Review Article

Diagnostic utility of programmed cell death ligand 1 (clone SP142) immunohistochemistry for malignant lymphoma and lymphoproliferative disorders: A brief review

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The programmed cell death 1 (PD1)/PD1 ligand (PD-L1) axis plays an important role in tumor cell escape from immune control and has been most extensively investigated for therapeutic purposes. However, PD-L1 immunohistochemistry is still not used widely for diagnosis. We review the diagnostic utility of PD-L1 (by clone SP142) immunohistochemistry in large-cell lymphomas, mainly consisting of classic Hodgkin lymphoma (CHL) and diffuse large B-cell lymphoma (DLBCL). Neoplastic PD-L1 (nPD-L1) expression on Hodgkin and Reed-Sternberg cells is well-established among prototypic CHL. Of note, EBV+ CHL often poses a challenge for differential diagnosis from peripheral T-cell lymphoma with EBV+ non-malignant large B-cells; their distinction is based on the lack of PD-L1 expression on large B-cells in the latter. The nPD-L1 expression further provides a good diagnostic consensus for CHL with primary extranodal disease conceivably characterized by a combined pathogenesis of immune escape of tumor cells and immunodeficiency. Compared with CHL, the nPD-L1 expression rate is much lower in DLBCL, highlighting some specific subgroups of intravascular large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and EBV+ DLBCL. They consist of nPD-L1-positive and -negative subgroups, but their clinicopathological significance remains to be elucidated. Microenvironmental PD-L1 positivity on immune cells may be associated with a favorable prognosis in extranodal DLBCL. PD-L1 (by SP142) immunohistochemistry has helped us to understand the immune biology of lymphoid neoplasms possibly related by immune escape and/or immunodeficiency. However, knowledge of these issues remains limited and should be clarified for diagnostic consensus in the future.

Keywords: programmed cell death 1 ligand 1, classic Hodgkin lymphoma, diffuse large B-cell lymphoma, immune escape, immunodeficiency

INTRODUCTION

Lymphoma diagnosis and classification continue to evolve in accordance with a deeper understanding of the biology related to programmed cell death ligand 1 (PD-L1), most exemplified by the great success of immunotherapies using PD-L1 blockade in classic Hodgkin lymphoma (CHL).[1-3] Roemer *et al*. recently identified chromosome 9p24.1/*PD-L1/PD-L2* alterations, which result in an increased expression of PD-L1, in almost all CHL cases (97%) in their series and reported that they are a defining feature of CHL.[1] CHL is now considered to be of B-cell origin and regarded as an eponym that encompasses multiple entities covering both EBV-positive and -negative diseases. PD-L1 overexpression is activated by genetic alterations affecting the PD-L1 locus in tumor cells or by viral infection that induces immune tolerance.[4]

The definition of CHL is an immune evasion-based disease characterized by neoplastic PD-L1 (nPD-L1) expression on Hodgkin and Reed-Sternberg (HRS) cells, prompting the reassessment of other large B-cell neoplasms. This resulted in the rare detection of chromosome 9p24.1/*PD-L1/PD-L2*

alterations and associated PD-L1 expression on tumor cells in systemic diffuse large B-cell lymphoma (DLBCL), excluding specific subgroups of primary mediastinal large B-cell lymphoma (PMBL), primary central nervous system (CNS) lymphoma, primary testicular lymphoma, intravascular large B-cell lymphoma (IVLBCL), and EBV+ DLBCLs.[1,5-8] Of note, the positivity for PD-L1 on these large tumor B-cells varies greatly depending on the cut-off value adopted (ranging from 5 to 30% positivity on neoplastic cells), the anti-PD-L1 monoclonal antibody used, and the cohorts applied. Moreover, in lymphoid malignancies, PD-L1 expression is detected variably not only on lymphoma cells, but also on the immune cells in the microenvironment, which is best exemplified by tissue macrophages. The nPD-L1 expression on tumor cells is associated with the efficacy of anti-PD-1 immunotherapy and the microenvironmental PD-L1 positivity on immune cells is associated with the prognosis. However, PD-L1 immunohistochemistry is not yet used widely in the diagnostic setting.

We focused on reviewing the diagnostic utility of PD-L1 (by clone SP142) immunohistochemistry during routine pathological assessment of large B-cell lymphomas, mainly CHL and DLBCL. The detailed clinicopathological and molecular findings are outside the scope of this brief review.

HODGKIN LYMPHOMA

Hodgkin lymphoma is a B-cell neoplasm encompassing distinct entities of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and CHL; the latter should be classified into four histopathological subtypes: nodular sclerosis CHL (NSCHL), lymphocyte-rich CHL (LRCHL), mixed cellularity CHL (MCCHL), and lymphocyte-deleted CHL (LDCHL).[1-3] Although each of these subtypes is known to have specific clinical and histological features, they may represent biologically heterogeneous groups, mainly depending on the presence of EBV association beyond their morphological characteristics. The pathogenesis of CHL may be further complicated by the impact of host immune status (i.e., immunocompetent or immunosuppressed patients). The distinction of CHL, which should be differentiated from the numerous other entities that morphologically and immunophenotypically overlap with CHL, is relevant to the therapeutic approach in upfront and relapsed settings.

Among malignant lymphoma entities, CHL has a high frequency (82 to 97%) of nPD-L1 expression in HRS cells.[1,9,10] Of note, the nPD-L1 expression in HRS cells is upregulated by at least two mechanisms, i.e., chromosome 9p24.1 alterations and EBV infection,[1,11-13] which seem to be mutually exclusive in some series.[11,13] Roemer *et al.* reported that 97% of 108 patients with newly diagnosed CHL had alterations in the *PD-L1/PD-L2* loci, including copy gain (56%) and amplification (36%), revealing a highly significant association with the overexpression of both proteins. These findings led them to assert that these genetic alterations define CHL and predict outcomes.[1] In our analysis of Japanese patients using PD-L1 (by clone SP142) immunohistochemistry,

PD-L1 expression on HRS cells was found in 70% of CHL cases.[7] In that series, all (100%) EBV-negative NSCHL cases and EBV+ CHL cases expressed nPD-L1.[7] However, none of the NLPHL, LRCHL, or EBV-negative MCCHL samples expressed PD-L1 on their large tumor cells, although we observed PD-L1 positivity on the microenvironment immune cells in some of those cases.[7] This suggested that PD-L1 immunohistochemistry using the SP142 clone is helpful in distinguishing between CHL and NLPHL. In contrast, Menter *et al.*[14] and Panjwani *et al.*[9] reported that 54% and 75% of NLPHL cases, respectively, were nPD-L1-positive using a different anti-PD-L1 antibody clone (clone E1L3N; Cell Signaling, Danvers, MA, USA). In addition, Menter *et al.* reported 90% positivity on tumor cells in LRCHL cases, with an emphasis on the theoretical diagnostic utility in discriminating between NLPHL and T-cell/histiocyte-rich large B-cell lymphoma based on the absence of nPD-L1 expression in the latter.[14] This discordance in nPD-L1 positivity is thought to be due to different anti-PD-L1 antibody clones (SP142 vs. E1L3N). We also hypothesize that LRCHL bears some similarity to NLPHL in terms of their immunobiological properties because these two diseases are morphologically indistinguishable without the aid of tumor markers.[7] However, as this was based on a limited number of patients, it should be further validated in a larger series.

NSCHL typically affects young patients in the second and third decades, usually presenting as a mediastinal mass in 80% of cases. Diagnostic criteria are well established on morphological grounds, i.e., nodular formation with collagen bands and lacunar cells (large pleomorphic CD30+ cells with artificial retraction of the cytoplasm as if sitting in lacunae). Prototypic NSCHL is consistently positive for PD-L1 (Figure 1A) among Japanese patients.[7] A syncytial variant (SV) of CHL was originally documented as an unusual histopathological variant of NSCHL in 1986[15] and was subsequently reported to have a more aggressive behavior in 1990.[16] SV is characterized by the presence of HRS cells in cohesive sheets and clusters, and has been expanded in the spectrum of NLPHL[17] and EBV+ CHL cases.[18] The recognition of SV is also required to avoid potential misdiagnosis in routine practice, which always poses a challenge for differential diagnosis from composite lymphoma and grey-zone lymphoma (GZL): B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL. Kohno *et al.* recently revealed absent or decreased expression of PD-L1 on tumor cells in confluent sheets (Figure 1B). Compared with positivity on HRS cells in typical areas of CHL, the difference suggests downregulation of nPD-L1 expression with the histopathological progression of CHL.[19] Hollander *et al.* also reported the decreased expression of PD-L1 in HRS cells in consecutive biopsies of a small subset (10-18%) of CHL cases regardless of the treatment setting, but there was no reference of their histopathological findings.[20]

MCCHL usually lacks nodular sclerosis and lacunar cells, although fine interstitial fibrosis may be observed. MCCHL and LDCHL may represent part of a biological continuum, most frequently with EBV-harboring HRS cells.[21] Panjwani
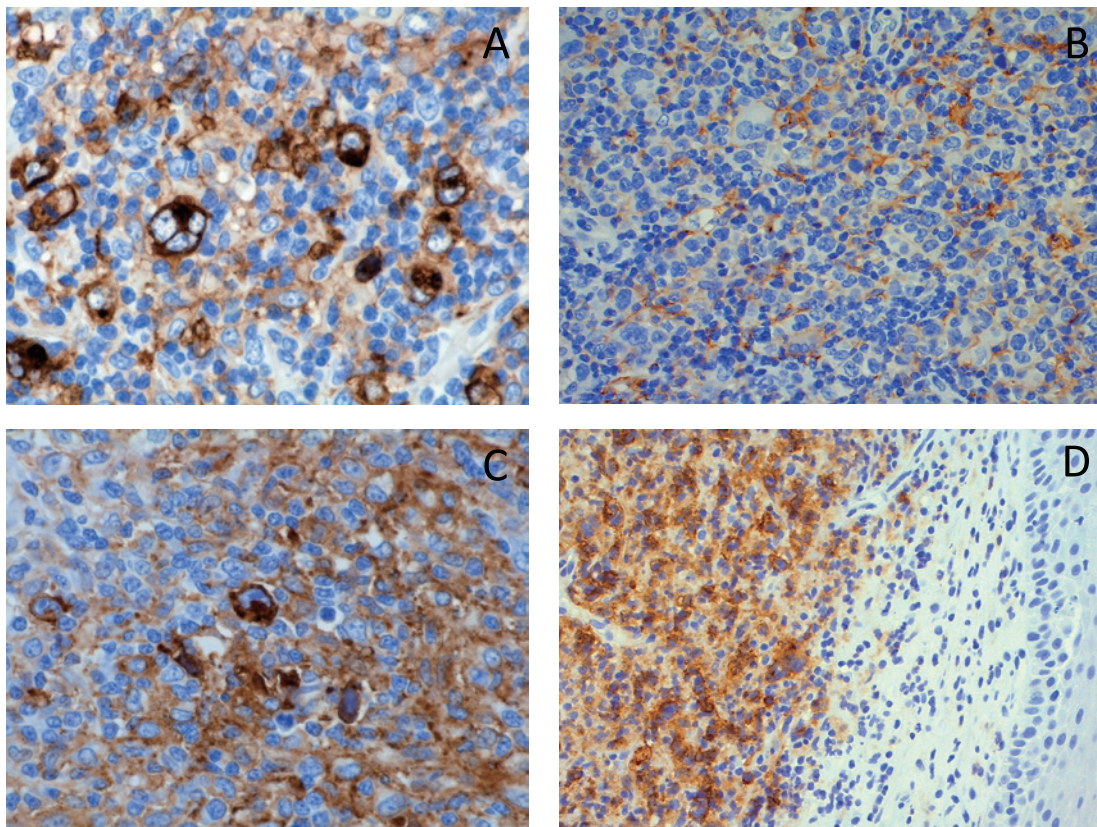
Fig. 1. (**A**) Nodular sclerosis classic Hodgkin lymphoma (CHL) that is EBV-negative. Hodgkin and Reed-Sternberg (HRS) cells were positive for PD-L1. (**B**) Syncytial variant of CHL. The area contains confluent sheets of HRS cells. nPD-L1 expression is absent, although microenvironmental PD-L1 positivity is noted on immune cells. (**C**) Mixed cellularity cHL that is EBV-positive. HRS cells are positive for PD-L1. (**D**) CHL with primary extranodal disease. HRS cells are positive for PD-L1.

et al. reported that EBV positivity detected by EBER *in situ* hybridization correlates with nPD-L1 expression based on 40 (93%) of their 43 EBV+ CHL cases being positive for PD-L1.[9] In our Japanese series, all EBV+ CHLs among immunocompetent patients were positive for PD-L1 on HRS cells (Figure 1C).[7] On the other hand, PD-L1 positivity remained around 90% in methotrexate (MTX)-associated CHL, which is histopathologically characterized by a vaguely nodular pattern, predominance of mononuclear cells, and strong expression of at least one pan-B-cell marker.[22] LDCHL is defined as a diffuse form of CHL rich in HRS cells and/or diminished in the other cell populations that are can be seen in CHL, and is frequently diagnosed in the context of human immunodeficiency virus (HIV) infection.[21,23] In CHL, primary extranodal presentation is rare,[23] but HIV-associated CHL exhibits unusually aggressive clinical behavior with advanced extranodal disease compared with CHL in the immunocompetent population.[24-26] This issue appears to have not been well addressed among patients without HIV infection. In general, EBV-positivity should prompt the suspicion of EBV-positive DLBCL, not otherwise specified (NOS), especially among patients with bulky extranodal disease.[27-29] This disease is known to be analogous to immunodeficiency-associated B-cell lymphoproliferative disorders (LPDs) and presents a broad spectrum of morphological

features with a CHL-like appearance in many, often posing a problem for differential diagnosis from CHL.[27,30-35] We recently found two cases of nPD-L1+ LDCHL with primary extranodal disease (Figure 1D) and their peculiar biological behavior of the immune escape-related lymphoid neoplasm arising in a patient with immunodeficiency due to immune senescence and human T-cell leukemia virus type 1 (HTLV-1) infection, with an emphasis on the diagnostic utility of PD-L1 immunostaining (by clone SP142) (Tsuyuki *et al*, J Clin Exp Hematop, submitted). This disease may affect the fragile elderly and its incidence is increasing with the aging of society in Japan.

On the other hand, peripheral T-cell lymphoma of follicular helper T-cell (T_{FH}) type, mostly exemplified by angioimmunoblastic T-cell lymphoma (AITL), is most common in HTLV-1 non-endemic areas and is now increasing in incidence.[36] The differential diagnostic problem between EBV+ CHL and nodal T-cell lymphoma (TCL) of T_{FH} type with EBV+ non-malignant HRS-like large B-cells has been well documented because of their overlapping histopathological features.[37-40] We recently reported that non-malignant HRS-like cells in nodal TCL of T_{FH}-type lack PD-L1 expression, which is helpful in discriminating them by our diagnostic approach.[7,41] This finding provides further insight into immune evasion and senescence or immunodeficiency in the

pathogenesis of EBV+ large cells, spanning reactive to neo-plastic processes, by our diagnostic approach. On the other hand, Moroch *et al.*[42] and Alikhan *et al.*[43] shed light on TCL of T$_{FH}$-type resembling LRCHL, with an emphasis on careful assessment of the T-cell population in the lesion. We also reported a Japanese patient with TCL of T$_{FH}$ type mimicking LRCHL, which was difficult to diagnose using the routine histopathological approach by the pathologists, to which special attention should be paid (Sakakibara *et al*, J Clin Exp Hematop, submitted).

GREY-ZONE LYMPHOMA

Mediastinal GZL (MGZL) is listed as a B-cell lymphoma, unclassifiable, between DLBCL and CHL in the latest World Health Organization (WHO) classification.[44] The diagnostic criteria of this neoplasm will likely benefit from a more precise definition.[3,21,45] Patients affected by MGZL most frequently present with a bulky mediastinal mass, whereas primary mediastinal large B-cell lymphoma (PMBL) and NSCHL are the most common B-cell neoplasms affecting the thymus.[23,46] Thus, MGZL was originally proposed as a missing link representative of a tumor with transitional features.[44,47] The distinction among these histogenetically related diseases is challenging for pathologists in routine practice.[21] In addition to these neoplasms, mediastinal composite lymphoma, in which NSCHL and PMBL occur synchronously in the same organ or anatomical site, exists.[47] Several authors recently reported PD-L1 expression on neoplastic cells in NSCHL, PMBL, and MGZL, generally finding the positivity to be highest in NSCHL, lowest in PMBL, and intermediate in MGZL.[48,49] Among reported series, nPD-L1 expression was variable in PMBL with different PD-L1 clones and cohorts, ranging from 29% to 100%,[9,14,50-53] suggesting the presence of nPD-L1-positive and -negative subgroups of this distinct lymphoma. Accordingly, among our Japanese patients, nPD-L1 expression was observed in 100% with mediastinal NSCHL (*n* = 7) and 18% with PMBL (*n* = 11),[54] the latter being similar (15%) to another Japanese series.[48] However, these rates may be lower than in Western populations, possibly because of the relative paucity (approximately one-third) of these mediastinal diseases in Asia.[55] We recently reported nPD-L1 expression and its correlation with pathological findings (i.e., anatomical position) in two cases of mediastinal composite lymphoma, one with nPD-L1-positive PMBL (Figure 2A, 2B) and the other with nPD-L1-negative PMBL components,[54] which may provide additional support to the assertion of the two distinct subtypes of PMBL being closer to and more distinct from CHL, respectively.

Non-mediastinal (systemic) GZL remains much more challenging to diagnose, and is characterized by an elderly onset and more advanced disease than MGZL without a bulky mass.[45] Anaplastic variant (av) DLBCL is also
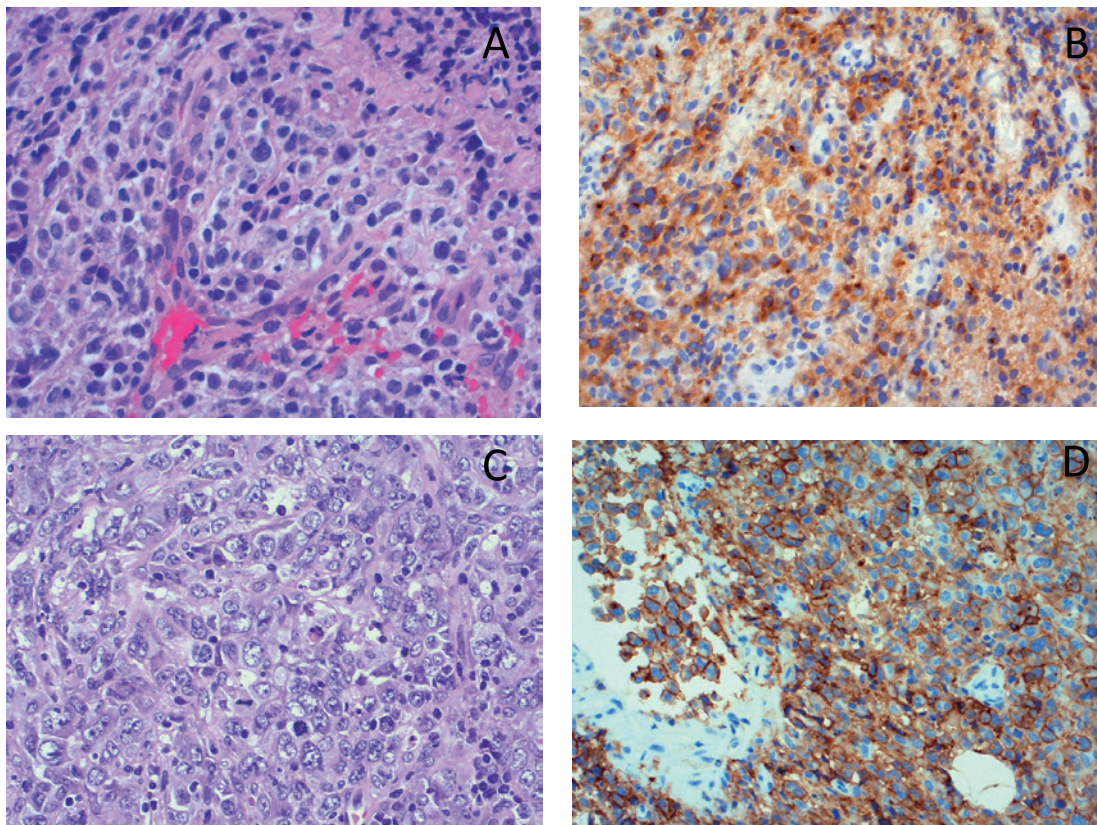

Fig. 2. (*A*) Primary mediastinal large B-cell lymphoma. (*B*) PD-L1-positive section from (*A*). (*C*) Nodal grey-zone lymphoma. (*D*) PD-L1-positive section from (*C*).

morphologically defined in the 2017 WHO classification[56] but remains an enigmatic disease in its clinicopathological distinctiveness, posing a problem for differential diagnosis from GZL and CHL.[57] Megahed *et al.* noted the distinctiveness of nodal avDLBCL with the sinusoidal pattern but without nPD-L1 expression,[58] which was considered to overlap with sinusoidal CD30+ large B-cell lymphoma according to Lai *et al.*[59] This issue that sinusoidal large B-cell lymphoma and avDLBCL have many overlapping clinicopathological and molecular features was also recently reported by Zhe Wang and his group.[60] Kohno *et al.* subsequently reported three cases of nodal nPD-L1+ DLBCL (Figure 2C, 2D) in fragile elderly patients,[61] which may be regarded as GZL, intermediate between CHL and de novo CD5+ DLBCL with nPD-L1 positivity.[62,63] These reports may provide refined diagnostic criteria for a more precise pathological and clinical characterization of these diseases that are currently ill-defined.

DIFFUSE LARGE B-CELL LYMPHOMA

The frequency of alterations in chromosome 9p24.1 and expression of PD-L1 in DLBCL (except some specific subtypes) is low. However, an increasing number of reports state that nPD-L1 expression is significantly associated with EBV-harboring tumor cells in DLBCL. The percentage of positive cases varies greatly depending on the cut-off value adopted (ranging from 5 to 30% positive cells) and the anti-PD-L1 monoclonal antibody used.[6,14,64] In contrast to this PD-L1 upregulation on EBV+ tumor cells, we recently documented that non-malignant EBV+ large B-cells, which are frequently seen in nodal peripheral T-cell lymphomas, especially the T_{FH} type (e.g., AITL), generally lack PD-L1 expression as described above for CHL.[41] The significance of this finding, which was underestimated, provided new diagnostic insight into immune evasion and senescence or immunodeficiency in the pathogenesis of EBV+ large cells from reactive to neoplastic processes. These issues were addressed in our recent brief review[29] emphasizing that immune evasion and senescence/immunodeficiency may be not mutually exclusive in EBV+ lymphoma/LPD developing in the elderly.

Extranodal DLBCLs have unique clinical characteristics and a predilection for specific anatomical sites, which often reflect an underlying biological distinctiveness, resulting in the latest WHO classification.[65] These entities include primary DLBCL of the CNS (CNS DLBCL), primary testicular DLBCL, primary cutaneous DLBCL, leg type, and IVLBCL. They have a propensity for exclusively affecting extranodal sites and a higher risk of secondary CNS relapse during their clinical course, but no association with EBV.[66-71] There is an increasing number of reports on the nPD-L1 expression in a subset of these extranodal DLBCLs, mostly exemplified by IVLBCL.[6,8,63,72-76] Kiyasu *et al.*[6] and Gupta *et al.*[8] reported that 5 (46%) of 11 and 4 (44%) of 9 of their IVLBCL cases, respectively, were positive for PD-L1 (clone EPR1161[2] by Kiyasu and SP142 by Gupta), but there was no detectable difference in clinical or pathological features between

PD-L1-positive and -negative groups. Shimada *et al.* also very recently reported that 8 (38%) of their 21 IVLBCL cases harbored rearrangements of *PD-L1/PD-L2* involving the 3′-UTR, which are implicated in immune evasion via PD-L1/PD-L2 overexpression, but resulted in little association between genetic alterations and patient survival.[77] In contrast, Suzuki *et al.* of our group recently found that the PD-L1+ group (n=10) among a series of 29 IVLBCL patients treated using rituximab-based chemotherapy had significantly lower overall and disease-specific survival rates than the PD-L1-negative group (P= 0.041 and 0.034, respectively).[76] In their entire series (n=34), the PD-L1+ group (n=12, 34%) was significantly younger (P= 0.036) with a smaller proportion of patients older than 60 years (P= 0.037), but was less frequently accompanied by respiratory symptoms (P= 0.018) than in the PD-L1-negative group (n=22).[76] They also surveyed nPD-L1 expression among 283 cases consecutively diagnosed as DLBCL between 2015 and 2017 and identified 6 (6%) nPD-L1+ cases among 108 extranodal EBV-negative DLBCLs, consisting of IVLBCL (2 of 4 cases, 50%), de novo CD5+ DLBCL (1 of 3, 33%), and DLBCL, NOS (3 of 76, 4%), and 4 (50%) nPD-L1 cases among 8 EBV-positive DLBCL, NOS cases.[63] These nPD-L1+ extranodal DLBCLs without EBV association presented varying degrees of intravascular pattern and exclusively affected extranodal sites with no nodal lesion during the clinical course. Immune evasion-related extranodal large B-cell lymphoma was thus proposed based on the hypothesis that PD-L1+ IVLBCL and PD-L1+ extranodal DLBCL may be categorized into one provisional entity that is defined by an exclusively extranodal disease, a varying degree of intravascular pattern, and nPD-L1 expression. A comparison of outcomes between these two groups revealed no significant difference in overall survival (OS), disease-specific, or progression-free survival (PFS).[76] Moreover, by surveying systemic nPD-L1 expression in 10 autopsy cases of IVLBCL, we found two PD-L1-positive cases with unique immunohistochemical findings; the divergence of nPD-L1 expression among the affected organs and anatomical sites and heterogeneity of nPD-L1 expression between these cases were assessed using multiple anti-PD-L1 clones.[75] In Case #1 in the series, nPD-L1 expression was highly restricted to the tumor cells located in the capillaries of the CNS, pituitary gland, kidneys, lungs (Figure 3A), and gastrointestinal tract, and to the sinuses/sinusoids of the spleen, liver, bone marrow, and lymph nodes. This was sharply contrasted with the absence of nPD-L1 expression in tumor cells located in the vessels of the adrenal gland, thyroid gland, pancreas, ovaries (Figure 3B), uterus, pleura, and lungs. Of note, immunostaining using the three commercially available anti-PD-L1 antibodies (clones SP142, E1J2J, and 28-8) yielded the same or a similar pattern of nPD-L1 expression, suggesting that this divergence is not related to the sensitivity of the applied antibodies. We found an unusual focus of nPD-L1+ tumor cells with minimal extravascular invasion in the ovary (Figure 3B), suggesting that a loss or disruption of the intravascular compartmentalization of tumor cells may lead them to PD-L1 positivity. It
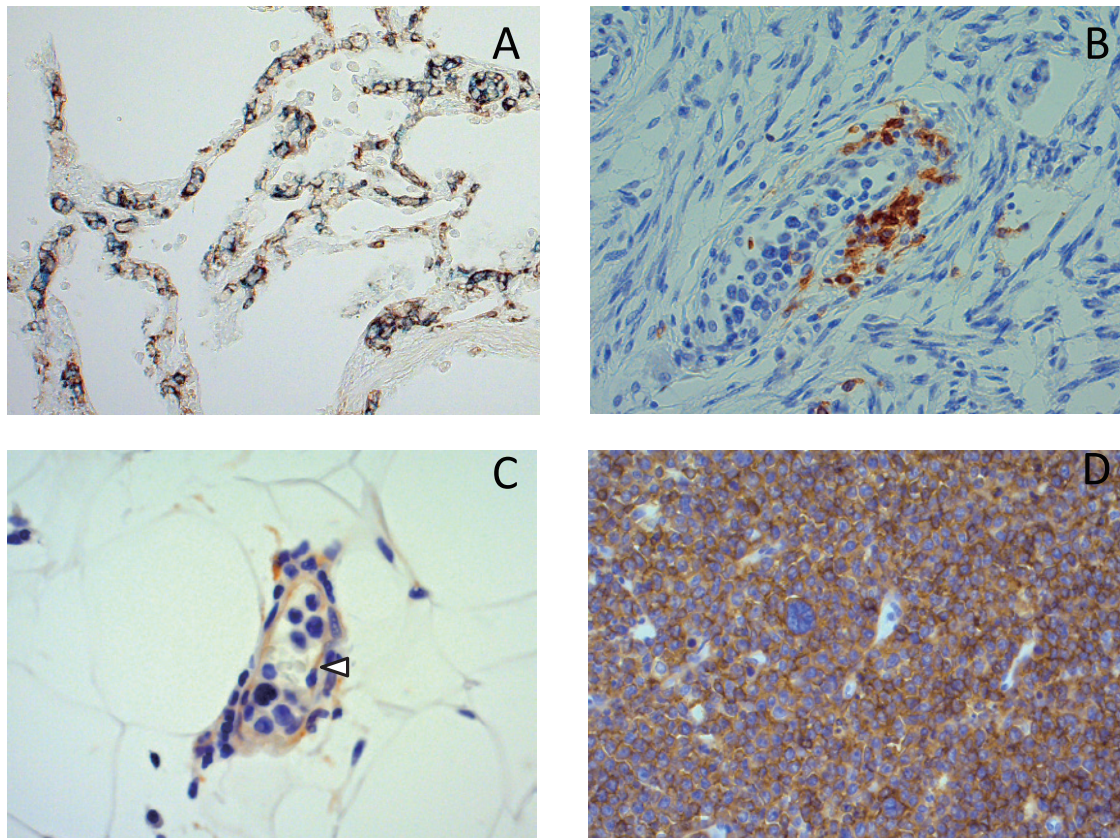
Fig. 3. (*A*) Intravascular large B-cell lymphoma (IVBCL) affecting the lung capillaries, which are double-stained with anti-CD20 (brown) and anti-PD-L1 (blue) antibodies.[75] (*B*) IVLBCL affecting the ovarian vessels. PD-L1 is absent from intravascular tumor cells, in contrast to an eventually detected focus of nPD-L1-positive tumor cells with minimal extravascular invasion. (*C*) PD-L1 immunostaining of IVLBCL affecting subcutaneous adipose tissue, in which the tumor cells lack nPD-L1 expression but are in direct contact with PD-L1-positive vascular endothelial cells (arrowhead). (*D*) Primary intestinal diffuse large B-cell lymphoma positive for PD-L1.

is well known that PD-L1 interacts with PD-1 and CD80 (B7.1),[78] and that the expression of PD-L1 and its receptor CD80 on vascular endothelial cells (VECs) has an inhibitory function on endothelial cell proliferation and angiogenesis.[79] The presence of CD80 on VECs in the affected organs may induce the divergent nPD-L1 expression among the anatomical sites. This phenomenon also suggests that the immunohistochemical PD-L1 negativity (Figure 3C) found in the small sample does not necessarily mean the absence of its neoplastic expression among patients with systemic extranodal lymphomas. In Case #2 of the series, nPD-L1 positivity was detected universally in the affected vessels and capillaries, as well as in all of the organs examined using clone 28-8 and E1J2J, but not when using SP142. The heterogeneity of nPD-L1 expression among IVLBCL cases was recently demonstrated to be driven by the different pattern of *PD-L1* genetic alterations (Satou *et al.*, manuscript in preparation).

On the other hand, Ishikawa *et al.*[74,80,81] recently reported that PD-L1 expression on microenvironment immune cells (miPD-L1 expression) was common in their series of primary gastrointestinal DLBCL (giDLBCL) cases without EBV association. Although nPD-L1 expression (Figure 3D) was rare (1 of 162 cases in their series, 0.6%), the miPD-L1 expression was related to identification of low-risk or high-risk

patients using currently applied immunochemotherapy regimens. They observed miPD-L1 expression in 59 (46%) of 128 primary gastric DLBCL (gDLBCL) cases and 30 (70%) of 43 primary intestinal DLBCL (iDLBCL) cases (*P*= 0.008). In each of these two anatomical groups, miPD-L1-positive cases had a better PFS and OS than miPD-L1-negative cases (*P*= 0.1750 and 0.0281 in gDLBCL and *P*= 0.0456 and 0.0061 in iDLBCL, respectively).[81] This miPD-L1 negativity was further identified as a poor independent prognostic factor of OS (*P*=0.030), in addition to advanced Lugano stage (II2/IIE/IV, *P*=0.068) by multivariate analysis.[81] These studies provided additional support to high miPD-L1 positivity identifying a better prognostic group among patients with DLBCL, as reported by McCord *et al.*,[82] and among patients with adult T-cell leukemia/lymphoma.[83,84] Furthermore, this phenomenon was validated in our separate series of primary CNS DLBCL.[85] Kiyasu *et al*. also emphasized the diagnostic utility of PD-L1/PAX5 double immunostaining in order to discriminate true/accurate nPD-L1 expression from miPD-L1 positivity on the background immune cells.[6]

The PD-L1 (by clone SP142) positivity in our large B-cell lymphoma series is presented in Table 1.

Table 1. PD-L1 expression in large B-cell lymphomas

Diagnosis	Ref. #	Cases N	PD-L1 expression on tumor large B-cells N (%)
CHL			
Nodular sclerosis CHL			
EBV-negative	#7	8	8/8 (100%)
Mixed cellularity CHL			
EBV-positive	#7	10	10/10 (100%)
EBV-negative	#7	2	0/2 (0%)
Methotrexate-associated CHL, EBV-positive	#22	8	7/8 (88%)
CHL with a primary extranodal disease	Tsuyuki *et al.*, submitted	2	2/2 (100%)
Syncytial variant of CHL	#19	4	0/4 (0%) in the confluent sheet of tumor cells
Lymphocyte-rich CHL, EBV-negative	#7	6	0/6 (0%)
Nodular lymphocyte-predominant Hodgkin lymphoma	#7	4	0/4 (0%)
Mediastinal lymphomas, EBV-negative			
Nodular sclerosis CHL	#54	7	7/7 (100%)
PMBL	#54	11	2/11 (18%)
Mediastinal composite lymphoma			
CHL	#54	2	2/2 (100%)
PMBL	#54	2	1/2 (50%)
Nodal DLBCL, EBV-negative	#63	275	0/275 (0%)
Nodal gray zone lymphoma, EBV-negative	#61	3	3/3 (100%)
Nodal anaplastic variant of DLBCL, EBV-negative	#58	11	0/11 (0%)
Extranodal DLBCL, EBV-negative			
IVLBCL	#76	34	12/34 (35%)
Autopsy cases with IVLBCL, showing the divergence and heterogeneity of PD-L1 expression on tumor cells	#75	10	2/10 (20%)
Primary DLBCL of the central nervous system	#85	39	1/39 (2.6%)
Primary cutaneous DLBCL, leg type	#63	2	0/2 (0%)
Others:			
Tonsil	#63	5	0/5 (0%)
Salivary gland	#63	4	0/4 (0%)
Pharynx	#63	4	0/4 (0%)
Lung	#63	4	0/4 (0%)
Gastrointestinal tract	#81	162	1/162 (0.6%)
Liver	#63	4	0/4 (0%)
Spleen	#63	4	0/4 (0%)
Kidney	#63	2	1/2 (50%)
Adrenal gland	#63	5	2/5 (40%)
Pelvic cavity	#63	1	1/1 (100%)
Soft tissue	#63	4	0/4 (0%)
Testis	#63	5	0/5 (0%)

Abbreviations: PD-L1, programmed cell death ligand 1; CHL, classic Hodgkin lymphoma; EBV, Epstein-Barr virus; PMBL, primary mediastinal B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; IVLBCL, intravascular large B-cell lymphoma

CONCLUSIONS

Our knowledge of the immune biology of lymphoid neoplasms is rapidly expanding. The recent finding of PD-L1 signaling/expression as an immune checkpoint and its blockade revolutionized therapeutic approaches for CHL and DLBCL patients with recurrent and/or refractory disease. We reviewed the diagnostic utility of PD-L1 (by clone SP142) immunohistochemistry for CHL, GZL, and specific subtypes of extranodal DLBCL. Although it remains limited in our routine practice, we demonstrated that the immunohistochemical assessment of PD-L1 can assist in the differential

diagnosis among CHL, GZL, and DLBCL. Moreover, immunostaining is useful for identifying a favorable prognostic group among extranodal DLBCL subtypes, which may vary at anatomical sites. More detailed pathological characterization of the neoplastic and microenvironmental immune cells based on PD-L1 positivity is expected.

CONFLICT OF INTEREST

None declared.

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