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LETTER TO THE EDITOR

Intratumoral expression of CD38 in patients with post-transplant lymphoproliferative disorder

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Background

Post-transplant lymphoproliferative disorders (PTLDs) are lymphoid proliferations that can arise as a complication to organ transplantation [1,2]. When compared with sporadically occurring lymphomas, the incidence of PTLD following solid organ transplantation (SOT) is greatly increased. Frequency estimates range from less than 1% to more than 5%, varying according to the observation time, population, graft type, and degree of immunosuppression [2–4]. Most PTLDs are thought to arise as a consequence of immunosuppression, which diminishes the protective functions of T cells and may lead to reactivation of Epstein Barr Virus (EBV) [2,3].

The first approach in PTLD treatment is to reduce immunosuppression. This may be sufficient (particularly with the nondestructive and polymorphic PTLD subtypes), but must be weighed against the increased risk of graft rejection [5]. In the majority of PTLD patients, conventional chemotherapy is poorly tolerated, with substantial toxicity and high mortality [6,7]. Treatment with rituximab, either as monotherapy or in combination with chemotherapy, has significantly improved the treatment results of B-cell PTLDs, although responses may be temporary [2,5,8]. In relapsed/refractory (R/R) patients, there is currently no standard therapy. Therefore, new studies are pivotal to identify novel biomarkers and suggest additional treatment options [5].

The transmembrane glycoprotein CD38 is expressed in various hematologic malignancies, making it a possible clinical target [9]. It is present on different lymphocyte subsets, with particularly high levels on plasma cells [9,10].

The identification of CD38 expression in hematological malignancies has prompted development of anti-CD38 antibodies [9]. Currently, chemo-immunotherapy with anti-CD38 antibodies is standard of care in treatment of multiple myeloma [11]. Given its high activity and favorable toxicity in myeloma patients [11], anti-CD38 therapy is also an attractive treatment option to consider for PTLD patients.

There is anecdotal evidence for CD38 expression in some PTLDs, but it is unclear how widespread such expression may be. Therefore, we investigated the intratumoral expression of CD38 in a population-based cohort of PTLDs, in an attempt to provide a rationale for the possible use of anti-CD38 therapy as a novel treatment approach in this vulnerable patient group.

Patients and methods

Detailed information on the patient cohort and methodologies are provided in the Supplementary material.

Patients

This study was conducted using a Danish national cohort of 108 PTLD patients established by Vase et al. [12], comprising patients with heart, kidney, heart-lung, or lung SOTs carried out 1981–2012.

All diagnoses of PTLD were reclassified by an expert hematopathologist according to the WHO 2016 Classification of Tumors of Hematopoietic and Lymphoid Tissues [1].

Adequate pretreatment formalin-fixed paraffin-embedded tumor tissue samples were available from 62 PTLD cases and used for tissue microarray (TMA) construction [12]. Two cases were excluded, as indolent B-cell lymphomas are not classified as PTLD [1].

Immunohistochemistry

Immunohistochemical (IHC) staining for CD38 was performed on an automated staining system (Ventana Benchmark Ultra,

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Supplemental data for this article can be accessed here.

Ventana Medical Systems, Tucson, AZ), according to a standard protocol in routine diagnostics.

Digital image analysis

The expression of CD38 was quantified using VIS (Visiopharm Integrator System 2020-01, Visiopharm, Hoersholm, Denmark). Regions of interest (ROI), comprising lymphoid tissue, were defined in each tissue core. Eight patients were excluded because of insufficient lymphoma tissue, resulting in a total of 52 cases. An analysis protocol package was designed to quantify the expression levels of CD38. The expression level was computed as an area fraction (AF) of the total area of the ROI.

Statistical analysis

Differences between groups were assessed using a Wilcoxon test for continuous variables and a χ^2-test or Fisher's exact test with two-sided p-values for dichotomous data. The patients were divided into two groups with high and low CD38 AF expression based on the median AF of CD38 expression. This was 1.4% for the entire cohort and 1.1% for the subgroup of diffuse large B-cell lymphoma (DLBCL). Outcome was examined by Kaplan-Meier analysis and a log-rank test. Differences with p-values $<.05$ were considered statistically significant.

Results

Clinical characteristics and correlations to CD38 expression

From our national cohort of PTLD following SOT ($n = 108$), 52 patients had adequate available tumor tissue for evaluation of CD38 expression. This study cohort included 12 women and 40 men. The tumors comprised 12 nondestructive (23%), 3 polymorphic (6%), 33 monomorphic (63%), and 4 classical Hodgkin lymphoma (cHL) (8%) PTLD cases (Table 1). The mean age at diagnosis was 44 years, ranging from 2 to 77. Overall, 46 cases (88%) were EBV positive.

All study cases included cells that showed predicted patterns of CD38 expression in the form of distinct cytoplasmic and/or membranous positivity. Positive and negative controls showed appropriate staining reactions. In PTLDs, CD38 expression was variably seen in both lymphoma cells and in the cells of the tumor microenvironment, sometimes predominantly in one cell type alone, sometimes in combination. These different reaction patterns could be clearly identified in some, but not all, cases. As a treatment target, we did not consider it relevant to differentiate the cells of positive CD38 staining (*e.g.* neoplastic *versus* non-neoplastic cells).

Patients were divided into two groups according to high and low CD38 AF expression. A comparison of the clinicopathological features of the two groups revealed no significant differences (Table 1).

CD38 is expressed in all subtypes of PTLD

CD38 was detected in all PTLD cases, although expression levels varied according to subtype (Figure 1(A–D)). Overall, the mean CD38 positive AF for the entire cohort was 4.2% ($n = 52$; range 0.01–52.7%). Cases of cHL PTLD had the highest mean AF ($n = 4$; mean 4.6%; range 3.3–9.7%), followed by DLBCL ($n = 31$; mean 3.4%; range 0.01–20.8%) and nondestructive PTLD ($n = 12$; mean 3.2%; range 0.1–10.6%), while polymorphic PTLD showed the lowest mean AF ($n = 3$; mean 2.0%; range 0.04–3.3%). Moreover, CD38 was expressed in anaplastic large cell lymphoma (ALCL) ($n = 1$; 0.1%) and plasmablastic PTLD ($n = 1$; 52.7%).

The group of nondestructive PTLD was subdivided into cases of plasmacytic hyperplasia (PH), florid follicular hyperplasia (FH), and infectious mononucleosis (IM) PTLD (Figure 1(D)). CD38 AF expression was highest in PH ($n = 5$; mean 4.5%; range 0.1–10.6%), while lower levels were observed in FH ($n = 3$; mean 1.6%; range 0.4–3.1%) and IM PTLD patients ($n = 4$; mean 2.8%; range 1.3–4.2%).

CD38 and survival

There were no significant differences in overall survival (OS) (Figure 1(E), $p = .917$) or progression-free survival (PFS) (Figure 1(F), $p = .573$) comparing patients with tumors showing high *versus* low CD38 AF expression in the entire cohort. Additionally, survival analysis was performed for the largest subcohort of 31 DLBCL cases; CD38 status had no impact on OS (Figure 1(G), $p = .737$) or PFS (Figure 1(H), $p = .580$).

Discussion

Studying a national, population-based cohort of PTLDs following SOT, we found varying degrees of CD38 expression in diagnostic tissue specimens in all cases. This is the first report identifying consistent positivity for CD38 in these lesions, and it provides a rationale for investigating the possible use of anti-CD38 directed therapy as a novel therapeutic strategy in PTLD patients. The possibility of administrating potentially therapeutically effective monoclonal antibodies, without further increasing the risk of organ damage, makes for an attractive treatment approach. This is exemplified by the effectiveness and tolerability of rituximab in PTLD [7]. However, no standard treatment is currently available for R/R PTLD patients [5]. In this regard, anti-CD38 antibodies could provide a new therapeutic opportunity, given their documented efficacy and overall favorable safety profile in R/R multiple myeloma [13,14]. In addition to targeting CD38 positive tumor cells, anti-CD38 therapy has the potential to deplete alloreactive plasma cells and thus reduce alloantibody levels and improve graft survival in transplant recipients [9,15–17]. The antibodies can potentially improve the general anti-tumor immune response, due to CD38 positivity on immune suppressor cells. Since this is largely independent of CD38 expression by tumor cells, it may even allow activity against CD38 low or negative tumors [11,18]. Future analyses must determine whether CD38 must be

Table 1. Demographic and clinical features of PTLD patients.

	All patients *N* (%)	Low CD38 *N* (%)	High CD38 *N* (%)	*p* Value (high vs. low CD38)
Patients	52 (100)	26 (50)	26 (50)	
Age, mean (range)	44 (2–77)	44 (5–71)	44 (2–77)	.892
Gender				
Female	12 (23)	5 (19)	7 (27)	.742
Male	40 (77)	21 (81)	19 (73)	
Organ transplantation				
Kidney	38 (73)	18 (69)	20 (77)	.749
Heart	8 (15)	4 (15)	4 (15)	
Lung	6 (12)	4 (15)	2 (8)	
Presentation				
Early (<1 y)	15 (29)	9 (35)	6 (23)	.540
Late (≥1 y)	37 (71)	17 (65)	20 (77)	
Ann Arbor stage				
I-II	30 (58)	16 (62)	14 (54)	.907
III-IV	21 (40)	10 (38)	11 (42)	
Unknown	1 (2)		1 (4)	
Localization				
Nodal	32 (62)	13 (50)	19 (73)	.154
Extranodal	20 (38)	13 (50)	7(27)	
Graft PTLD				
No graft involvement	47 (90)	22 (85)	25 (96)	.350
Graft involvement	5 (10)	4 (15)	1 (4)	
Course				
Only monomorphic/cHL	36 (69)	21 (81)	15 (58)	.212
Only nondestructive/polymorphic	13 (25)	4 (15)	9 (35)	
Both types of lesions	3 (6)	1 (4)	2 (8)	
Type PTLD				
Nondestructive	12 (23)	4 (15)	8 (31)	.676
Polymorphic lesions	3 (6)	1 (4)	2 (8)	
Monomorphic PTLD	33 (63)	19	14 (54)	
DLBCL	31 (60)	18 (69)	13 (50)	
PTCL, NOS	0 (0)	0 (0)	0 (0)	
T-ALCL	1 (2)	1 (4)	0 (0)	
Burkitt	0 (0)	0 (0)	0 (0)	
MZL	0 (0)	0 (0)	0 (0)	
Plasmablastic	1 (2)	0 (0)	1 (4)	
cHL-type PTLD	4 (8)	2 (8)	2 (8)	
cHL, NS	2 (4)	1 (4)	1 (4)	
cHL, MC	2 (4)	1 (4)	1 (4)	
EBV status				
EBV positive	46 (88)	24 (92)	22 (85)	.668
EBV negative	6 (12)	2 (8)	4 (15)	
WHO PS				
0–2	43 (83)	23 (88)	20 (77)	.555
3–4	6 (12)	2 (8)	4 (15)	
Unknown	3 (6)	1 (4)	2 (8)	
B symptoms				
Present	18 (35)	11 (42)	7(27)	.304
Absent	30 (58)	13 (50)	17 (65)	
Unknown	4 (8)	2 (8)	2 (8)	
Immunosuppressives				
Ciclosporin	39 (75)	20 (77)	19 (73)	1.000
Tacrolimus	14 (27)	8 (31)	6 (23)	.823
MMF	36 (69)	18 (69)	18 (69)	1.000
Azathioprine	8 (15)	4 (15)	4 (15)	1.000
PTLD treatment				
Monotherapy rituximab (R)	14 (27)	7 (27)	7(27)	1.000
Multiagent chemotherapy (CT)	9 (15)	5 (19)	4 (15)	1.000
R-CT	7 (13)	4 (15)	3 (12)	1.000
Other	20 (38)	9 (35)	11 (42)	.773
Response to treatment				
CR	28 (54)	15 (58)	13 (50)	.904
Other response	19 (37)	9 (35)	10 (38)	
Unknown	5 (10)	2 (8)	3 (12)	

cHL: classical Hodgkin lymphoma; CR: complete response; CT: multiagent chemotherapy; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; MC: mixed cellularity; MMF: mycophenolate mofetil; MZL: marginal zone lymphoma; NOS: not otherwise specified; NS: nodular sclerosing; PS: performance status; PTCL: peripheral T-cell lymphoma; PTLD: post-transplant lymphoproliferative disorder; R: rituximab; T-ALCL: anaplastic large T-cell lymphoma; WHO: World Health Organization.

expressed specifically on the tumor cells or merely on cells in the microenvironment to obtain effects from treatment with anti-CD38 antibodies. In addition, the possible advantages of administrating anti-CD38 antibodies may depend on the subtype of PTLD. Since nondestructive and polymorphic cases are commonly defined by non-clonal

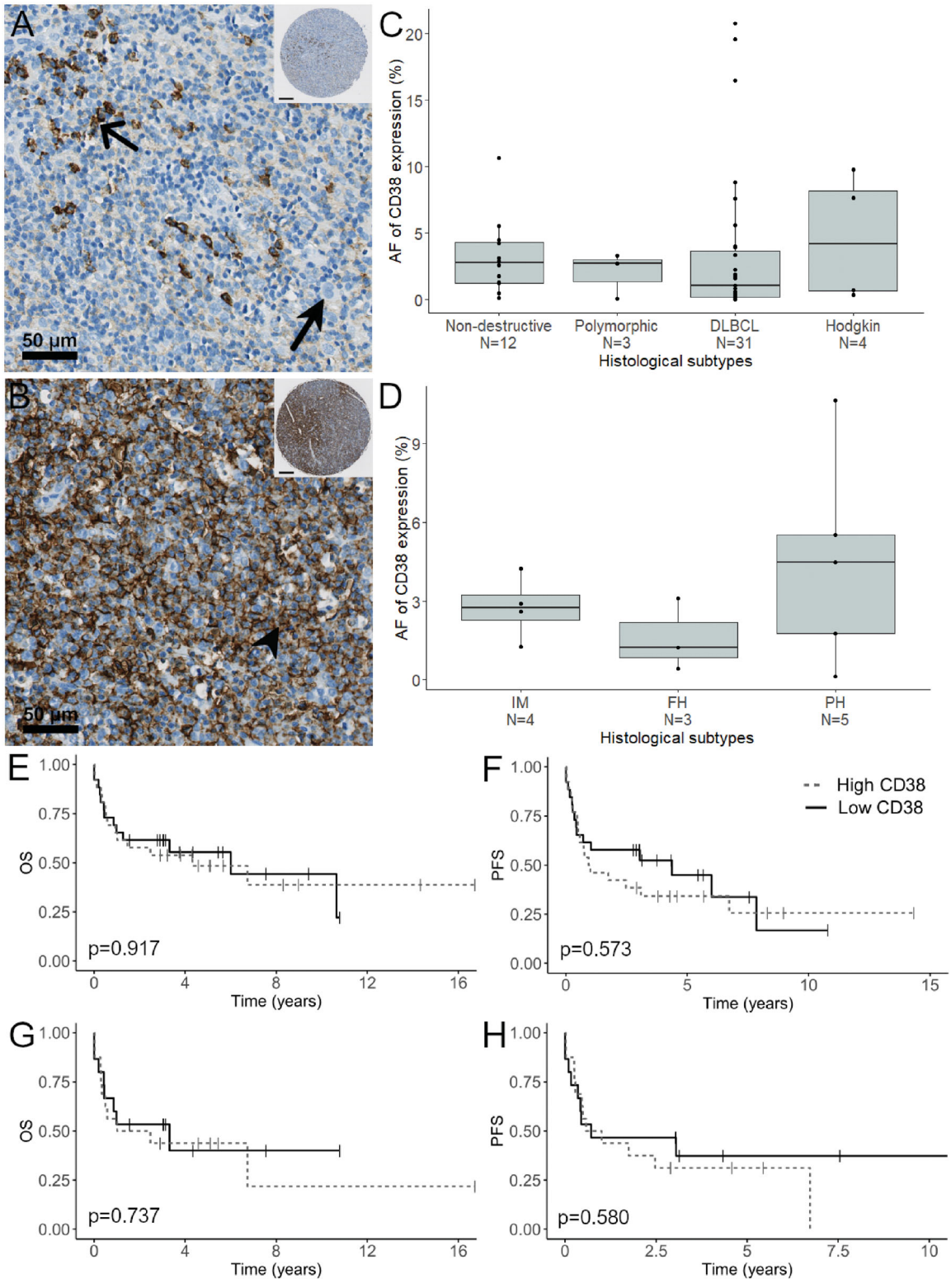

Figure 1. (A,B) Immunohistochemical staining of tissue microarray tumor cores showing expression of CD38 in cases of: (A) cHL, MC PTLD with CD38 expression in bystander cells (open arrow), but not in neoplastic Reed-Sternberg cells (closed arrow); (B) plasmablastic lymphoma PTLD with high CD38 expression in both tumor cells (arrowhead) and bystander cells (main image scale bars: 50 µm). Inserts show images from the corresponding tissue cores (scale bars: 200 µm). (C) Boxplot showing CD38 AF expression in nondestructive PTLD ($n = 12$), polymorphic PTLD ($n = 3$), monomorphic PTLD (DLBCL type; $n = 31$), and cHL PTLD ($n = 4$). Other PTLD subtypes, comprising T-ALCL ($n = 1$) and plasmablastic PTLD ($n = 1$) also expressed CD38 but were excluded from the boxplot because of low sample size. (D) Boxplot showing CD38 AF expression in nondestructive PTLD of types IM ($n = 4$), FH ($n = 3$), and PH ($n = 5$). (E–H) Overall survival and progression free survival in all subtypes of PTLD (E,F), and in the DLBCL subgroup (G,H), with regard to CD38 status. AF: area fraction; cHL: classical Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FH: follicular hyperplasia; IM: infectious mononucleosis; MC: mixed cellularity; OS: overall survival; PFS: progression-free survival; PH: plasmacytic hyperplasia; PTLD: post-transplant lymphoproliferative disorder; T-ALCL: anaplastic large T-cell lymphoma.

lymphoproliferation and often initially respond to reduction in immunosuppression, with or without rituximab [1,5], the feasibility of CD38 as a predictive biomarker in this group is unknown.

So far, daratumumab, a monoclonal anti-CD38 antibody, has been tested as monotherapy in various subtypes of sporadically occurring lymphoma. A phase 2 study of daratumumab in patients with R/R DLBCL and follicular lymphoma (FL) showed overall response rates of only 6.7% and 12.5%, respectively, resulting in termination of the study [19]. It was later shown that daratumumab enhances the antitumor activity of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and rituximab-CHOP in xenograft mouse models [20]. Various preclinical studies and case reports have also demonstrated efficacy of anti-CD38 antibodies for treatment of acute lymphoblastic leukemia (ALL) and T-cell lymphoma [21–25]. However, a clinical trial examining another anti-CD38 antibody, isatuximab, for treatment of lymphoblastic leukemia was terminated on account of an unsatisfactory benefit/risk ratio (NCT02999633). Further clinical trials are currently recruiting or ongoing for treatment of non-immunosuppressed lymphomas (NCT03769181, NCT01084252, NCT04251065), ALL (NCT03384654, NCT03860844), and chronic lymphocytic leukemia (NCT03447808, NCT03734198).

To date, no clinical trials have examined anti-CD38 antibodies for treatment of PTLD. However, a case report showed complete response and tolerability of a patient with PTLD following SOT to a daratumumab-based regimen as second-line therapy (daratumumab, pomalidomide, dexamethasone). As expected, this was associated with an increased risk of infection [26]. Moreover, a patient with rituximab-refractory PTLD following allogenic hematopoietic stem cell transplantation was treated with daratumumab. The therapy was well tolerated with a rapid but non-sustained response [27]. These data prompt further investigation of anti-CD38 antibodies in the treatment of PTLD.

In the present study, CD38 was expressed in all cases with varying positivity across the PTLD subtypes. We found higher CD38 AF expression in PH compared with IM and FH. This is in line with the morphology, PH cases being characterized by numerous plasma cells [1]. Similarly, plasmablastic lymphoma shows prominent plasmablastic differentiation [1]. As expected, the single case of plasmablastic PTLD in our study showed a very high CD38 AF expression. In contrast, DLBCL PTLD exhibited the lowest mean AF expression, albeit with three outliers, while the mean AF positivity was highest in cHL PTLD. The various expression levels must be taken into account, should future studies indicate anti-CD38 treatment effectiveness in only patients with a certain CD38 tumor expression level.

Other studies using IHC to examine the expression of CD38 in lymphomas in the immunocompetent setting have reported CD38 expression in approximately 80% of angioimmunoblastic T-cell lymphomas, 60% of peripheral T-cell lymphomas, not otherwise specified [28], and 95% of extranodal natural killer/T cell lymphomas, nasal type [29]. In addition, Salles et al. demonstrated a mean percentage of CD38 positive tumor cells of 55% (ranging from 0–100%) in *de novo* DLBCL, FL, and mantle cell lymphoma (MCL) [19].

The CD38 assessment in the present study included both neoplastic cells and cells in the tumor microenvironment and we found no impact of CD38 expression on survival in the PTLD cohort. In contrast, previous studies have shown that CD38 was significantly correlated with a poorer prognosis in sporadically occurring MCL [30] and extranodal natural killer/T cell lymphoma, nasal type [29,31], and that high CD38 expression was associated with a favorable outcome in ALL [32,33]. Comparison with PTLD may be impeded by differences in immunocompetence [34]. The feasibility of comparison may be lowered further by the heterogeneity of the PTLD cohort, resulting from the various subtypes, varying follow-up times, and treatment regimens. However, considering the rarity of PTLD, including patients diagnosed over a long time period is necessary to obtain a larger cohort.

In summary, in this national, population-based cohort, we report for the first time the expression of CD38 throughout all subtypes of PTLD following SOT. CD38 status did not have an impact on OS or PFS within the entire cohort, nor within the subgroup of DLBCL PTLD. Importantly, the expression of CD38 in all cases provides an incentive for further investigation of anti-CD38 directed treatment as a novel therapeutic option in this patient group, particularly for the R/R PTLD patients, where no standard therapy exists.

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Disclosure statement

The authors declare no relevant conflict of interest.

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