11 CD20-Negative Aggressive Lymphomas

Jorge J. Castillo

11.1 Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma, accounting for approximately 30% of the cases. The addition of the anti-CD20 monoclonal antibody rituximab to combination chemotherapy has increased response and survival rates in patients with DLBCL in randomized studies [1, 2]. A small proportion of DLBCL show marked plasma cell differentiation with loss of CD20 expression.

In general, patients diagnosed with CD20-negative DLBCL tend to have extranodal involvement, a more aggressive clinical course, resistance to chemotherapy, and a poor prognosis. The use of rituximab has not been of benefit in these cases. Given its rarity, most of the available evidence in CD20-negative DLBCL consists of case reports and small case series. Due to lack of prospective data, there are no standards of care for these patients.

In this chapter, we review the most common variants of CD20-negative DLBCL including plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease (MCD), and anaplastic lymphoma kinase (ALK)-positive DLBCL. This is an evolving field, and patients with CD20-negative DLBCL not meeting criteria for the ones mentioned above have been described [3–5]. These cases of CD20-negative DLBCL are beyond the scope of this review.

11.2 Plasmablastic Lymphoma

Delecluse et al. first described PBL as a separate entity in 1997 [6]. This report included 16 patients, 15 were HIV-positive, who presented with aggressive lesions located primarily in the oral cavity. These patients had a high rate of relapse resulting in poor survival. PBL was then included within the group of B-cell malignancies more commonly seen in HIV-infected individuals [7].

Morphologically, the malignant cells have round to oval shape with abundant cytoplasm, eccentric nucleus, prominent nucleolus, and a perinuclear hof [7]. The background is usually composed by small lymphocytes, mitotic figures, and tingible body macrophages that can impart a starry-sky pattern. Immunophenotypically, the malignant PBL cells express plasma cell markers such as CD38, CD138, or multiple myeloma 1/interferon regulatory factor 4 protein (MUM1/IRF4) but do not express CD20. The proliferation index is usually high with Ki67 > 80%. Recently,

J. J. Castillo (✉)
Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
e-mail: jorgej_castillo@dfci.harvard.edu

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novel markers such as BLIMP1 and XBP1 have been identified [8]. A representative profile of PBL is shown in Fig. 11.1. The cell of origin in PBL is thought to be the plasmablast, an activated B-cell that has already undergone the germinal center reaction but has not yet fully matured into a plasma cell. PBL is sometimes difficult to distinguish from plasmablastic myeloma [9], especially in the setting of immunodeficiency. However, the presence of monoclonal paraproteinemia and/or skeletal lytic lesions favors a diagnosis of myeloma.

MYC gene rearrangements and Epstein-Barr virus (EBV)-encoded RNA (EBER) expression are common molecular markers present in PBL. EBER has been reported in approximately

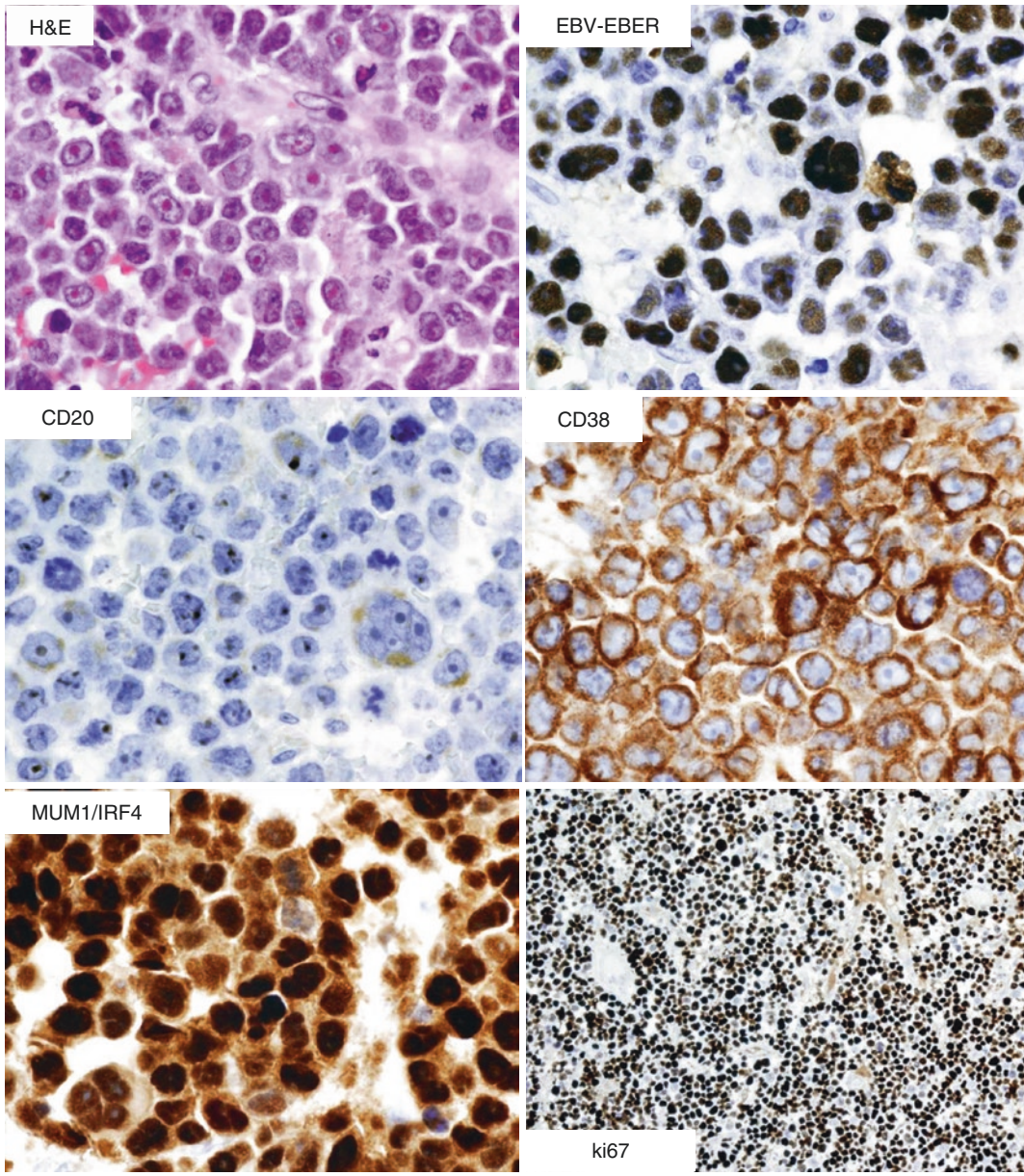

Fig. 11.1 Representative case of plasmablastic lymphoma

80% of cases with HIV-positive PBL and suggests a role of EBV in the pathogenesis of PBL [10]. *MYC* gene rearrangements can be seen in approximately 40% of cases of HIV-positive PBL and have been associated with a worse prognosis [11]. A study has suggested that EBV-positive PBL cases are more likely to carry *MYC* gene rearrangements than EBV-negative cases [12].

A systematic review of the literature that included 112 HIV-positive patients with PBL showed a median age at presentation of 38 years with a male predominance, with a median time from HIV infection to PBL diagnosis of 5 years [13]. Approximately 50% of the patients presented with stage III or IV disease and 50% with primary site of involvement in the oral cavity. Approximately 75% of the patients received some type of combination chemotherapy, most commonly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with an overall response rate (ORR) of 72%. These findings have been confirmed by a more recent meta-analysis on approximately 300 patients with PBL [14].

A later systematic review identified 76 HIV-negative patients with a pathological diagnosis of PBL [15]. The median age at diagnosis was 57 years with a male-to-female ratio of 1.7:1. Advanced-stage disease was seen in 60% of the cases with 90% presenting with extranodal involvement. The most common sites of involvement were the oral cavity and the gastrointestinal tract. Approximately 50% of the patients received treatment with CHOP. The ORR was 66%. Another study showed that approximately 30% of HIV-negative PBL patients had some form of immunosuppression such as posttransplantation, concurrent malignancy, or autoimmune disorders [16].

A study comparing 157 HIV-positive and 71 HIV-negative PBL patients showed that HIV-positive PBL patients were younger with more pronounced male predominance and higher proportion of oral cavity involvement [10]. There were no differences in stage distribution, bone marrow involvement, or presence of B symptoms. Of note, HIV-positive patients experienced higher rates of ORR to chemotherapy (81% vs. 56%). CR rates were 52% and 41% for HIV-positive and HIV-negative PBL patients, respectively.

The prognosis of patients with PBL remains poor. Systematic reviews have reported median OS times that have ranged between 9 and 15 months [14, 15]. More recently, a multicenter study on 50 HIV-positive PBL patients treated in the highly active antiretroviral therapy (HAART) era reported a median OS of 12 months [11]. Other smaller case series in PBL patients treated in the ART era have shown median OS ranging between 5 and 12 months [17, 18]. An Italian study has shown better outcomes in PBL patients with 3-year OS of 67% [19]. The reasons for this difference are unclear although the patients in the Italian study had shorter HIV diagnosis to PBL diagnosis time and presented with median CD4+ count >200 cells/mm^3.

Comparative studies between HIV-negative and HIV-positive PBL patients showed that HIV-negative status might be associated with worse survival, but results are inconsistent [10, 14]. Advanced-stage and poor performance status have shown to be indicators of worse prognosis in PBL [11, 18]. Hence, the use of the International Prognostic Index (IPI) score should be appropriate in PBL [11, 18, 19]. The association of EBV expression and outcomes in PBL is unclear [14, 18]. CD4+ counts <200 cells/mm^3 might be associated with shorter progression-free survival (PFS) time [11, 18]. More recently, the presence of *MYC* gene rearrangements has shown to be associated with worse OS [11, 14]. In patients with HIV-positive PBL who are treated with chemotherapy, the attainment of CR has been associated with longer survival [11, 20]. In the HIV-negative setting, concurrent immunosuppression has been associated with a worse outcome [16].

Current guidelines recommend against the use of CHOP, as it is considered inadequate therapy [21]. This recommendation is reasonable given the poor outcomes seen in patients with PBL. However, studies evaluating survival benefits in HIV-positive PBL patients treated with regimens more intensive than CHOP have failed to show survival benefits [11, 20]. Based on consensus opinion, regimens such as dose-adjusted

infusional etoposide, vincristine, and doxorubicin along with bolus cyclophosphamide and prednisone (EPOCH), cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with ifosfamide, etoposide, cytarabine (CODOX-M/IVAC), or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyperCVAD) are appropriate for PBL therapy. These regimens could include the administration of intrathecal agents to minimize the risk of central nervous system (CNS) involvement by PBL. In HIV-infected patients, initiation or optimization of HAART is highly recommended and should be directed by an infectious disease specialist. Finally, for the small portion of PBL cases that express CD20, rituximab should be considered in addition to chemotherapy. The EPOCH regimen is being evaluated prospectively in high-risk DLBCL patients, which could include PBL patients (NCT01092182).

High-dose chemotherapy followed by autologous stem cell support (ASCT) can be an option in patients with PBL. This topic has been recently reviewed [22]. Based on case reports and small case series, ASCT does have limited value in the relapsed setting. However, the use of ASCT as consolidation after achieving CR to frontline treatment (CR1) might be associated with longer OS times [19, 22]. A case series on nine HIV-negative PBL patients suggested longer OS time in patients who received ASCT in first remission [16]. There are no reports on the use of allogeneic SCT in PBL patients.

The poor results observed with current available treatments warrant the identification of novel agents for PBL patients. Given the plasmacytic nature of PBL, the use of anti-myeloma agents appears reasonable. The proteasome inhibitor bortezomib alone and in combination with chemotherapy has been used with limited efficacy in patients with relapsed PBL [23–25]. Recently, the combination of bortezomib and chemotherapy has been tried with success in the frontline treatment of patients with HIV-positive and HIV-negative PBL [26–28]. In a few case reports, the immunomodulatory drug lenalidomide induced a temporary response in relapsed PBL [23, 29, 30]. CD30 expression has been reported in approximately 30% of PBL cases [12, 31]. Recently, a case report described the antitumor activity of brentuximab vedotin in a patient with CD30-expressing relapsed PBL [32].

There is an almost universal expression of CD38 by PBL cells, and about 50% of PBL patients carry MYC gene rearrangements, providing potential treatment options. Daratumumab is a monoclonal antibody that targets CD38, which is a membrane glycoprotein expressed by B-cells, T-cell, NK-cell, and plasma cells. The FDA has approved daratumumab for the treatment of multiple myeloma. However, no reports on the use of daratumumab in PBL have been published. The *MYC* gene regulates multiple cellular functions influencing cell division, metabolic adaptation, and survival [33]. The *MYC* gene itself is not easily targetable, as it lacks a ligand-binding domain. *MYC* transcription depends on the assembly of complexes called bromodomains. BRD4 is a member of the bromodomain and extraterminal (BET) subfamily of human bromodomain proteins and seems to be an important factor for *MYC*-dependent transcription [34]. BET inhibition has shown to downregulate *MYC* transcription and to induce a genome-wide downregulation of *MYC*-dependent target genes [35]. Furthermore, BET inhibition has induced cell cycle arrest and cell senescence in cellular and animal myeloma models. Finally, recent studies have shown that EBV-positive lymphoma cells express PD-L1 and that PD-1 blockade inhibits their growth and survival [36, 37], providing the rationale on trying the monoclonal antibodies nivolumab or pembrolizumab in PBL. Nivolumab is FDA approved for the treatment of melanoma, non-small cell lung cancer, head and neck cancer, renal cell carcinoma, and Hodgkin lymphoma. Pembrolizumab is FDA approved for melanoma, non-small cell lung cancer, head and neck cancer, and Hodgkin lymphoma.

11.3 Primary Effusion Lymphoma

PEL is an aggressive lymphoma that affects body cavities without detectable tumor masses in the setting of HIV infection. It was recognized as a new entity in 2001 [38]. The Kaposi

sarcoma-associated herpesvirus, also known as human herpesvirus 8 (HHV-8), is universally present in PEL tumor cells [38].

Knowles and colleagues reported the first case of PEL in an HIV-infected patient in 1989 [39]. Later, in 1995, Cesarman and colleagues reported on a case series, in which seven out of eight HIV-positive patients presented with malignant pleural effusions. B-cell lineage was demonstrated by clonal rearrangement, as flow cytometry was unable to show typical CD20 expression. DNA analysis found sequences of HHV-8 and EBV genome in the neoplastic cells. The survival was short with poor tolerance to chemotherapy [40].

The diagnosis of PEL is based on morphologic, immunophenotypic, and molecular analysis of the affected tissue along with demonstration of viral infection by HHV-8. As effusion fluid is universally present, the diagnosis is made on cell blocks or cytospin samples. Morphologically, PEL cells are large with variable nuclear size and form, with prominent nucleoli. Sometimes PEL cells can resemble plasmablasts, or large immunoblasts with eccentric nuclei containing nuclear hof, or anaplastic cells with large polygonal cells with pleomorphic nuclei [38].

Immunophenotypic studies in PEL malignant cells reveal a "null" lymphocyte phenotype with expression of CD45 but no expression of CD19 or CD20. PEL cells can express markers of lymphocyte activation such as CD30, CD38, CD71, and HLA-DR and the plasma cell-related antigens CD138 and MUM-1/IRF4 [41]. In addition, PEL cells are negative for Bcl-6 and for anaplastic lymphoma kinase 1 (ALK-1), and the Ki-67 index is usually high. A representative case of PEL is shown in Fig. 11.2.

Recurrent chromosome translocations of *BCL2*, *BCL6*, and *MYC*, typically present in other B-cell lymphomas, are absent in PEL [42, 43]. Gene expression profile demonstrated that PEL cells have features of immunoblasts and plasma

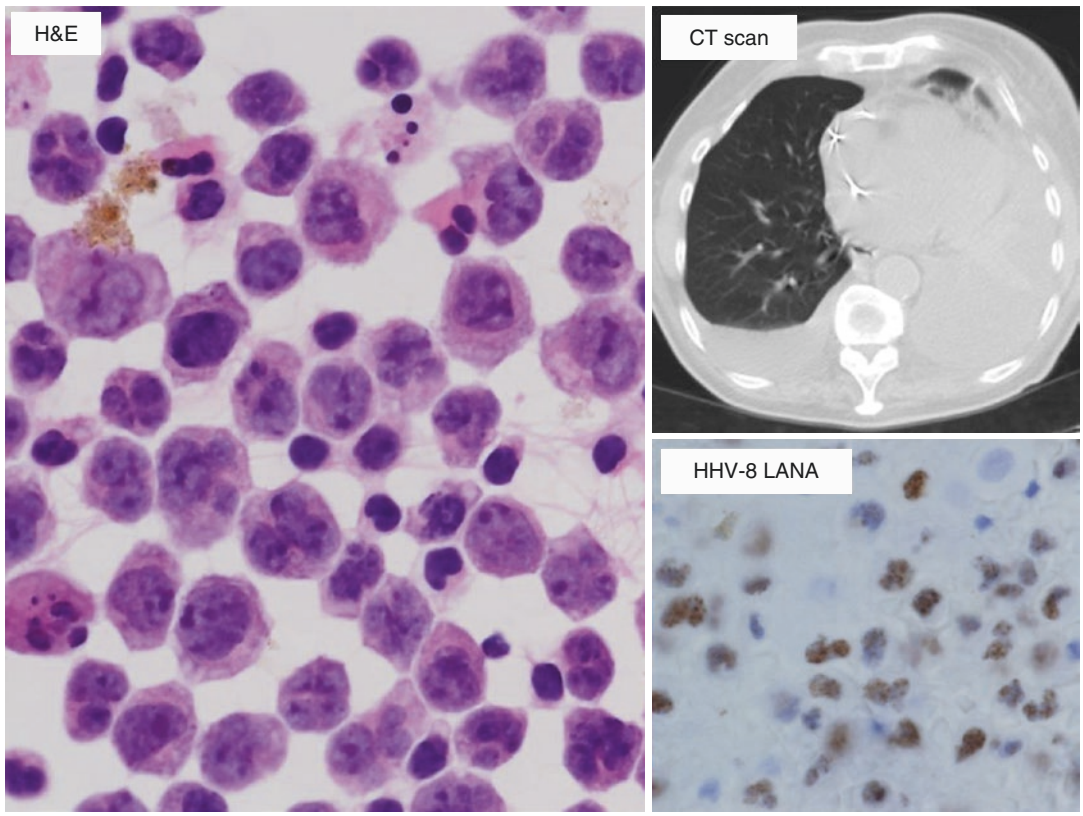

Fig. 11.2 Representative case of primary effusion lymphoma

cells. In addition, immunoglobulin gene rearrangements and somatic hypermutation are present in PEL. These findings suggest that the cell of origin in PEL is a post-germinal B-cell that has undergone plasma cell differentiation [44]. Array-based comparative genomic hybridization (CGH) studies showed gain and losses of several chromosomes including chromosomes 1, 5, 11, 12, and 17q, among other abnormalities [45].

HHV-8 plays an important role on promoting PEL. It is also useful to differentiate from other lymphomas complicated by effusions, which are consistently negative for HHV-8 infection [41]. The immunohistochemical staining for HHV-8 latent nuclear antigen 1 (LANA-1) is the standard assay performed. Although not standardized, detection of HHV-8 viral load by quantitative PCR could be useful, and its prognostic significance is still under investigation [44, 46]. Detection of EBV occurs in approximately 70% of cases using EBER in situ hybridization [41].

Cases of PEL have also been observed in the setting of post solid organ transplant and in debilitated elderly patients with chronic comorbidities [47]. Commonly, these patients present with other AIDS-associated diseases such as KS and MCD due to the association with HHV-8 infection in addition with severe immunosuppression caused by HIV [40, 48]. In general, PEL is characterized by the presence of malignant pleural, pericardial, or peritoneal effusions without evident mass or tumor. Due to the effects of malignant fluid accumulation, patients can experience chest pain, progressive dyspnea, abdominal distension, or constitutional symptoms. The pleural space is the most commonly affected (70% of cases). By definition, all PEL patients have stage IV disease [49]. Cases of extracavitary (solid) PEL with no evidence of malignant effusions have been described. Extracavitary PEL is morphologically and genetically identical to classic PEL [50]. The gastrointestinal tract is commonly affected, but there are also reports of involvement of the skin, lungs, lymph nodes, and CNS. Extracavitary PEL cases are also universally associated with HHV-8 infection [51, 52].

The prognosis of PEL is generally poor with few patients being cured from the disease. The 1-year survival rate is less than 40% [53, 54]. The multivariate analysis showed that poor performance status and no HAART at diagnosis were independent predictors of poor OS. The impact of HAART on PEL prognosis is similar to other AIDS-associated lymphomas [54, 55]. The number of body cavities involved in PEL seems to be prognostic, with more than one cavity associated with poorer prognosis. Isolated pericardial involvement appears to correlate with longer survival [56]. Integrating the number and type of body cavities into a prognostic score specific for PEL might warrant further investigation. The IPI score has not been validated in PEL to date. CD4 count and HHV-8 viral load at diagnosis were not prognostic of worse outcomes, although some studies suggest that the HHV-8 viral load might correlate with survival in HHV-8-associated lymphoproliferative disorders, including MCD [57].

There is no standard treatment for PEL. Response rates with CHOP are approximately 40% with a median OS of 6 months [53]. Other regimens such as doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) and CHOP plus methotrexate have been administered to PEL patients with variable response rates [54, 58]. Methotrexate should be used with caution as it could accumulate in effusions and lead to increased toxicity [54]. Dose-adjusted EPOCH has been reported in individual cases as well [59]. Recently, EPOCH has been associated with better outcomes than CHOP in patients with HIV-associated lymphomas [60]. Initiation of HAART is essential at HIV-infected PEL patients. In some cases, prolonged remissions and lymphoma regression have been reported with HAART alone [54, 61]. The experience of autologous or allogeneic SCT in PEL is limited to case reports, and consideration for the procedure should be based on individual cases [62, 63]. Provided the poor prognosis associated with PEL, SCT constitutes an attractive option, but larger studies are needed to assess efficacy and toxicity.

The constitutive activation of the NF-kB pathway appears critical for survival of PEL cells [64], and inhibition of the NF-kB pathway by bortezomib induced apoptosis in PEL cell lines

[65]. Despite these promising findings, the activity of bortezomib has been modest [66]. However, it appears that combination therapy could be promising [67]. There is limited preclinical and clinical data supporting the use of lenalidomide in PEL [68, 69]. CD30 is frequently expressed in PEL cells, and targeting with the conjugated monoclonal antibody anti-CD30 brentuximab vedotin improved the survival of a xenograft mouse PEL model by inhibiting proliferation and causing arrest in G2/M cell cycle phase [70]. PEL cells express CD38, making daratumumab an interesting, commercially available treatment options. Immunotherapy has emerged as a potential target for B-cell malignancies. Programed cell death ligand-1 (PD-L1) is an attractive target in PEL, as approximately 50% of HHV-8-associated PEL cases express PD-L1 [71]. Another interesting therapeutic option is NOTCH1 inhibitors. NOTCH1 expression has been demonstrated in almost 80% of PEL cells [72]. Other agents of interest in PEL are the PI3K/AKT/mTOR inhibitors and histone deacetylase inhibitors, which have shown preclinical activity [67, 73].

11.4 Large B-Cell Lymphoma Arising in HHV-8-Associated Multicentric Castleman Disease

Dupin and colleagues reported the first cases of this rare condition [74]. The authors described patients with HHV-8-associated MCD that later developed "plasmablastic" lymphoma. Most of these patients died within months of MCD diagnosis and some within weeks of overt lymphoma diagnosis.

Patients with HIV and MCD have a 15-fold greater risk of developing lymphoma than the general HIV-positive population [75]. Specific lymphoma types associated with HHV-8 infection are cavitary and extracavitary PEL and large B-cell lymphomas with plasmablastic differentiation arising in HHV-8-associated MCD [74–76]. While PEL shows typically hypermutated Ig and dim expression of surface and cytoplasmic immunoglobulin, large B-cell lymphomas in MCD show unmutated Ig and expression of IgM and λ chain restriction suggesting HHV-8-positive plasmablasts as the cell of origin [76]. However, the molecular events leading from polyclonal HHV-8-positive plasmablastic expansions in MCD to monoclonal HHV-8-positive large cell lymphoma are unknown.

Large B-cell lymphoma arising in HHV-8-associated MCD is histopathologically defined by large confluent sheets of plasmablasts with HHV-8 expression [77]. These blasts are not coinfected with EBV, show cytoplasmic IgM with λ chain restriction, and have a phenotypic profile characterized by loss of B-cell markers such as CD20 and PAX-5, and acquisition of phenotypic profile of plasma cells such as upregulation of MUM-1/IRF-4, PRDM-1/BLIMP-1, and surface markers such as CD38 [8, 75, 78]. A representative case of large B-cell lymphoma arising from HHV-8-associated MCD is shown in Fig. 11.3.

The histopathological differences between overt lymphoma and the so-called plasmablastic microlymphoma are not well defined, and the latter might represent an intermediate step in the progression from MCD to large B-cell lymphoma. While MCD is polyclonal in nature and overt lymphoma is monoclonal, plasmablastic microlymphomas in the lymph node have been found monoclonal in only two of eight cases with subsequent development of lymphoma in one. However, another case with associated polyclonal microlymphoma also developed overt lymphoma [76]. A similar picture is found in three cases reported as severe MCD with polyclonal IgMλ plasmablastic lymphocytosis successfully treated with combined chemotherapy [79].

MCD is a distinct type of lymphoproliferative disorder associated with IL-6 dysregulation [75]. Clinically, patients may have systemic symptoms such as fever, night sweats, polyclonal hypergammaglobulinemia, and cytopenias. HHV-8 infection is commonly associated with MCD in patients infected with HIV and also in some HIV-negative patients [80]. HHV-8 replicates in immunoblasts and plasmablasts and signals the

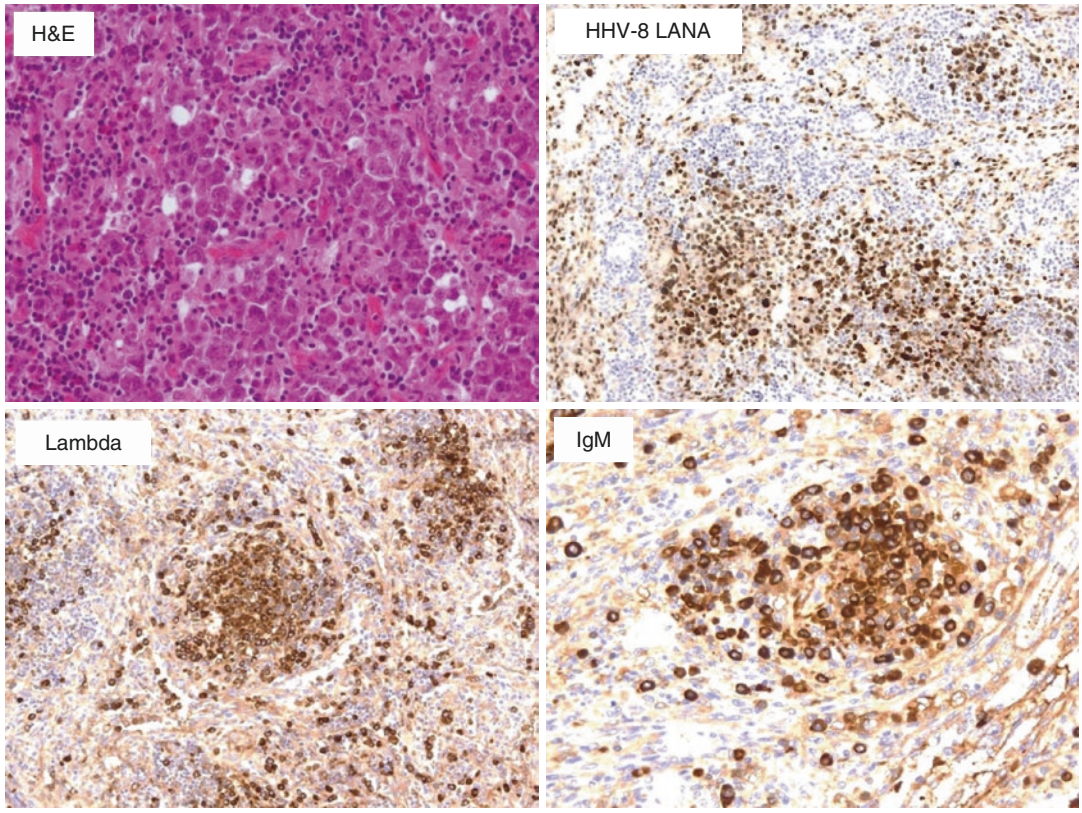

Fig. 11.3 Representative case of a large B-cell lymphoma arising from HHV-8-associated multicentric Castleman disease

release of viral-derived and human-derived IL-6 and other inflammatory cytokines [81], which induce B-cell and plasma cell proliferation and angiogenesis, and an acute phase reaction [82]. B-cell proliferation leads to the accumulation in the lymph nodes of clusters of HHV-8+, IgM+, λ chain restricted but polyclonal plasmablasts [74, 83]. These plasmablasts were found to be polyclonal/multiclonal in nature when Ig clonality analyses were performed and do not fulfill the current histopathological criteria to be considered DLBCL.

The outcome of patients with HHV-8-associated MCD is poor and is measured within few to several months from the development of MCD [74, 75]. The median OS is shorter (several weeks) in patients who develop overt lymphoma and extremely poor (few weeks) in cases of leukemic phase. Patients with so-called plasmablastic microscopic lymphomas should be treated as high-risk MCD [76, 79, 84]. Given the definite risk of developing overt lymphoma in patients with HHV-8-positive MCD, control of HHV8-positive MCD is the primary step for lymphoma prevention.

Rituximab, alone or in combination with chemotherapy, has significant activity in both HIV-negative and HIV-positive MCD. In HIV-positive patients, it has been evaluated in observational and retrospective analysis showing higher response rates and longer response duration than chemotherapy [60]. In one prospective study, the incidence of lymphoma was significantly reduced (>90% reduction) in patients receiving rituximab [85]. For most HIV-positive, HHV-8-positive patients with MCD, a combination of ganciclovir plus rituximab with etoposide added for aggressive/high-risk disease is suggested. In patients with uncontrolled HIV infection defined by low CD4 counts and/or high HIV viral load and/or

active KS, HAART should be included. Treatment with rituximab alone or rituximab plus combination chemotherapy such as CHOP or EPOCH can be given at time of relapse or if the patient is refractory to initial therapy.

Agents to consider in the relapsed setting are bortezomib, lenalidomide, and the anti-IL-6 monoclonal antibody siltuximab. In xenograft mouse model of HHV-8-positive PEL, bortezomib induced apoptosis and lytic reactivation of HHV-8 in lymphoma cells [86]. Siltuximab has shown to be safe and efficacious in a randomized study in patients with HIV-negative, HHV-8-negative MCD [87, 88]. Finally, there are case reports supporting the use of lenalidomide in MCD [89, 90].

11.5 ALK+ Diffuse Large B-Cell Lymphoma

ALK is a receptor tyrosine kinase originally described at the breakpoint of the t(2;5) translocation observed in patients with anaplastic large cell lymphoma (ALCL) [91]. ALK+ DLBCL is a rare subtype of DLBCL. In contrast with ALCL, ALK+ DLBCL is commonly associated with t(2;17) in which the ALK gene is juxtaposed to the clathrin (CLTC) gene. Delsol and colleagues originally described seven patients with ALK+ DLBCL [92]. Since then, no more than 100 cases of ALK+ DLBCL have been reported in the literature [93–95].

Pathologically, ALK+ DLBCL is comprised of monomorphic large immunoblastic or plasmablastic cells, containing large central nucleoli that tend to invade the lymphatic sinuses. The cells exhibit a high proliferative index, perhaps related to MYC overexpression. In contrast to ALCL, ALK+ DLBCL does not express CD30 [92]. The immunophenotype of ALK+ DLBCL is characterized by the expression of CD138, CD38, EMA, and cytoplasmic immunoglobulin and the absence of CD20 expression [92]. In addition, ALK+ DLBCL expresses other plasma cell differentiation antigens such as BLIMP1 and XBP1 [93]. The t(2;17) is the most common cytogenetic abnormality observed in ALK+ DLBCL and leads to the expression of the CLTC-ALK fusion gene. However, other chromosomal rearrangements involving the ALK gene had been described such as the t(2;5) (NMP-ALK) [96]. Of interest, ALK+ DLBCL does not seem to carry MYC translocations [97, 98]. A representative case of ALK+ DLBCL is shown in Fig. 11.4.

The precise mechanism(s) by which ALK fusion genes induce the oncological transformation of lymphoid cells are unclear. However, laboratory studies suggest that NPM-ALK and to a lesser degree CLTC-ALK activate the signal transducer and activator of transcription (STAT) family proteins, specifically STAT3 and STAT5 [99–101]. Studies have shown that STAT3 activation was induced by the NPM-ALK fusion gene and was necessary for NPM-ALK lymphomagenesis. STAT3 and STAT5 activation is associated with the upregulation of anti-apoptotic proteins [102]. In addition, STAT3 activation observed in ALK+ DLBCL results in the upregulation of BLIMP1 and c-MYC accounting for the plasmacytic differentiation and increase in cell proliferation observed, respectively [98].

Clinically, there is a male predominance, pediatric and adult patients can be affected, and it appears there is no relation with viral infections [103]. Patients present with advanced-stage disease in 60% of the cases and with bone marrow involvement in 25%. In a retrospective study on 38 patients, the survival rates were poor with a 5-year OS of 25%. Half of the patients died within the first year following diagnosis. It seems that patients with early-stage disease may have a better prognosis with an estimated 5-year OS of 50%.

ALK+ DLBCL has poor clinical outcomes despite current available therapy that includes systemic multi-agent chemotherapy. Targeted agents against CD20 or CD30 are unlikely to produce clinical benefit in ALK+ DLBCL given the lack of expression of these surface receptors. The current management of patients with ALK+ DLBCL consists on the administration of systemic chemotherapy using regimens commonly used for other subtypes of DLBCL in the first-line or second-line setting. However, given the poor clinical results observed with this approach

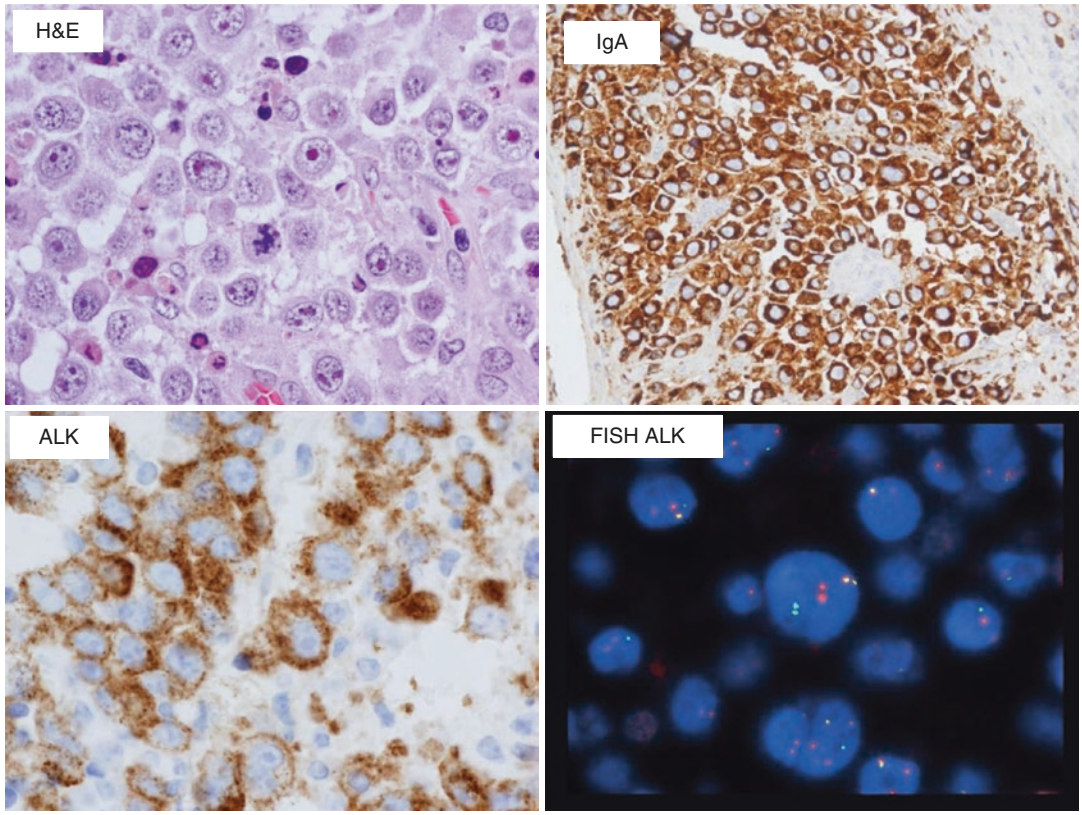

Fig. 11.4 Representative case of ALK+ diffuse large B-cell lymphoma

with median OS ranging from 10 to 20 months, there is a need to develop novel therapeutic approaches.

Crizotinib is the only ALK inhibitor approved by the FDA for the treatment of ALK+ non-small cell lung cancer and relapsed ALK+ ALCL. Anecdotal case reports had described the clinical use of crizotinib in ALK+ relapsed/refractory DLBCL. Wass et al. reported significant antitumor activity in a refractory ALK+ DLBCL patient treated with crizotinib single agent. However, the patient experienced a very short duration of response [104]. Preclinical studies have suggested that pharmacological inhibition of STAT3 or CLTC-ALK fusion protein results in antitumor activity against lymphoma cell lines or lymphoma xenograft murine models [105, 106]. Given CD38 expression by ALK+ DLBCL cells, daratumumab could also be an attractive therapeutic option.

11.6 Conclusion

CD20-negative lymphomas are rare, and they pose a significant diagnostic challenge given their atypical morphology. Additionally, CD20-negative lymphomas are associated with clinical courses characterized by primary chemoresistance, early relapse, and the obvious lack of benefit from anti-CD20 therapy. Furthermore, the survival of patients with CD20-negative lymphomas is measured in several months to a few years. Despite recent advances in the biology of CD20-negative DLBCL, several questions remain unanswered. It is interesting to see that these conditions, with exception of ALK+ DLBCL, occur mainly in immunosuppressed patients with chronic viral infections. Given the rarity associated with these conditions, therapeutic standards of care have not been established. It is encouraging to see clinical data showing that novel agents

such as bortezomib, lenalidomide, and brentuximab vedotin have activity in some of these patients. Given overexpression of CD38, PD-L1, and PD-1 in CD20-negative DLBCL, novel agents such as daratumumab, nivolumab, and pembrolizumab can prove to be helpful in treating these patients. Similarly, the use of BET inhibitors could be of value in *MYC*-positive lymphomas. Finally, crizotinib should be evaluated in patients with ALK+ DLBCL. However, given the aggressive nature of CD20-negative DLBCL, it is unlikely that molecular or targeted agents used alone would induce durable responses or be curative. In that sense, the combination of novel agents with chemotherapy such as CHOP or dose-adjusted EPOCH might be reasonable. The answers to these questions should come from well-designed multicenter prospective studies.

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