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The Histological Classification of Diffuse Large B-cell Lymphomas

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Abstract

Diffuse large B cell lymphomas (DLBCLs) are aggressive B-cell neoplasms with considerable clinical, biologic and pathologic diversity, in part reflecting the functional diversity of the B-cell system and multiple pathways of transformation. In recent years, the advent of new high-throughput genomic technologies has provided new insights into the biology of DLBCL, leading to the identification of distinct molecular identities and novel pathogenetic pathways. This increasing complexity had led to an expanding number of entities in the WHO classification. Using a multi-modality approach, the updated 2008 classification delineated some new subgroups, including DLBCLs associated with particular age groups or specific anatomic sites, as well as two borderline categories: tumors at the interface between classical Hodgkin lymphoma (cHL) and DLBCL as well as between Burkitt Lymphoma (BL) and DLBCL. This article reviews the histopathologic features of the various aggressive B-cell lymphoma subtypes included in the 2008 classification, with emphasis on some of the new entities as well as areas of diagnostic challenge.

Introduction

Diffuse large B cell lymphoma (DLBCL) is an aggressive B-cell lymphoma, histologically characterized by diffuse proliferation of large neoplastic B lymphoid cells with a nuclear size equal to or exceeding normal histiocyte nuclei.¹ It is the most common form of lymphoma, accounting for 30–40% of adult non-Hodgkin lymphoma worldwide. DLBCLs are clinically and pathologically diverse, partially reflecting the diversity of the B-cell system. As the response to treatment is different, there has been vast clinical and basic research devoted to identifying prognostically or biologically distinct subgroups. Over the past few years, significant efforts focused on the identification of molecular signatures and pathogenetic pathways that might be the subject of molecularly targeted therapy. The 2008 WHO classification lists a large number of entities that fall under the broad heading of

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DLBCL based on distinct clinical, pathologic or biologic features. This review summarizes current knowledge, with emphasis on some of the new entities as well as areas of diagnostic challenge.

DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (DLBCL, NOS)

DLBCL, NOS is the most common category of DLBCL. As the name implies, it is a diagnosis of exclusion, applying to DLBCL cases that do not fit into any specific disease subgroups. DLBCL is more common in the elderly but may be seen in any age group. It can arise de novo or as a progression or transformation from low grade B-cell malignancy, such as follicular lymphoma or chronic lymphocytic leukemia (CLL), so-called Richter's transformation. Patients may present with nodal or extranodal diseases. Frequent extranodal sites of involvement include gastrointestinal tract, bone, testis, spleen, thyroid, and lung.

DLBCL, NOS demonstrates a broad cytologic spectrum. Three common morphologic variants have been described, referred to as centroblastic, immunoblastic and anaplastic variants (Figure 1A and B).² The designation of immunoblastic was reserved for tumors with greater than 90% of immunoblasts and was associated with a worse prognosis.^{3, 4} However, the results have not been reproducible in other studies, probably reflecting variation in criteria for the immunoblastic designation and poor inter-observer reproducibility. All variants may be admixed with a variable number of T cells and/or histiocytes. In contrast to T-cell/histiocytes rich large B-cell lymphoma (THRLBCL) described below, the neoplastic B cells in DLBCL, NOS are more numerous and tend to form clusters or sheet out.

In recent years, the development of high-throughput technologies has greatly accelerated our understanding of the molecular complexity of DLBCL. Using gene expression profiling (GEP), Staudt and colleagues identified two molecularly distinct forms of DLBCL which were morphologically overlapping but had gene expression patterns indicative of different stages of B-cell differentiation, resembling either germinal center B-cells (GCB) or activated B-cells (ABC).⁵ Consistent with their putative "cell-of-origin" (COO), GCB DLBCLs display high-level expression of the master regulator BCL6 and harbor hypermutated immunoglobulin genes with ongoing somatic hypermutation, whereas ABC DLBCLs show activation of NF- κ B and BCR signaling pathways, and upregulation of genes required for plasmacytic differentiation.⁶ The COO classification has been shown to identify distinct DLBCL prognostic subgroups, with GCB DLBCLs being associated with a significantly better outcome as compared with the ABC subgroup.^{7, 8} While the introduction of Rituximab to traditional CHOP therapy has decreased the impact of the COO distinction, the ABC subtype remains less responsive to therapy than the GCB subtype.⁹ Importantly, more recent studies have shown that DLBCL subgroups harbor different genetic lesions and/or disrupted signaling pathways, providing a genetic rationale for the development of potential therapeutic targets,¹⁰⁻¹³ as discussed in other articles in this issue.

Because of the technical difficulties in applying GEP in daily clinical practice, various immunohistochemical (IHC) algorithms have been developed as surrogates of the GEP. The classic Hans algorithm utilized antibodies against CD10, BCL6 and MUM-1/IRF4.¹⁴ With the development of new IHC antibodies, the panel has been expanded in newer iterations

known as “Choi”, “Tally” and “Visco-Young” algorithms.^{15–17} The degree to which the IHC categorizations, ABC vs. GCB, correlate with COO as defined by GEP is variable, and whether they have prognostic value in the rituximab era is controversial.¹⁸ As highlighted by several studies examining reproducibility among different laboratories, this lack of concordance may be in part due to sampling and technical issues as well as interpretation variations.^{19–21}

In addition to COO classification, DLBCL prognostic models based on limited sets of genes or immunohistochemical markers have been proposed. More recently, DLBCLs with translocations of *MYC*, or *MYC* and *BCL2* (“double-hit” lymphomas) have been shown by many studies, to have an extremely poor outcome with standard R-CHOP therapy.^{22–24} It is less clear if high protein expression of *MYC* and/or *BCL2* in the absence of translocations carries the same adverse prognosis.^{22, 25} While the optimal treatment has not yet been determined, in preliminary data from NCI, *MYC*⁺ and *MYC*[−] DLBCLs treated with DA-EPOCH-R had a similar event-free survival at 5 years.²⁶

DLBCL SUBTYPES IN SPECIFIC ANATOMIC SITES

The 2008 WHO classification recognizes several subtypes of DLBCL with distinctive sites of presentation. These include primary DLBCL of the central nervous system (CNS), primary cutaneous DLBCL, leg type, and intravascular large B-cell lymphoma.

Primary CNS DLBCL refers to DLBCL arising in and confined to the CNS. It also includes cases presenting with intraocular disease, and patients with intraocular disease often have simultaneous or sequential CNS involvement. Histologically, the lymphomas mostly show a diffuse growth pattern and characteristically involve the perivascular spaces. Very rarely, the tumor cells are widely scattered in the white matter without mass formation or perivascular accumulation, so called “lymphomatosis cerebri”. GEP studies have demonstrated some unique molecular characteristics that distinguish CNS lymphomas from nodal and/or extranodal DLBCL.^{27–29} However, a consistent pattern as ABC or GCB has not emerged. Interestingly, primary CNS DLBCL shares many pathological and biological features with DLBCL presenting in the testis, perhaps because both arise in immune privileged sites.^{30, 31}

Primary cutaneous DLBCL, leg-type often presents as rapidly growing tumors on the leg, but it may arise at other sites. Most patients are elderly women, with a M:F ratio of 1: 3–4. Morphologically, the lymphoma is characterized by a generally monotonous proliferation of immunoblasts or centroblast-like cells with few admixed reactive cells. By GEP and immunophenotype, it resembles the activated B-cell type of nodal DLBCL.³² Unlike primary cutaneous follicle center lymphoma (PCFCL), which may be composed predominantly of large B-cells in some cases, primary cutaneous DLBCL, leg type nearly always express strong *BCL2*, *IRF4/MUM1* and *FOX-P1*.³³ They are more aggressive than PCFCLs and usually require chemotherapy for clinical management.³⁴

Intravascular large B-cell lymphoma is a rare type of extranodal DLBCL characterized by the selective growth of lymphoma cells within the lumina of small or intermediate vessels.³⁵ Many organs can be affected, but lymph nodes are usually spared. There are two distinct

patterns of clinical presentation, a Western form with neurological and cutaneous manifestations and an Asian form with pancytopenia, hepatosplenomegaly, multiorgan failure and hemophagocytic syndrome.³⁵ Cases with cutaneous involvement appear to have a better prognosis, perhaps because of earlier diagnosis. The disease is often not diagnosed until autopsy because of the lack of definitive radiological or clinical evidence of disease, and diverse symptomatology. Using immunophenotyping as a surrogate for the GEP, the majority of intravascular DLBCL has an ABC phenotype.³⁶ Coexpression of CD5 has been seen in most intravascular large B-cell lymphomas.³⁷

T-CELL/HISTIOCYTE RICH LARGE B-CELL LYMPHOMA (T/HRLBCL)

T-cell/histiocyte-rich large B-cell lymphoma is a morphological variant of DLBCL in which there is a limited number of scattered large atypical B cells embedded in a T-cell/histiocytes rich background. T/HRLBCL accounts for approximately 10% of DLBCL.^{38, 39} It occurs more commonly in middle-aged males, and the patients often present with advanced stage disease with liver, spleen and bone marrow involvement.³⁹ Recent studies have focused on the mechanisms of recruitment of inflammatory cells and the relationship to the microenvironment.⁴⁰

T/HRLBCL shares several morphologic and immunophenotypic similarities with nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL), posing a great diagnostic challenge in some cases. The neoplastic cells in T/HRLBCL have a wide cytologic spectrum. They may mimic the LP cells of NLPHL, centroblasts or Hodgkin/Reed-Sternberg (HRS) cells. Their immunophenotype is similar to the LP cells, with the exception of more frequent lack of BCL6 and expression of IRF4/MUM1. The histologic distinction between T/HRLBCL and NLPHL largely relies on immunohistochemical analysis of the background population. Features that favor T/HRLBCL include the absence of background small B-cells and lack of remnants of follicles such as follicular dendritic cell meshworks. Despite a rich T-cell background, well-formed T-cell rosettes are usually absent. The distinction between these two entities can be problematic in needle core biopsy specimens, and is best rendered on excision biopsies. Although the clinical presentation and behavior of these two diseases are generally quite different, some cases of T/HRLBCL appear related to NLPHL.⁴¹ In addition, NLPHL may progress to a process indistinguishable from *de novo* T/HRLBCL. The relationship of primary and "secondary T/HRLBCL" is not fully resolved.

Other cases with an overlapping morphological appearance may be composed of EBV-positive cells resembling HRS-like cells in a background rich in T-cells.⁴² Once considered a subtype of T/HRLBCL, EBV-positive cases are now included within EBV-positive large B-cell lymphoma.⁴² T/HRLBCL patients are generally treated similarly to their DLBCL, NOS counterparts with anthracycline containing chemotherapy, prednisone and Rituximab.⁴³

EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

First described by Oyama et al. in elderly Japanese patients, this entity is now included as a provisional category in the WHO classification as EBV positive diffuse large B-cell lymphoma of the elderly.⁴⁴ It is defined as an EBV+ clonal B-cell lymphoproliferation that

occurs in patients who are generally over the age of 50 without any known immunodeficiency or history of lymphoma. The lesion is thought to be related to immunosenescence, the natural decay of the immune system as a consequence of aging.⁴⁴ However, similar lesions can also be seen more rarely in younger patients.⁴⁵ The clinical course is usually aggressive, with frequent extranodal involvement, B symptoms and overall poor prognosis.⁴⁴

Two morphologic variants have been described, the polymorphic and monomorphic variants. The more common polymorphous lesion has variable amounts of reactive cells such as small lymphocytes, histiocytes and plasma cells, whereas the monomorphic variant has sheets of tumor cells with minimal reactive component. However, both variants may contain large transformed cells, immunoblasts or HRS-like cells. The tumor cells often have an ABC immunophenotype. They may be weak or negative for CD20. CD30 is frequently expressed whereas CD15 is negative. The differential diagnoses of EBV+ DLBCL include various EBV related benign lymphoproliferations as well as other lymphomas like lymphomatoid granulomatosis, plasmablastic lymphoma and Hodgkin lymphoma. Historically, cells resembling HRS cells have been described in many EBV-associated conditions.^{46–48} In some cases, distinction from Hodgkin lymphoma may be particularly problematic. The correct diagnosis requires integration of clinical and pathological features, with the immunophenotype interpreted in context.

Adding to the spectrum of EBV+ B-cell lymphoproliferative disorders, Dojcinov et al. described EBV-driven proliferations presenting in cutaneous or mucosal sites, termed mucocutaneous ulcer.⁴⁹ The cells in mucocutaneous ulcer often have an HRS-like morphology and an immunophenotype resembling cHL, with expression of CD30, CD15 and variable CD20. Despite the alarming histology, this lesion has a much more indolent and often self-limited clinical course.^{48, 49}

Another distinctive form of EBV-positive DLBCL is **DLBCL associated with chronic inflammation**. This lesion was initially described in patients with chronic pyothorax, hence the name “Pyothorax-associated lymphoma (PAL)”.⁵⁰ However, lymphomas with similar features are also recognized in other chronic inflammatory conditions. Most cases involve body cavities or narrow spaces, such as pleural cavity, bone (especially femur) and joints.⁵¹ In most cases, the tumor cells exhibit a type III EBV latency (EBER+, LMP1+, EBNA-2+). Occasional cases may lose CD20 and/or CD79a, or exhibit aberrant expression of one or more T-cell markers, causing problems in lineage assignment.^{52, 53}

PRIMARY MEDIASTINAL (THYMIC) LARGE B-CELL LYMPHOMA (PMBL)

PMBL is a distinct clinicopathologic entity thought to be derived from thymic B cells.^{54–56} It mainly affects adolescents and young adults (median age in the fourth decade), and there is a female predominance.⁵⁷ Clinically, patients usually present as early stage, bulky mediastinal mass. At progression, dissemination to distant extranodal sites including kidney, adrenal, liver and central nervous system may occur, but bone marrow involvement is rare. PMBL shows a wide cytological spectrum, like many other DLBCLs (Figure 1C). The cells express CD20 and CD79a, but often do not express surface immunoglobulin. CD30 is positive in most of the cases but its expression is usually weak and heterogeneous. At the

genetic level, PMBL demonstrates a GEP differing from other DLBCL and resembling cHL, with activation of the NF- κ B pathway.^{56, 58–60} In some cases the distinction from nodular sclerosis cHL can be difficult, so-called “grey zone lymphomas”.⁶¹ PMBL is reviewed in depth in other articles within this issue.

DIFFUSE LARGE B-CELL LYMPHOMAS WITH PLASMA CELL IMMUNOPHENOTYPE

ALK-positive large B-cell lymphoma is a rare subtype of DLBCL that expresses the ALK protein.⁶² This disease mainly affects adults, but can be seen in children. There is a marked male predominance. The cells have plasmablastic morphology and phenotype. They express CD138, EMA and most commonly, cytoplasmic IgA lambda immunoglobulin, and often lack mature B-cell associated antigens such as CD20 and PAX-5. The overexpression of ALK protein is associated with abnormal fusion between *ALK* and other partner genes. The t(2;17) involving *ALK* and clathrin is the most common of these, but the classical t(2;5) of anaplastic large cell lymphoma (ALCL) has also been reported.⁶³ Unlike ALK+ ALCL, CD30 is negative and the prognosis is poor.^{64, 65}

Plasmablastic lymphoma (PBL) is an aggressive neoplasm that predominantly occurs in the setting of immunodeficiency, most commonly HIV infection, but can also occur in other settings such as advanced age and congenital or acquired iatrogenic immunosuppression.^{66, 67} PBL typically presents in extranodal sites, often with a mucosal or cutaneous localization. The median age of presentation is 50 years with a striking male predominance. Histologically, the lymphoma cells usually demonstrate immunoblastic or plasmablastic morphology, with expression of plasma cell markers (CD138 and/or CD38) and frequent loss of B-cell markers (CD20 and CD79a). Nearly all cases of PBL are EBV-positive, and they are negative for HHV8 (Figure 2A and B). In addition to overlapping morphological and immunophenotypic features, recent studies have shown similar cytogenetic changes with a high incidence of *MYC* translocations in PBL and plasmablastic variant plasma cell myeloma, indicating a close relationship between these two neoplasms.^{68–70}

Primary effusion lymphoma (PEL) is a human herpesvirus 8 (HHV-8)-associated, unique form of large B cell lymphoma that typically manifests as malignant effusion in the body cavities.⁷¹ It occurs most frequently in young or middle-aged males with HIV infection. Usually, there is co-infection with EBV. The disease also occurs in iatrogenically immunosuppressed transplant patients and elderly individuals.⁷² Some affected patients also have a history of Kaposi sarcoma, and less frequently multicentric Castleman’s disease.⁷³ The most common sites of involvement are the pleural, pericardial and peritoneal cavities. Rare cases may present as solid tumor masses involving the gastrointestinal tract, soft tissue and other extranodal sites, termed extracavitary PEL.⁷⁴

The neoplastic cells exhibit a range of appearances, from immunoblastic, plasmablastic to frankly anaplastic. Immunophenotypically, the cells typically display activation and plasma cell markers, such as CD30, CD38, CD138 and EMA, but routine B-cell markers (CD20, CD19, CD79a and surface immunoglobulin) are absent. T-cell antigens may be aberrantly expressed.⁷⁵ Immunohistochemistry for the HHV8/KSHV-associated latent protein (LANA) is most useful in making the diagnosis (Figure 2C and D). The lesion may simulate

pyothorax-associated DLBCL, which is usually EBV-positive, but HHV-8 negative.⁷⁶ Interestingly, stabilization of MYC also has been implicated in pathogenesis of PEL through unknown mechanisms.^{77, 78} PEL has an extremely poor prognosis with a median survival reported to be less than 6 months.

Large B-cell lymphoma arising in HHV-8 associated multicentric Castleman disease (MCD) is a controversial lesion, and may represent a variant of MCD rich in HHV-8 infected cells, and not true transformation to large cell lymphoma.

B-CELL LYMPHOMA, UNCLASSIFIABLE, WITH FEATURES INTERMEDIATE BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA AND BURKITT LYMPHOMA (B-UNC/BL/DLBCL)

B-UNC/BL/DLBCL was introduced in the 2008 WHO classification to address aggressive B-cell lymphomas that have morphologic, immunophenotypic or cytogenetic features intermediate between DLBCL and BL.⁷⁹ DLBCL and BL can have overlapping morphologic and immunophenotypic features. For years, a variety of terms, such as “small non-cleaved”, “non-Burkitt”, “atypical BL”, and “Burkitt-like lymphoma”, have been used to describe these borderline cases. Recently, GEP studies have provided some insights into the aggressive B-cell lymphomas bordering on BL.^{80, 81} In one study, a group of cases diagnosed as DLBCL or high grade B-cell lymphomas were identified to have the GEP similar to BL.⁸⁰ While some of these cases may represent true BL that have atypical features precluding their diagnosis, some cases have a complex karyotype and *MYC* translocations with non-IG gene partners, differing from BL. Similarly, another GEP study identified a group of tumors with an intermediate expression profile between BL and DLBCL and frequently, a *MYC* complex karyotype.⁸¹ Many of these cases have dual translocations involving *MYC* and *BCL2* (or *BCL6*), so called “double-hit lymphomas”. Less frequently, translocations involving *MYC*, *BCL2* and *BCL6* are seen together, hence the term “triple-hit lymphomas”.

Double hit and triple hit lymphomas comprise the largest cohort within the category of B-UNC/BL/DLBCL. Many cases in this category morphologically resemble BL, but exhibit atypical features such as a greater cytologic pleomorphism or an aberrant immunophenotype (strong to moderate *BCL2* expression, or Ki-67 proliferative index <95%) (Figure 1D). Clinically, these tumors most often present in middle aged to elderly adults. Advanced stage is common with generalized adenopathy or extranodal disease.⁸² Double-hit lymphomas are generally refractory to standard chemotherapy regimen and have a poor prognosis.^{24, 25, 83} Currently, specific histological or immunophenotypic criteria to recognize double-hit lymphomas have not been defined. However, most cases with *MYC* translocations have high levels of nuclear staining for MYC, whereas cases negative for the BCL-2 protein are unlikely to carry a *BCL2* translocation. Therefore immunohistochemistry for MYC and BCL2 may be a useful screening tool to determine which cases require further genetic testing.

The term B-UNC/BL/DLBCL should be used with discretion. The mere presence of *MYC* translocation or high proliferation index (100%) by itself in an otherwise typical DLBCL would not qualify for an entry into this category. There is also a subset of cases that otherwise would be classified as BL, but exhibit minor morphologic variability or weak

BCL-2 expression. In the presence of a classical cytogenetic profile (i.e. isolated *MYC* translocation), such cases can be retained as BL.⁸⁴ However, FISH studies for *BCL2* and *BCL6* should be performed to rule out more aggressive double-hit and triple-hit lymphomas.

B-CELL LYMPHOMA, UNCLASSIFIABLE, WITH FEATURES INTERMEDIATE BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA AND HODGKIN LYMPHOMA (B-UNC/cHL/DLBCL)

B-UNC/cHL/DLBCL, also referred to as grey zone lymphoma (GZL), is defined as a large B-cell lymphoma that demonstrates overlapping clinical, morphologic and immunophenotypic features between cHL and DLBCL, especially the PMBL type. While these lymphomas are most commonly associated with mediastinal disease, involvement of peripheral lymph nodes has been reported. Unlike cHL and PMBL which occur more commonly in young women, GZL patients are more likely to be young man of 20–40 years of age.⁸⁵ Non-mediastinal GZLs tend to affect an older patient population.⁸⁵ This category was originally termed “Hodgkin-like anaplastic large cell lymphoma” and was believed to be a disease with poor prognosis with standard treatment.⁸⁶

The morphologic pattern of GZL is transitional with features of both cHL and PMBL. Sheets or clusters of tumor cells reminiscent of HRS-cells or PMBL may be seen in a diffusely fibrotic stroma. The inflammatory infiltrate is usually scant, but scattered eosinophils, lymphocytes, and histiocytes may be present. The immunophenotype of GZL is also intermediate, with frequent asynchrony between the morphology and immunophenotype.⁶¹ Many of these cases morphologically resemble cHL but have unusual features, including a large number of mononuclear variants, diminished inflammatory background, or aberrant phenotype with retention of B-cell program in concert with Hodgkin markers. Alternatively, cases may resemble PMBL but contain HRS-like cells and demonstrate CD15 positivity or loss of CD20. While a close relationship between cHL and PMBL has been demonstrated via GEP, gene profiling studies of grey zone lymphomas have not yet been undertaken. In a recent large-scale methylation profiling, principle component analysis indicated that GZL did not cluster with either cHL or PMBL, but demonstrated a unique epigenetic profile distinct from both parent entities.⁸⁷

GZLs are extremely rare and the optimal treatment of GZL is not yet established. Historical data indicate that they have done poorly with traditional approaches developed for the treatment of either cHL or NHL.^{86, 88} Prospective studies from NCI have shown that DA-EPOCH-R is an effective treatment for GZL. However, compared with PMBL patients who received the same chemotherapy regimen, GZL patients have an inferior survival.⁸⁹ These patients are more likely to require radiation than patients with PMBL.⁹⁰

Conclusion

Diffuse large B-cell lymphomas are heterogeneous neoplasms including a group of common and rare entities with distinct clinical and histopathologic characteristics. Over the past few years, the use of new technologies, such as GEP, miRNA profiling, and DNA sequencing, has yielded novel insights into its biology and allowed the recognition of at least three molecularly distinct subtypes, GCB, ABC and PMBL. These subtypes arise from different stages of B-cell differentiation and are associated with distinct genetic abnormalities and

diverse clinical outcomes. GEP has led to the development of immunohistochemistry algorithms that are more readily available in routine practice. Identification of double-hit lymphomas also has important implications due to its extremely dismal outcome. To date, most patients with newly diagnosed DLBCL are treated with R-CHOP. However, there are a significant percentage of patients who fail the conventional therapy. Further studies are needed to determine the optimal treatment approach for the high risk categories, such as double-hit lymphomas. With improved understanding of tumor biology and transformation pathways, it is anticipated that the future management of DLBCL will increasingly employ therapies tailored for individual subtypes and targeted towards specific molecules or deregulated genetic pathways.

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Figure 1.

DLBCL subtypes. (A) DLBCL, centroblastic variant. The cells have vesicular chromatin and often membrane-bound nucleoli. Polylobated centroblasts may be common, as in this case. (B) DLBCL, immunoblastic variant. The cells are round with prominent central nucleoli. (C) PMBL. The cells have clear cytoplasm and fine compartmentalizing fibrosis. (D) B-UNC/BL/DLBCL is composed of monomorphic medium-sized cells without a starry sky pattern. This case had translocations involving both *MYC* and *BCL2*, so-called double hit.

Figure 2.

DLBCLs associated with virus infection. (A) Plasmablastic lymphoma involving the oral cavity. There is sheet-like growth of tumor beneath the mucosa. The tumor cells are positive for EBV by EBER in situ hybridization (B). (C) PEL, pleural fluid containing large, atypical cells with a plasmacytoid appearance. The nuclei are strongly positive for the HHV8-associated latent protein, LANA (D).

Table 1

Histological Subtypes of Diffuse Large B-cell Lymphomas according to the WHO Classification.

Diffuse large B-cell lymphoma, not otherwise specified*
Primary DLBCL of the central nervous system ^{##}
Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma
T cell/histiocyte rich large B-cell lymphoma
EBV-positive DLBCL [#]
DLBCL associated with chronic inflammation
Primary mediastinal (thymic) large B-cell lymphoma
ALK positive large B-cell lymphoma
Plasmablastic lymphoma [#]
Primary effusion lymphoma [#]
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman Disease
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma ^{##}

Abbreviations: DLBCL, diffuse large B-cell lymphoma.

* Term used when no specific subtype is designated.

[#] Subtypes associated with EBV infection of tumor cells.

^{##} Subtypes less often associated with EBV.