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Lymphoproliferative Neoplasms With Plasmablastic Morphology
An Overview and Diagnostic Approach

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Context.—Plasmablastic morphology can be seen in several uncommon lymphoproliferative neoplasms. Sometimes it is difficult to distinguish these neoplasms from each other.

Objective.—To review the current understanding of major lymphoproliferative neoplasms with plasmablastic morphology; summarize the clinical, morphologic, immunophenotypic, cytogenetic, and molecular characteristics of each disease entity; and highlight a practical approach for differential diagnosis.

Data Sources.—Peer-reviewed medical literature and the authors’ personal experience.

Conclusions.—Plasmablastic lymphoma; plasmablastic myeloma; primary effusion lymphoma; human herpesvirus 8–positive diffuse large B-cell lymphoma, not otherwise specified; and anaplastic lymphoma kinase (ALK)–positive large B-cell lymphoma are major lymphoproliferative neoplasms with plasmablastic morphology. These neoplasms share many common morphologic and immunophenotypic characteristics. Definitive diagnosis requires a thorough understanding of disease phenotype and diagnostic criteria of each category. Recognition of expression pattern of Epstein-Barr virus–encoded small RNA, human herpesvirus 8, and ALK in these neoplasms is critical for diagnosis in cases with typical presentation. Additional ancillary studies and clinical findings may help in difficult cases.

The goal of B-cell maturation is development of memory B cells or plasma cells, with or without T-cell interaction. After antigen encounter in germinal centers, intermediary cells called plasmablasts are formed and then home to bone marrow to become mature plasma cells.1 These cells can be seen in peripheral blood as plasmacytoid lymphocytes normally or more often during inflammatory episodes or with autoimmune disease as they transition to bone marrow.2 A group of lymphoproliferative neoplasms demonstrate morphologic and immunophenotypic features similar to those of the plasmablasts. Therefore, plasmablastic features are useful clues for diagnostic workup.

The most common lymphoproliferative neoplasms that typically present with plasmablastic morphology are plasmablastic lymphoma (PBL); plasmablastic myeloma (PBM); primary effusion lymphoma (PEL); human herpesvirus 8 (HHV8)–positive diffuse large B-cell lymphoma (DLBCL), not otherwise specified; and anaplastic lymphoma kinase (ALK)–positive large B-cell lymphoma (LBCL).3 Infrequently, some other lymphomas can occasionally present with plasmablastic morphology, such as Epstein-Barr virus (EBV)–positive LBCL and DLBCL, not otherwise specified. However, these other entities are beyond the scope of the current review.

PLASMA BLASTIC LYMPHOMA
Epidemiology and Clinical Presentation

Plasmablastic lymphoma was initially considered an AIDS-associated lymphoma because the prototypic PBL was reported in HIV-positive patients.4 It is estimated that PBL comprises approximately 2% of all HIV-related lymphoma cases. Subsequently, PBL was also identified in HIV-negative populations, particularly in individuals with compromised immune systems for various reasons including organ transplantation and immunosuppressive medications. Although uncommon, PBLs have been reported in individuals without overt immunosuppression. Plasmablastic lymphoma has a striking male predominance with a median age of fourth decade in HIV-positive patients. By contrast, PBL shows a slight female predominance with a median age of fifth decade in HIV-negative populations.5,6 Plasmablastic lymphoma primarily involves extranodal organs, including oral cavity/jaw, gastrointestinal system, and skin. Lymphadenopathy occurs uncommonly. Most...
patients present at advanced stage (III/IV) with frequent bone marrow involvement. B symptoms are common, including weight loss, fever, and night sweats. M protein is rarely reported in PBL. Hypercalcemia, renal deficiency, and osteolytic lesions are not clinical features of PBL.7

Morphology/Immunophenotypic Features

Plasmablastic lymphoma is typically composed of monomorphic sheets of large plasmablasts. Cases comprising a mixed plasmablastic component and a variable extent of more mature plasmacytic component also exist, particularly in HIV-negative populations.9 Typical PBLs often present with starry-sky morphology with increased tingible body macrophages, brisk mitosis, and frequent apoptosis. Foci of necrosis are frequently encountered.9 The immunophenotypic features of PBL are closer to those of plasma cells than to those of mature B cells.10 Lymphoma cells are almost always positive for IRF4/MUM1 and PRDM1. Other plasma cell–associated markers, including CD38, CD138, and XBP1, are usually positive.9,11,12 Expression of immunoglobulins with light-chain restriction can be occasionally demonstrated by immunophenotyping. Plasmablastic lymphoma tumor cells are usually negative for conventional B-cell markers, including CD19, CD20, and PAX5, although cases with weak and focal positivity have been reported.10 CD79a, another common B-cell marker, and CD45 are detected in 30% to 50% of PBLs.7 Two B-cell lineage–related transcription cofactors, BOB1 and OCT2, are usually positive in PBL. CD10 and BCL6 expression are usually negative or focally positive. Cyclin D1 expression was reported to be negative in a limited study.8 Expression of CD30 and EMA is variable. The Ki67 proliferation index is high, higher than 90% in the majority of cases.10 Epstein–Barr virus–encoded small RNA (EBER) in situ hybridization is positive in approximately 50% in patients without demonstrable immunodeficiency.13–15 MYC expression is detected in a significant portion of cases, particularly in EBV+ cases. Human herpesvirus 8 is uniformly negative.

Cytogenetics and Molecular Findings

The karyotypic data of PBL are limited. The karyotype is usually complex, characterized by rearrangements of chromosomes 1 and/or 6, loss of 13q and 17p, and whole or partial gains of odd-numbered chromosomes, including 3, 5, 7, 9, 11, and/or 15.16 Fluorescence in situ hybridization analysis demonstrates that MYC abnormalities are the most common genetic findings, seen in up to 60% of PBLs, the majority of which are translocations involving MYC with immunoglobulin heavy chain or light chain. Translocations between MYC and immunoglobulin genes are relatively unique for PBL in LBCL with plasmablastic morphology.12,16–18 A subset of PBL cases also demonstrate gain of MYC. Another common genetic abnormality in PBL is PRDM1 missense mutations, which lead to the upregulation of PRDM1 protein. It is believed that cooperation between MYC and PRDM1 is crucial in terminal differentiation and growth arrest in B cells that eventually lead to PBL oncogenesis.12 A recent next-generation sequencing study of HIV-positive PBL cases demonstrated that there are recurrent mutations in genes of STAT-JAK pathways including STAT3, JAK1, and SOCS1, as well as genes of RAS-MAPK pathways including NRAS, KRAS, and BRAF.19 These mutations lead to activation of their respective signal cascades, contributing to PBL pathogenesis and providing potential therapeutic targets in disease treatment.

PLASMABLASTIC MYELOMA AND PLASMABLASTIC PLASMACYTOMA

Epidemiology and Clinical Presentation

Plasmablastic myeloma is an uncommon morphologic variant of plasma cell myeloma (PCM) but is not recognized as a distinct entity in the World Health Organization classification of hematopoietic neoplasms.23 Plasmablastic myeloma was originally defined as presence of more than 2% of neoplastic plasma cells with plasmablastic morphology in aspirate smear.20 However, there are no set standards for defining PBM on extramedullary tissue biopsies. The plasmablastic morphology can be seen in de novo cases but is more commonly seen in plasmablastic transformation of a known PCM. The overall prevalence of PBM among PCMs is approximately 8% to 10%. Studies have shown that the plasmablastic morphology is an independent poor prognostic indicator associated with high tumor proliferation, abnormal karyotype, aggressive disease course, and shortened survival.21,22 Like PCM, PBM is a disease of the elderly with male predominance. The median incidence age is between 60 and 70 years. Plasmablastic myeloma is a bone marrow–based systemic disease commonly presenting with M protein and associated with end organ damage including hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (CRAB signs). Plasmablastic plasmacytoma is a single localized plasma cell neoplasm with plasmablastic morphology but lacking clinical features of a systemic PCM.

Morphology/Immunophenotypic Features

Morphologically, PBM may present as sheets of plasmablasts or subset of neoplastic plasma cells with plasmablastic morphology, sometimes indistinguishable from the morphology of PBL. The immunophenotype of PBM is same as that of PCM: positive for plasma cell markers (CD38, CD138, MUM1, XBP1, and PRDM1) and B-cell transcription cofactors (BOB1 and OCT2), negative for B-cell markers (CD19, CD20 and PAX5), and with variable expression of CD45 and CD79a. Tumor cells commonly demonstrate light-chain restriction by immunohistochemistry or in situ hybridization. Expression of CD117 and cyclin D1 can be detected in a subset of PBM.23 Although very rare cases have been reported positive for EBER,24,25 the majority of PBM and plasmablastic plasmacytoma cases are negative for EBER expression. Increased MYC expression is seen in the majority of cases of PCM, indicating activation of MYC pathway.

Cytogenetics and Molecular Findings

Plasma cell myeloma has demonstrated a variety of cytogenetic abnormalities, including hyperdiploidy, del(13), t(11;14), t(4;14), del(17), and t(14;16). Del(13q) demonstrated by fluorescence in situ hybridization studies appears to be associated with plasmablastic morphology. Interestingly, although PBM is associated with adverse prognosis, the high-risk cytogenetic abnormalities, including del(2p), t(4;14), and t(14;16), are not associated with plasmablastic morphology.25 Although there is increased MYC expression in PBM as demonstrated by immunohistochemistry, cytogenetic studies of MYC abnormality have mainly been performed in PCM; the data regarding PBM are limited. Fluorescence in situ hybridization studies have demonstrat-
ed that up to 15% of newly diagnosed PCMs harbor MYC translocation with various partner genes. Next-generation sequencing studies have suggested MYC translocation is more common than previously estimated. In addition, unlike PBL, most rearrangement (approximately two-thirds) juxtaposes MYC to a nonimmunoglobulin partner gene in PCM. MYC rearrangement is considered a secondary genetic event associated with high disease burden and an independent adverse prognostic factor. Interestingly, Glitza et al. reported that MYC translocation was associated with plasmablastic morphology in PCM with extramedullary presentation. Recent next-generation sequencing studies have expanded our understanding of the genomic landscape of PCM. The most common somatic mutated genes include KRAS, NRAS, TP53, BRAF, CCND1, and IRF4.

**PRIMARY EFFUSION LYMPHOMA AND EXTRACAVITARY (SOLID) PRIMARY EFFUSION LYMPHOMA**

**Epidemiology and Clinical Presentation**

Primary effusion lymphoma is a rare aggressive B-cell lymphoma that is seen mostly in HIV+ individuals. The affected HIV+ patients are predominantly young and middle-aged males. Less frequently, HIV-negative cases are seen in elderly individuals or patients with organ transplant. Primary effusion lymphoma is universally associated with HHV8 infection. Many PELs occur in patients with Kaposi sarcoma, another HHV8-associated neoplasm. There is frequent coinfection of EBV in PEL, although EBV-negative PELs have been reported, particularly in the HIV-negative population. The majority of PELs are effusion-based or present with cavitary-based mass. Patients classically present with symptoms and signs of an effusion of pleural, pericardial, or peritoneal spaces. Most PELs remain confined to the body cavity. However, lymph node and extranodal solid organ involvement can take place as secondary events when disease progresses. In addition, PEL can present with extranodal mass, organomegaly, or, less frequently, lymphadenopathy without evidence of lymphomatous effusion. These cases have been classified as extracavitary or solid variant of PEL. Extracavitary PEL demonstrates similar morphologic, immunophenotypic, and gene expression profiling characteristics to its effusion-based counterparts.

**Morphology/Immunophenotypic Features**

Cytology preparations of effusion-based PEL show medium to large lymphoid cells resembling immunoblasts/plasmablasts with ample basophilic cytoplasm, large irregular nuclei, one or more nucleoli, and variable perinuclear clear Golgi zone. Multinucleated cells can occasionally be found. In cases with extracavitary involvement, the neoplastic cells efface the lymphoid architecture with diffuse and occasional sinusoidal pattern. Immunophenotypically, the tumor cells are negative for pan-B–cell markers (PAX5, CD19, CD20, and CD79a) and positive for plasma cell markers (CD138, VS38c, MUM1 and XBP1) and CD45. BOB1 and OCT2 are usually positive in PEL. The expression of PRDM1 has not been extensively investigated in PEL. Expression of immunoglobulin is either absent or very low. Primary effusion lymphoma is uniformly positive for HHV8-associated latent protein LANA1 with a distinct nuclear and granular staining pattern on immunohistochemistry. The positive LANA1 expression is required for PEL diagnosis. EBER in situ hybridization is essentially positive in all HIV-positive PEL cases. However, expression of EBER in HIV-negative patients is less consistent. As a rule, EBV latent membrane protein (LMP) 1 expression is not detected. Additionally, lymphoma cells in PEL are usually positive for MYC and CD30. Cases with aberrant expression of T-cell markers and/or epithelial antigen positivity have been reported. Compared with effusion-based PEL, extracavitary PEL shows more frequent pan-B–cell marker/immunoglobulin expression, less frequent CD45 expression, stronger CD30 expression, and more frequent aberrant T-cell marker expression and cytokeratin positivity.

**Cytogenetics and Molecular Findings**

Primary effusion lymphoma usually demonstrates a complex karyotype, although disease-defining recurrent cytogenetics abnormalities are lacking. Most PELs show immunoglobulin rearrangement with somatic hypermutation, indicative of post–germinal center B-cell origin. Furthermore, gene expression profiling of PEL has defined the neoplastic cells to be plasmablastic with features of both immunoblasts and plasma cells. Human herpesvirus 8 viral genomes are uniformly identified in all PEL cases, and the EBV viral genomic sequences are seen in the majority of PEL cases, indicating the critical role of HHV8 in PEL tumorigenesis. Pathogenesis has been attributed to HHV8 genome open reading frames such as viral interleukin 6 (v-IL6) and latent nuclear antigen 1 (LANA-1) homology to host cellular genes. Multiple studies have suggested that LANA-1 promotes binding of HHV8 DNA to chromosomes during mitosis to permit segregation of HHV8 episomes to the progeny cells, inhibit tumor suppressor genes, and activate EBV promoter regions in infected cells. These steps are considered essential in PEL oncogenesis. Although MYC protein overexpression is detected in PEL, the MYC gene is structurally intact. MYC is dysregulated at the posttranslational level because of the activity of HHV8-encoded proteins LANA1 and LANA2, which enhance the stability of MYC and stimulate its transcriptional activity.

**HHV8-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED**

**Epidemiology and Clinical Presentation**

Human herpesvirus 8–positive DLBCL, not otherwise specified, belongs to the HHV8-associated lymphoproliferative disorders group, which also include multicentric Castleman disease (MCD) and germinaltropic lymphoproliferative disorder. It is a rare B-cell lymphoma usually arising from the background of multicentric Castleman disease in HIV-infected patients, although cases without preceding or concurrent multicentric Castleman disease have been reported. This is a lymphoma category recently established by the current World Health Organization classification of lymphomas and predominantly presents with lymphadenopathy and splenomegaly. Secondary involvement of peripheral blood and extranodal organs can occur as disease progresses.

**Morphology/Immunophenotypic Features**

Human herpesvirus 8–positive DLBCL presents as sheets and confluent clusters of monomorphic large plasmablasts.
or immunoblasts resulting in effacement of lymphoid architecture.

Immunophenotypic features of HHV8+ DLBCL have been reported in a limited number of cases. Based on the current available information, the lymphoma cells have variable expression of CD45 and some common B-cell markers (CD20 and PAX5). The tumor cells express MUM1; however, other plasma cell–associated markers, including CD138 and CD38, are usually negative. Expression status of XBP1, PRDM1, BOB1, and OCT2 in HHV8+ DLBCL has not been extensively studied. Human herpesvirus 8–positive DLBCL is universally positive for HHV8 LANA1, whereas EBER in situ hybridization is essentially always negative. As an additional diagnostic clue, immunohistochemical studies show that the lymphoma cells express cytoplasmic immunoglobulin M (IgM) with light-chain restriction.

**Cytogenetics and Molecular Findings**

Human herpesvirus 8–positive DLBCL shows IGH gene rearrangement and lack of somatic hypermutation in the IGH variable regions, suggesting a naive B-cell origin. Other information regarding cytogenetics and molecular characteristics of HHV8+ DLBCL is sparse, probably because of its rarity.

**ALK-POSITIVE LARGE B-CELL LYMPHOMA**

**Epidemiology and Clinical Presentation**

ALK+ LBCL is a rare disease, accounting for less than 1% of all BCLs. It can occur in all age groups, with a predilection for the pediatric population and young to middle-aged adults (median age of 30–40). It affects more males than females and shows no association with immunosuppression. ALK+ LBCL usually presents as a mediastinal mass or diffuse lymphadenopathy. Cases with extranodal involvement are less common. The majority of cases present with advanced stage at the time of diagnosis, including 25% of cases showing bone marrow involvement.

**Morphology/Immunophenotypic Features**

Morphologically, ALK+ LBCL demonstrates diffuse, sinusoidal, or mixed diffuse and sinusoid growth pattern. Not uncommonly, the tumor cells demonstrate cohesive appearance. The neoplastic cells are predominantly monomorphic large plasmablasts or immunoblasts, typically with a single prominent, centrally placed nucleolus. In some cases, the tumors show focal anaplastic and/or multinucleated cytopathology. Immunophenotypically, ALK+ LBCL has common features of plasmablasts. The tumor cells are negative or only weakly positive for B-cell markers, including CD19, CD20, CD79A, and PAX5, but positive for plasma cell markers, including CD138, MUM1, VS38c, XBP1, and PRDM1. Most cases show restricted light-chain expression by either immunohistochemistry or in situ hybridization. BOB1 and OCT2 are also positively expressed. MYC protein is upregulated in almost all ALK+ LBCs via MYC translocation–independent mechanisms. Approximately 50% of cases show aberrant CD4 expression but are negative for more specific T-cell markers such as CD3 and CD2. The majority of ALK+ LBCs show expression of CD45 and EMA but are negative for cytokeratin. All ALK+ LBCs are positive for ALK expression, with most cases showing a distinct cytoplasmic granular staining pattern. In contrast to ALK+ anaplastic large cell lymphoma, a T-cell neoplasm with ALK expression, ALK+ LBCL is negative for CD30 expression. Neither EBV nor HHV8 is expressed in ALK+ LBCL.

**Cytogenetics and Molecular Findings**

Rare reports of chromosomal analysis of ALK+ LBCL are available and have shown complex karyotypes with multiple numerical and structural abnormalities. The central abnormalities are associated with the ALK gene located on chromosome 2, which encodes a cytoplasmic receptor with tyrosine kinase activity. The most common abnormalities are translocations of ALK, with the majority of cases demonstrating a t(2;17)(p23;q23) CLTC–ALK. Less frequently, ALK partners with other genes, including NPM1, SQSTM1, and SEC31A. Corresponding to ALK translocations, ALK protein expression is detected with a cytoplasmic pattern in the majority of ALK+ LBCL tumor cells, except for a nuclear and cytoplasmic pattern in cases with NPM1–ALK fusion. In addition, gain of ALK gene has been reported. The result of all these ALK gene-related abnormalities is overexpression and oncogenic activation of the ALK protein, which in turn leads to activation of downstream signaling, particularly in the STAT3 pathway. Studies have demonstrated the upregulation of phosphorylated STAT3 in ALK+ LBCL. It is believed that the expression of MYC protein in ALK+ LBCL is caused by STAT3 pathway activation. MYC translation is absent.

**DIFFERENTIAL DIAGNOSIS AMONG LYMPHOPROLIFERATIVE NEOPLASMS WITH PLASMABLASTIC MORPHOLOGY**

Lymphoproliferative neoplasms with plasmablastic morphology include PBL; PBM; PEL; HHV8+ DLBCL, not otherwise specified, and ALK+ LBCL. In general, these are aggressive neoplasms with poor prognosis. Definitive diagnosis of each entity is often challenging, mainly because of rarity of diseases and overlapping histopathologic features. Morphologically, all these neoplasms comprise sheets of plasmablasts/immunoblasts (Figure 1, A) except cavity-based PEL, which demonstrates plasmablasts/immunoblasts in the effusion (Figure 1, B). Immunophenotypically, most of these neoplasms are negative for expression of common mature B-cell antigens, including CD19, CD20, PAX5 (Figure 1, C), and CD79a, and positive for plasma cell markers (CD138, VS38c, MUM-1) (Figure 1, D through F). The exception is HHV8+ DLBCL, which has variable B-cell antigen and less plasma cell antigen expression. With the aid of EBER in situ hybridization (Figure 1, G) and immunohistochemical examination of HHV8 LANA1 (Figure 1, H) and ALK (Figure 1, I) a definitive diagnosis can be rendered in most circumstances. In typical cases, PBL is EBER+/HHV8+/ALK+, PBM is EBER+/HHV8+/ALK, PEL and extracavitary PEL are EBER+/HHV8+/ALK, HHV8+ DLBCL is EBER+/HHV8+/ALK−, and ALK+ LBCL is EBER+/HHV8−/ALK− (Figure 2).

ALK+ LBCL is probably the most straightforward diagnosis among these 5 categories because of the unique expression of ALK protein. In addition, unlike PBL, PEL, and HHV8+ DLBCL, ALK+ LBCL has no preference in the HIV+ or immunocompromised populations. Because of its expression of ALK, the differential diagnosis of ALK+ LBCL should also include ALK+ anaplastic large cell lymphoma and ALK+ nonhematopoietic malignancies. Expression of BOB–1 and OCT2, as well as lack of CD30 expression, is
sufficient to distinguish ALK+ LBCL from other ALK+ malignancies.

It is clinically important to differentiate PBL from PBM because the management for these 2 neoplasms is significantly different. Plasmablastic lymphoma and PBM are essentially identical in terms of morphology. Immunophenotypically these entities share a great extent of similarity. Both neoplasms are positive for plasma cell-associated antigens (MUM1, CD138, CD38, and PRDM1) and negative for B-cell specific antigens (CD19, CD20, and PAX-5). The majority of PBL cases show positive EBER expression, particularly in HIV-positive cases, whereas very rare PBM cases show EBER expression. Cyclin D1 expression is detected in a subset of PBM. By contrast, PBL is negative for cyclin D1 expression. Aberrant expression of CD117 has been reported in some cases of PBM, whereas no expression of CD117 has been reported in PBL. Therefore, from an immunophenotypic point of view, and in the context of plasmablastic morphology, EBER expression is essentially diagnostic for PBL in the majority of cases, and expression of cyclin D1 or CD117 favors a diagnosis of PBM (Figure 3). Both PBL and PBM express MYC by immunohistochemistry. However, MYC translocation detected by interphase fluorescence in situ hybridization is more commonly seen in PBL, particularly when the translocation partners are immunoglobulin genes (Figure 3). Limited next-generation sequencing studies on both PBL and PBM suggest that gene mutational study does not seem to play an important role in distinguishing PBL and PBM. When EBER, cyclin D1, and CD117 are all negative, the separation of these 2 neoplasms relies heavily on clinical presentation and laboratory findings. The diagnosis of PBL is favored if there is significant extramedullary involvement or lymphadenopathy in immunocompromised patients. By contrast, the diagnosis of PBM is favored if the disease is predominantly a bone marrow–based presentation or there are findings

Figure 1. Representative images of morphology, immunophenotypic, and in situ hybridization findings in lymphoproliferative neoplasms with plasmablastic morphology. A, Hematoxylin-eosin stain of plasmablastic lymphoma (PBL). B, Wright stain of cytospin of pleural fluid from a patient with primary effusion lymphoma (PEL). C through G, Immunohistochemical stains of PAX5 (C), CD138 (D), VS38c (E), and MUM-1 (F), and Epstein-Barr virus–encoded small RNA (EBER) in situ hybridization (G) of a PBL. H, Human herpesvirus 8 latent nuclear antigen 1 (LANA1) immunohistochemical stain of a solid PEL. I, Anaplastic lymphoma kinase (ALK) immunohistochemical stain of an ALK-positive large B-cell lymphoma, courtesy of Zenggang Pan, MD, PhD from Yale University (original magnifications ×400 [A and C through I] and ×1000 [B]).
fulfilling CRAB criteria as well as high levels of M protein (Figure 3). Occasionally, when no definitive distinction can be made after thorough clinical and histopathologic evaluation, a diagnosis of plasmablastic malignancy with PBL and PBM as differential diagnoses may be rendered.

Separating HHV8⁺ DLBCL from PEL, particularly extracavitary PEL, can be at times challenging. Typical PEL is HHV8⁺/EBER⁺, whereas HHV8⁺ DLBCL is usually HHV8⁺/EBER⁻. However, a subset of PEL is negative for EBER expression, particularly in HIV-negative individuals. There are some findings that may provide clues to distinguish HHV8⁺ LBCL from PEL when EBER is negative (Figure 4). Clinically, concurrent body cavity involvement is a feature of PEL but not HHV8⁺ DLBCL. On the other hand, HHV8⁺ DLBCL can be evolved from a lower-grade HHV8⁻ associated lymphoproliferative disorder. Therefore, the history or concurrent identification of features suggesting HHV8⁺ multicentric Castleman disease or germinotropic lymphoproliferative disorder supports a diagnosis of HHV8⁺ DLBCL.

Immunophenotypically, HHV8⁺ DLBCL often shows variable expression of pan–B-cell markers and less consistent CD138 and CD38 expression. The tumor cells are positive for IgM and cytoplasmic λ light-chain expression. By contrast, PEL is typically negative for pan–B-cell markers and positive for CD138 and CD38. Lymphoma cells of PEL do not express immunoglobulin heavy chain or light chain. From the point of view of cell of origin, lymphoma cells in HHV8⁺ DLBCL are believed to be naive (pre–germinal center) B cells without somatic hypermutation. Lymphoma cells in PEL are terminally differentiated (post–germinal center) B cells with immunoglobulin gene somatic mutations. Molecular study to determine status of somatic mutation, when available, is useful for definitive diagnosis in difficult cases. Although rare cases of HHV8⁺ DLBCL have been reported to be EBER positive in the literature, from a practical point of view, the coexpression of EBER and HHV8 LANA1 with plasmablastic/immunoblastic proliferation is essentially indicative for PEL diagnosis unless there is strong evidence that it is transformed from a preceding HHV8-associated lymphoproliferative disorder or exclusively nodal/splenic disease.

CONCLUSIONS

In summary, lymphoproliferative neoplasms with plasmablastic morphology comprise a group of aggressive B-cell–lineage malignancies that share many morphologic and immunophenotypic similarities. Application of immunohistochemical stains for ALK and HHV8 LANA as well as EBER in situ hybridization often provides a definitive diagnosis for cases with typical immunophenotype. For cases with unusual features, the diagnosis requires integration of clinical and pathologic findings. A practical diagnostic approach is presented in Figures 2 through 4. Nevertheless, there will be some cases with overlapping features of different disease categories, and even experts may have different opinions on the final diagnosis.
most neoplasms with plasmablastic morphology are uncommon, data regarding the genetic characteristics are either sparse or incomplete. Further understanding of the pathogenesis and genetic characteristics of each neoplasm may provide helpful information in differential diagnosis and disease management.

References


