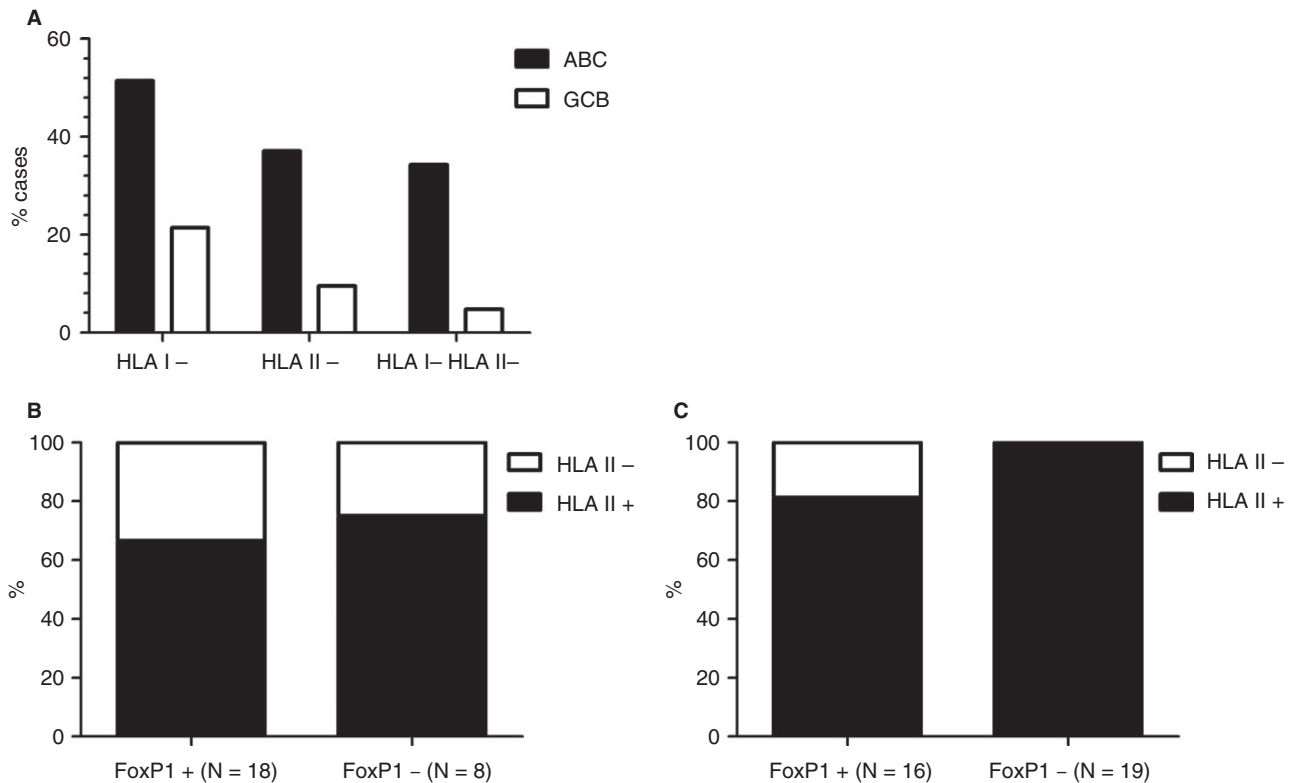
IPI, International Prognostic Index; HLA, Human leucocyte antigen; FoxP1, Forkhead box protein 1; GCB, Germinal centre B cell; DLBCL-NOS, Diffuse large B cell lymphoma, not otherwise specified.

\*Transformation from a pre-existent or concurrent indolent lymphoma; see text.

of which showed additional loss of class II (13%). As transformation from follicular lymphoma is associated with the GCB-type, we studied GCB-type DLBCL separately, and found loss of HLA class I in five of 14 transformed cases (36%) versus four of 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

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**Figure 1.** Difference in loss of human leucocyte antigen (HLA) class I and HLA class II between non-germinal centre B cell (GCB) and GCB diffuse large B cell lymphoma (DLBCL). A, Percentage of HLA class I and II negative cases in non-GCB and GCB DLBCL and double-negative cases; B, percentage of FoxP1 positive and negative cases in HLA class II negative and positive non-GCB DLBCL cases; C, percentage of FoxP1 positive and negative cases in HLA class II negative and positive GCB-type DLBCL.

transformed cases: 55% of non-GCB versus 14% of GCB cases showed loss of expression ( $P \leq 0.01$ ). Thus, these results were not influenced by the 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 related inversely with HLA class II expression.<sup>4</sup> 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.<sup>5</sup> 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.<sup>2,6</sup> We studied the correlation between FoxP1 expression and HLA class II expression in 61 DLBCL cases (Figures S1 and S3). FoxP1 expression was not associated significantly 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 associated very weakly 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.<sup>4</sup> Furthermore, while most FoxP1-positive cases showed homogeneous staining of the tumour cells and only a few cases showed partial loss of HLA class II expression, a qualitative (intensity of staining) analysis of both proteins is not accomplished easily 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.<sup>6</sup> The preferential loss of HLA class II expression in non-GCB-type DLBCL cannot be explained by a higher expression of FoxP1 alone.

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## Conflicts of interest

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

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Methods.

**Figure S1.** Percentage of FOXP1 positive cells. A cut-off of  $\geq 80\%$  was used as in the literature,<sup>4</sup> 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.

**Figure S3.** FoxP1 expression.