B-cell and classical Hodgkin lymphomas associated with immunodeficiency

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Abstract

Objectives. The 2015 Workshop of the Society for Hematopathology/European Association for Haematopathology studied submitted large B-cell lymphomas (LBCLs), including classical Hodgkin lymphoma (cHL) in the context of immunodeficiency.

Methods. Clinicopathologic and molecular features were studied to explore unifying concepts in malignant B-cell proliferations across immunodeficiency settings.

Results. Submitted LBCLs formed a spectrum from diffuse large B-cell lymphoma (DLBCL) to cHL across immunodeficiency settings. Additional studies demonstrated overexpression of PD-L1 and molecular 9p24 alterations in the LBCL spectrum and across different immunodeficiency settings.

Conclusions. LBCL include a spectrum from DLBCL to cHL across all immunodeficiency settings; immunohistochemical and molecular features are suggestive of shared pathogenic mechanisms involving PD-L1 immune checkpoints.
Drs. Daphne de Jong and John K.C. Chan chaired Session 2 of the workshop on B-cell and classical Hodgkin lymphomas associated with immunodeficiency and, together with Margaretha G.M. Roemer functioned as the co-lead authors of this article. In this session, the spectrum of immunodeficiency-associated B-cell proliferations included those with features of various lymphoma classes according to World Health Organization (WHO) nomenclature in immunocompetent patients. These included histologically aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) and its morphological variants, Burkitt lymphoma and classical Hodgkin lymphoma (cHL). Similarities and important differences were noted in various immunodeficiency backgrounds that were further substantiated by additional molecular studies by Dr. Roemer. Here, we discuss the spectrum and boundaries of these proliferations and explore possible unifying and differing aspects in oncogenesis.

**Concept of monomorphic versus polymorphic B-cell proliferations**

The spectrum of posttransplant lymphoproliferative disorders (PTLD) has been the subject of extensive study, and among the immunodeficiency-related lymphoproliferations in the WHO classification, their terminology and definitions are the most clearly defined. Therefore, PTLD serves as the conceptual basis for B-cell lymphoproliferative disorders (LPD) in other immunodeficiency states.\(^1\) The boundary between polymorphic versus monomorphic PTLD as defined in the WHO classification, however, raises a number of challenges. Polymorphic PTLD is defined as a lesion which shows a full range of B-cell maturation stages admixed with variable numbers of large transformed cells/immunoblasts, some of which may show Hodgkin/Reed-Sternberg-like morphology.\(^2,3\) The transition between polymorphic and monomorphic PTLD is subjective. Conceptually, the morphological distinction between polymorphic PTLD and monomorphic PTLD was designed to predict response to treatment and especially to guide the choice between tapering of immunosuppression (+/- Rituximab) only versus the need to add chemotherapy.\(^4-7\) Polymorphic PTLD was viewed as a process in which the lymphoid proliferation was not autonomous, and that if immune surveillance were restored, the process might regress spontaneously. In contrast, monomorphic PTLD has been viewed as a lymphoma, in which treatment beyond reduction of immunosuppression is required. In practice, for many pathologists, the distinction has been based on the assessment of whether there is a preponderance of large transformed cells/immunoblasts. It should be realized, however, that the current pathologic definitions have proven not to be sufficient to predict this clinical behavior and in practice, B-LPD that entirely fulfill the criteria for monomorphic B-LPD do regress upon reduction of immunosuppression only.\(^5,7\) Polymorphic PTLD is driven by EBV alone in most instances, whereas monomorphic PTLD may have secondary genetic aberrations...
leading to deregulated growth of the lymphoid cells. Thus far, there are only very few experimental data available to support this notion, however.⁸⁻¹³ On clinical grounds, polymorphic PTLD usually occurs closer to the time of transplant, whereas monomorphic PTLD occurs late, often many years after the transplant. Therefore, the currently used morphological definitions do not serve their intended purpose. Ideally, the distinction between polymorphic and monomorphic PTLD, or rather the classes that require chemotherapy or not, should be determined on objective pathogenetic and biological features. Such features have yet to be identified and validated, and collaborative and multi-institutional studies of large numbers of well-defined cases are needed to move this area forward.

Once the determination is made that the lesion is a monomorphic PTLD, then the WHO recommends that further subclassification follow the WHO categories of lymphomas in immunocompetent patients. The range of morphologies considered acceptable for the designation of monomorphic PTLD is broad and includes those with sheets of transformed cells (typical of DLBCL and Burkitt), those with scattered large cells in a T-cell and histiocyte-rich background (typical of T-cell/histiocyte-rich large B-cell lymphoma [TCRBCL]), and those that resemble cHL. This boundary therefore is a continuum with polymorphic PTLD, and is well recognized as a problematic one with little agreement even among experts. While typical cases of polymorphic PTLD and monomorphic PTLD are not difficult to separate, there are B lymphoproliferations in immunodeficiency settings that clearly overlap this boundary. Furthermore, similar proliferations that straddle this boundary are not included in the WHO classification, and guidelines as to how they should be classified are not well defined, leading to inconsistent use of WHO terminology. Among workshop cases, a similar spectrum of lesions was noted in various immunodeficiency backgrounds; however, some differences specific to certain immunodeficiency background were also noted.

**Large B-cell lymphomas**

Large B-cell lymphomas (LBCLs) are by far the most frequently reported lymphoid proliferations in immunodeficiency states. They cover a large morphological spectrum ranging from typical DLBCL to large cell proliferations with a dominant reactive immune infiltrate with morphological features similar to those of TCRBCL and cHL.¹⁴⁻¹⁷ In the WHO classification, it is recommended that these lymphomas be classified according to their counterparts in immunocompetent patients, but various classes are listed separately in sections on PTLD, iatrogenic-associated and HIV-associated settings. Nomenclature is non-uniform between the different immunodeficiency backgrounds, however, and the criteria to distinguish various
lesions are not consistent or specified across categories. This for example holds true for nomenclature currently used such as Hodgkin-type, Hodgkin-like and TCRBCL in the primary immunodeficiency, HIV, iatrogenic and posttransplant settings, which refers to the difficult differential diagnosis of “grey zone-type” proliferations with ambiguous morphology and immunophenotypes with features of DLBCL and cHL.

Depending on the immunodeficiency background and the clinical condition of the patient, the first treatment approach may be the correction of the immunodeficiency, if applicable. In iatrogenic immunodeficiency, removal of immunosuppressive treatment results in complete regression of lymphoma in a varyingly reported, but considerable percentage of patients. Rituximab monotherapy is also an attractive approach with relatively high success rates and is the method of choice in organ transplant patients in whom the transplant organ should not be put at risk for rejection.6-6,18-21 Both non-chemotherapeutic strategies are equally successful in EBV positive (EBV+) and EBV negative (EBV-) proliferations.6,7,18

Once chemotherapy is chosen, treatment protocols are selected similarly to what is done in immunocompetent patients.7,22 Therefore, the diagnosis of LBCL versus cHL by the pathologist will likely determine therapy. A total of 94 cases of large B-cell proliferations spanning features of DLBCL, TCRBCL and cHL are listed in Table 1 according to their category of underlying immunodeficiency or immune dysregulation.

**Morphologic spectrum of large B-cell lymphomas, including classical Hodgkin lymphoma**

Examples of the complete spectrum of histologically aggressive B-cell proliferations were received by the workshop in all immune deficiency states. Fifty-one cases were diagnosed as DLBCL and showed confluent sheets of large transformed cells with a vesicular chromatin structure and one or more nucleoli. All cases had expression of the complete range of B-cell defining markers such as CD20, CD79a, PAX5, BOB1 and OCT2. EBV positivity ranged from 39% in the posttransplant setting to 75% in the iatrogenic immunodeficiency setting, while immune senescence related cases were all EBV+ by definition. While formerly an age-limit was set for EBV+ DLBCL, it is now recognized that this disease may occur in all age groups.23-27

See Table 1 for further details.
Twenty-one cases were diagnosed as cHL, based on the presence of scattered large, often multinucleated tumor cells in a mixed background of small lymphocytes, plasma cells, histiocytes and eosinophils. The tumor cells exhibited a phenotype consistent with cHL, lacking a complete range of B-cell markers and most often expressing CD15. EBER was generally positive, except in one patient who was post-renal transplantation. A diagnosis of TCRBCL was favored in 17 cases, based on a complete B-cell immunophenotype (CD20, CD79a, PAX5, BOB1, OCT2), (almost completely) lacking eosinophils and B-cells in the background infiltrate, which was dominated by T-cells and histiocytes. All cases were positive for CD30, although CD15 was seen sporadically.

It was noted that in various cases the distinction among the three classes (DLBCL, TCRBCL and cHL) tended to be morphologically arbitrary; intermediate phenotypes were found and different components spanning the spectrum could be present within a single patient or single biopsy sample. Examples are illustrated in Figure 1. In a case of a 83-year old female patient without known causes of immunodeficiency and who presented with generalized lymphadenopathy (case SH2015-201, Dr. S. Thibodeaux, University of Pennsylvania, USA), morphology was fully consistent with cHL. However, the tumor cells were positive for the complete range of B-cell differentiation markers as well as for CD30, CD15, LMP1 and EBER. Therefore, a diagnosis of aggressive B-cell lymphoma with features intermediate between LBCL and cHL might be considered. The clinical context, however, does not imply a diagnostic dilemma between primary mediastinal B-cell lymphoma (PMBL) and cHL, which is the main content of the so-called mediastinal gray zone lymphoma and this classification therefore seems to be inappropriate in the present context. In a series of 46 patients with EBV+ DLBCL below the age of 45 years, Nicolae and co-workers noted seven cases of so-called gray zone lymphoma, further attesting to the presence of a true continuum. The nomenclature in the WHO classification does not distinguish this group of cases; in order to put together these cases for further discussion and study by the panel, we have employed the descriptive term of DLBCL, Hodgkin lymphoma-like.

In four cases, overlapping morphology and immunophenotypes were observed within single biopsy samples. Case SH2015-510 (Dr. Low, City of Hope Medical Center, USA) was that of an 81-year-old patient with a long history of rheumatoid arthritis and treatment with methotrexate (MTX), steroids and tumor necrosis factor-α inhibitor who developed an aggressive EBV+ lymphoma, possibly in the context of an underlying EBV+ extranodal marginal zone lymphoma in the salivary gland. Large EBER+ multinucleated Hodgkin-like cells were present in areas with a dense
Figure 1. The morphological spectrum of large B-cell proliferations. Case SH2015-116 (Dr. Thibodeaux, University of Pennsylvania, USA) of a 63 year old female patient shows a lesion with morphology of Hodgkin-type tumor cells in a Hodgkin-type background (A, B, C). The tumor cells express a complete B-cell phenotype, but also CD15 (D) and Fascin (E). In case SH2015-308 (Dr. Thousseyn, Leuven, Belgium) in a lymph node of a renal transplant patient, a spectrum of Hodgkin-type morphology (F, H: CD20) and DLBCL morphology (collision)(G, I: CD20) are present in the same biopsy.
reactive background pattern, and merged into confluent sheets of necrosis, which was consistent with the diagnosis of DLBCL. Similar classification problems were encountered in cases of LBCL that arose in a patient with B-CLL who was treated with fludarabine, cyclophosphamide and Rituximab (SH2015-298), a renal transplant patient (SH2015-308) and a renal transplant patient with common variable immunodeficiency (SH2015-122). This underlines that a similar range of overlapping morphologic and immunophenotypic features is found in these lesions irrespective of the immunodeficiency background (posttransplant, iatrogenic and immune senescence), both in young and elderly patients.

These features challenge the principle that LBCLs represent separate entities equivalent to morphologically similar lymphoproliferations encountered in immune competent individuals (Figure 2). An alternative hypothesis might be that LBCLs arising in immunodeficiency states share similar pathogenic mechanisms that may culminate in a variety of different morphologies, although additional studies are required to explore this further. Nevertheless, highly unusual clinical presentations of well-defined lymphoma entities should provide food for thought in this respect and a diagnosis of cHL with a presentation as a single soft tissue mass in the right buttock (SH2015-222, Dr. Blankenship, Austin, USA) in a patient with systemic lupus erythematosus treated with MTX should not be readily accepted as cHL despite its apparent similarity of morphology and immunophenotype to cHL in immunocompetent patients.

**Molecular pathogenesis of LBCLs in the immunodeficiency setting**

Thus far, the pathogenesis of immunodeficiency related B-LPD has been studied in most detail in the posttransplant and immune senescence settings. Here, we would like to discuss possible common underlying pathogenetic mechanisms across the various immunodeficiency settings in light of the common morphological spectrum.

Most immunodeficiency related B-LPDs are reported to be ABC-type proliferations based on studies of PTLD and age-related immune senescence B-LPD. This holds true of both EBV⁺ and EBV⁻ PTLD. The mechanisms behind this common phenotype are different, however, and in EBV⁻ cases a spectrum of MYD88, CD79B and CARD11 mutations result in constitutive nuclear factor-κB activation as in immunocompetent patients, while in EBV⁺ proliferations, EBV seems to substitute for this mechanism, suggesting a unique oncogenesis rather than a common type of ABC-type DLBCL. Indeed, the landscape of chromosomal gains and losses in EBV⁺ PTLD and immune senescence
B-cell and classical Hodgkin lymphomas associated with immunodeficiency

Figure 2. Large B-cell lymphomas in immunodeficiency states form a spectrum with arbitrary boundaries. The figure illustrates the overlapping features between DLBCL, TCRBCL and cHL. While at the extremes of the spectrum, the morphology and immunophenotype of the tumor cells and the composition of the reactive infiltrate may be typical and comparable to the corresponding entities in immunocompetent patients; however, frequently discordant features are present in immunodeficient patients; precluding unequivocal classification.

related B-LPD bears important similarities and differs from EBV− cases and those in immunocompetent patients, including ABC-type DLBCL. Although difficult to compare between studies in different immunodeficiency settings, amplification of the 9p24.1 region containing CD274 (PD-L1), PDCD1LG2 (PD-L2) and JAK2 seems to be most characteristic37, and this is reflected in the high protein expression of PD-L1 that is shared by EBV− PTLD, immune senescence related B-LPD and EBV− iatrogenic immunodeficiency-related B-LPD (60-100%, >20% tumor cells) in contrast to DLBCL in immunocompetent patients24,38-40, but very similar to the genotypic characteristics that are shared by DLBCL in immune privileged sites (central nervous system [CNS], testis), PMBL and cHL.41-43 In these diseases, immune evasion mediated by a tolerogenic microenvironment via dysregulation of the PD-1/PD-L1 immune checkpoint is essential and distinguishes these diseases from common types of DLBCL.
To assess for a role of immune checkpoint abnormalities in B-LPDs across immunodeficiency settings, the panel performed additional PD-L1 and PD-L2 immunohistochemistry (anti-PD-L1 clone: E1L3N, rabbit mAb from Cell Signaling Technology, performed in the Department of Pathology, Stanford University, CA) on a series of 59 submitted B-LPD. PD-L1 was expressed in the majority of cases in tumor cells irrespective of EBV status and immunodeficiency setting in 22 of 22 DLBCLs; 13 of 13 cHLs; four of four DLBCL, Hodgkin-like; seven of eight plasmablastic lymphomas; and nine of 12 polymorphic B-LPD (Table 2). Expression of PD-L2 was only very sporadically observed. Moreover, expression of PD-L1 could be

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B-LPD, B-cell lymphoproliferative disorder; CHL, classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV+, Epstein-Barr virus positive; EBV–, Epstein Barr negative; HIV, human immunodeficiency virus; HL, Hodgkin-like; PBL, plasmablastic lymphoma; PID, primary immunodeficiency; PTLD, posttransplant lymphoproliferative disorder.

To assess for a role of immune checkpoint abnormalities in B-LPDs across immunodeficiency settings, the panel performed additional PD-L1 and PD-L2 immunohistochemistry (anti-PD-L1 clone: E1L3N, rabbit mAb from Cell Signaling Technology, performed in the Department of Pathology, Stanford University, CA) on a series of 59 submitted B-LPD. PD-L1 was expressed in the majority of cases in tumor cells irrespective of EBV status and immunodeficiency setting in 22 of 22 DLBCLs; 13 of 13 cHLs; four of four DLBCL, Hodgkin-like; seven of eight plasmablastic lymphomas; and nine of 12 polymorphic B-LPD (Table 2). Expression of PD-L2 was only very sporadically observed. Moreover, expression of PD-L1 could be
appreciated in macrophages. In a selection of these cases (n=25), 9p24.1 genetic alterations were studied by fluorescent in situ hybridization (FISH) according to methods previously reported\(^43\) (performed by M.G.M. Roemer in collaboration with A.H. Ligon and M.A. Shipp, Dana-Farber Cancer Institute, Boston, USA). Results are listed in Table 3 and illustrated in Figure 3. Of 23 evaluable cases, seven of seven EBV\(^-\) and 11 of 16 EBV\(^+\) LBCLs showed alterations at the PD-L1/PD-L2 locus, ranging from low level polysomy to high level copy gain and amplification. Two cases with structural rearrangements were noted (one EBV\(^-\), one EBV\(^+\)). Most important, 9p24.1 genetic alterations were again observed across all immunodeficiency settings, including posttransplant, immune senescence, iatrogenic/autoimmune, HIV infection and primary immunodeficiency, and occurred in both EBV\(^+\) as well as EBV\(^-\) cases. This finding substantiates the proposed “unifying approach” for classification of immunodeficiency-related lymphoproliferations across immunodeficiency settings. Moreover, similar alterations were found in the morphological classes of DLBCL, TCRBCL/Hodgkin-like, and cHL, and this preliminary data support the notion that large B-cell proliferations in the immunodeficiency setting may form a single spectrum driven by a specific pathogenic mechanism rather than direct counterparts of lymphoproliferative disorders and lymphomas in immunocompetent patients. This small series precludes strong conclusions regarding the role of EBV in this context, and further studies are warranted to confirm and validate these observations. Based on current literature and supported by data derived from cases submitted to the Workshop, a common oncogenesis across various immunodeficiency settings with a dominant role for immune evasion and a tolerogenic microenvironment is suggested.

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B-cell and classical Hodgkin lymphomas associated with immunodeficiency 67
Figure 3. Examples of PD-L1 and PD-L2 protein expression and 9p24.1 genetic alterations by FISH analysis. Polysomy (A) in a case of DLBCL, immune senescence-related EBV+ (SH2015-192), and expression of PD-L1 protein (B) and lack of PD-L2 protein (C) by immunohistochemistry. Copy gain (D) in a case of DLBCL, posttransplant, EBV+ (SH2015-286) and expression of PD-L1 protein in a subset of PAX5-positive large atypical B-cells (PD-L1, brown; PAX5, pink; E) and expression of PD-L2 protein (F) by immunohistochemistry. Amplification (G) in a case of DLBCL, HIV, EBV+/HHV8 negative (SH2015-071), and expression of PD-L1 protein by single and double immunohistochemistry (H, I). Structural chromosomal alterations (translocation) (J) in a case of DLBCL, immune senescence, EBV+ (SH2015-241), and expression of PD-L1 protein by single and double immunohistochemistry (K, L).
Clinicopathologic correlations
A high proportion of immunodeficiency-related B-cell lymphomas may present at extranodal sites. However, only in the posttransplant setting do formal epidemiological data suggest an excess of extranodal gastrointestinal presentations as compared to immunocompetent patients.  

Specific clinic-pathological correlations, such as hepatosplenic T-cell lymphoma and thiopurine treatment are well-established in the field of immunodeficiency-related T-cell lymphomas. It has been reported that cHL may be more prevalent in the MTX and HIV settings. This notion is not supported by the submitted cases to the workshop, however. This may be due to selection bias in the submitted cases, but may also result at least in part from the use of different classification criteria in the morphological spectrum of DLBCL, Hodgkin-like proliferations and cHL across immunodeficiency settings as described above. One highly specific association of primary CNS lymphomas in the iatrogenic setting should be mentioned. In an epidemiological survey, Crane and coworkers noted a steep increase in the incidence of primary CNS B-LPD to 36% of all PTLD and iatrogenic B-LPD cases diagnosed between 2005 and 2014, as compared with preceding 5-year cohorts. The common denominator in primary CNS lymphomas in both the posttransplant and the iatrogenic setting was the use of mycophenolate mofetil (MMF), particularly when patients were taking MMF in the absence of calcineurin inhibitors. Calcineurin inhibitors were associated with a strong protective effect against primary CNS lymphoma when given alone or in combination with MMF. Case SH2015-337 (Dr. Crane, Johns Hopkins School of Medicine, USA) is a prototypical example of a 76-year-old patient who was treated with azidothymidine and steroids for eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis) and later with MMF and subsequently presented with multifocal cerebral lymphoma. The morphology and immunochemistry typically showed overlapping features of large B-LPD as described above with mostly EBV+ Hodgkin-like tumor cells. After discontinuation of MMF and Rituximab treatment, the lymphoma regressed almost completely and the patient remained stable.

Other novel types of chemotherapy may cause relative immune suppression in specific immunologic cellular compartments, leading to various forms of B-LPD. Dasatinib-related hyperplasias are an example. However, morphologically malignant proliferations may also occur within the spectrum of DLBCL to cHL. In EBV+ proliferations, an association with the presumed immunodeficiency seems likely, but in EBV- cases, this association may not be proven. Both lenalidomide and alemtuzumab (anti-CD52 treatment) lead to severe imbalances in T-cell subsets including suppression of Treg populations, and cases of EBV+ B-LPD are also
reported in this setting.\textsuperscript{50-53} These cases should prompt alertness for as yet undefined immunodeficiency states with the expanding clinical use of novel immune modulatory drugs, since new patterns of LPD may emerge with these new therapeutic agents. Fludarabine has been used in B-CLL treatment over a much longer period, and more data are available. Indeed, in fludarabine-treated patients, a high incidence of EBV\textsuperscript{+} B-cell proliferations have been described covering the spectrum of DLBCL to cHL, which are generally not clonally related to the underlying CLL. Therefore, these lesions do not comply with the strict definition of large cell (Richter) transformation, which is now limited to a direct, clonally related transformation of the original indolent B-CLL/SLL, but rather should be regarded as iatrogenic B-LPD. Two cases of B-CLL treated with fludarabine illustrate this concept: SH2015-183 (Dr. Gong, Thomas Jefferson University, USA) and SH2015-298 (Dr. Ozkaya, Istanbul University, Turkey) both with EBV\textsuperscript{+} B-LPD with features of DLBCL and with cHL-like tumor cells.

Conclusions
The spectrum of B-cell proliferations with morphologically malignant features is broad and spans the spectrum of DLBCL, TCRBCL and cHL. A similar distribution is seen across various immunodeficiency settings; there are also some specific associations between specific iatrogenic immune modulators and manifestations of LPD. The morphologic range in individual cases, both synchronous and metachronous, together with preliminary genetic data on the role of 9p24 alterations, suggests that these various appearances may represent a single oncogenic spectrum with varying morphologies and may not show a one-to-one correspondence to their morphologic counterparts in immunocompetent patients.

Table 4 summarizes the key features of large B-cell lymphomas associated with immunodeficiency that were addressed in this workshop session.

To view full-slide images and case write-ups for selected 2015 SH/EAHP Workshop case numbers mentioned in this article, go to http://bit.ly/2kCMFvR.

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B-cell and classical Hodgkin lymphomas associated with immunodeficiency

**Table 4**

**Summary Table: B-Cell and Classical Hodgkin Lymphomas Associated With Immunodeficiency**

<table>
<thead>
<tr>
<th>CHL</th>
<th>Must meet the criteria for CHL in an immunocompetent patient</th>
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<tbody>
<tr>
<td></td>
<td>Must be separated from mucocutaneous ulcer, polymorphic LPD, and DLBCL with Hodgkin-like cells</td>
</tr>
<tr>
<td></td>
<td>Be wary of unusual clinicopathologic presentation, extranodal localization, and aberrant immunophenotype</td>
</tr>
<tr>
<td></td>
<td>Shows overlapping features with TCRCBL and cannot always be reproducibly separated</td>
</tr>
<tr>
<td></td>
<td>More likely forms a spectrum with DLBCL and TCRCBL, and some cases may or may not represent the counterpart of CHL in immunocompetent patients</td>
</tr>
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</table>

**Large B-cell lymphoma**

|     | Mycophenolate mofetil specifically predisposes to the development of cerebral large B-cell lymphoma; calcineurin inhibitors exert a protective effect in this setting |
|     | Distribution of EBV+ and EBV− DLBCL varies in immunodeficiency settings (iatrogenic, PTLD, immune senescence, HIV related) |
|     | Most tumor cells should be demonstrably EBV+ for the diagnosis of EBV+ DLBCL |
|     | A polymorphous background is helpful to separate large B-cell lymphoma from polymorphic B-LPD with Hodgkin-like cells |
|     | A subset of EBV+ DLBCL exhibits a prominent T-cell/histiocyte-rich or Hodgkin-like background, and this spectrum may not be reproducibly separated from each other |
|     | Frequently shows deregulation of the PD-1/PD-L1/2 axis, potentially inducing a tolerogenic microenvironment and immune evasion |

**Molecular mechanisms, including 9p24.1 copy number alterations that contain the locus, are likely shared in all immunodeficiency settings and offer opportunities for targeted therapy**

**References**


