Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: http://www.tandfonline.com/loi/ierr20

CD20-negative diffuse large B-cell lymphomas: biology and emerging therapeutic options

Jorge J Castillo, Julio C Chavez, Francisco J Hernandez-Ilizaliturri & Santiago Montes-Moreno

To cite this article: Jorge J Castillo, Julio C Chavez, Francisco J Hernandez-Ilizaliturri & Santiago Montes-Moreno (2015) CD20-negative diffuse large B-cell lymphomas: biology and emerging therapeutic options, Expert Review of Hematology, 8:3, 343-354, DOI: 10.1586/17474086.2015.1007862

To link to this article: http://dx.doi.org/10.1586/17474086.2015.1007862

Published online: 01 Feb 2015.

Submit your article to this journal

Article views: 165

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=ierr20

Download by: [North Shore Med Ctr], [Jorge Castillo] **Date:** 16 March 2016, At: 07:44

EXPERT REVIEWS

CD20-negative diffuse large B-cell lymphomas: biology and emerging therapeutic options

Expert Rev. Hematol. 8(3), 343–354 (2015)

Jorge J Castillo*[1], Julio C Chavez[2], Francisco J Hernandez-Ilizaliturri[3] and Santiago Montes-Moreno[4]

[1]*Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, M221, Boston, MA 02215, USA*
[2]*Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA*
[3]*Medical Oncology and Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA*
[4]*Department of Pathology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain*
**Author for correspondence:*
Tel.: +1 617 632 6045
Fax: +1 617 632 4862
jorgej_castillo@dfci.harvard.edu

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

CD20-negative diffuse large B-cell lymphoma (DLBCL) is a rare and heterogeneous group of lymphoproliferative disorders. Known variants of CD20-negative DLBCL include plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising in human herpesvirus 8-associated multicentric Castleman disease and anaplastic lymphoma kinase-positive DLBCL. Given the lack of CD20 expression, atypical cellular morphology and aggressive clinical behavior characterized by chemotherapy resistance and inferior survival rates, CD20-negative DLBCL represents a challenge from the diagnostic and therapeutic perspectives. The goals of the present review are to summarize the current knowledge on the biology of the distinct variants of CD20-negative DLBCL, provide future therapeutic directions based on the limited preclinical and clinical data available, and increase awareness concerning these rare malignancies among pathologists and clinicians.

Keywords: ALK-positive DLBCL • CD20-negative • multicentric Castleman disease • plasmablastic lymphoma • primary effusion lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype seen in the general population, accounting for approximately 30–35% of the cases. The addition of rituximab, a chimeric anti-CD20 monoclonal antibody, to combination chemotherapy has shown to increase response and survival rates in young and elderly patients with DLBCL in large randomized controlled studies [1,2]. A small proportion of large B-cell lymphomas show marked plasma cell differentiation with downregulation of the B-cell antigen repertoire and acquisition of plasma cell markers. The plasma cell differentiation observed in these cases is so advanced that the expression of CD20 is lost.

In general, patients diagnosed with CD20-negative DLBCL tend to have extranodal involvement of their disease, a more aggressive clinical course with resistance to chemotherapy and a poor prognosis. Intuitively, the use of rituximab would not be of benefit in these cases. Most of the available evidence in CD20-negative DLBCL consists of case reports and small retrospective case series, and no prospective trials have been done to establish standards of care for these patients.

Here, we present a systematic review on the most common variants of CD20-negative DLBCL, including plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), large B-cell lymphoma arising in human herpesvirus 8 (HHV-8)-associated multicentric Castleman disease (MCD) and anaplastic lymphoma kinase (ALK)-positive DLBCL. We also provide an overview of the therapeutic approach based on the limited existing data. We acknowledge that this is an evolving field and that patients with CD20-negative DLBCL not meeting the criteria for the ones mentioned above have been described [3–5]. Also, CD20-negative DLBCL has been reported after exposure to anti-CD20 monoclonal antibodies [6,7]. These cases of CD20-negative DLBCL are beyond the scope of this review.

Plasmablastic lymphoma

First report

Delecluse *et al.* described PBL as a separate entity for the first time in 1997 [8]. This report

 10.1586/17474086.2015.1007862 © 2015 Informa UK Ltd ISSN 1747-4086

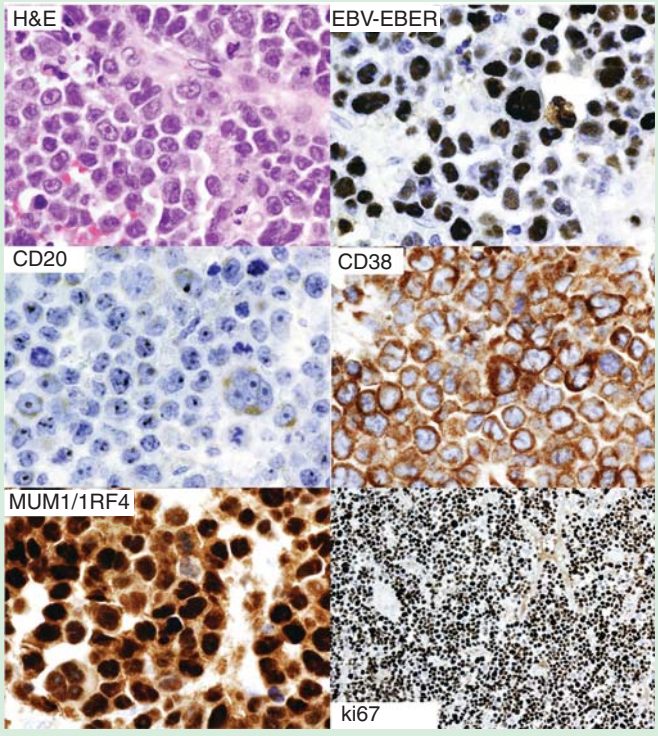

Figure 1. Representative case of plasmablastic lymphoma. H&E (400×) staining from a lymph node biopsy shows a typical case of DLBCL with plasmablastic morphology. EBER (400×) by *in situ* hybridization demonstrates EBV infection. CD20 (400×) is negative in these cases, but they often express plasma cell markers such as CD38 (400×) and MUM-1/IRF-4 (400×). The proliferation rate is high as represented by Ki67 expression (200×). DLBCL: Diffuse large B-cell lymphoma; EBER: EBV-encoded RNA.

included 16 patients, 15 of them infected with HIV, who presented with aggressive lesions located primarily in the oral cavity. These patients had an initial response to chemotherapy but also 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 [9].

Pathological features & cell of origin

Morphologically, the malignant cells have round to oval shape with abundant cytoplasm, eccentric nucleus, prominent nucleolus and a perinuclear hof [9]. The background is usually composed of small lymphocytes, mitotic figures and tingible body macrophages that can impart a starry-sky pattern. Immunophenotypically, the malignant PBL cells express markers of plasmacytic differentiation such as CD38, CD138 or multiple myeloma 1/interferon regulatory factor 4 protein (MUM-1/IRF-4) but do not express CD20 or CD10, and variably express CD45. The proliferation index is usually high with Ki67 >90%. Recently, novel markers such as BLIMP1 and XBP1 have been identified [10]. A representative profile of PBL is shown in Figure 1. The cell of origin (COO) in PBL is thought to be the plasmablast, an activated B cell that has already undergone the germinal center reaction (i.e., somatic hypermutation and class-switching recombination) but has not yet fully matured into a resting plasma cell. PBL is sometimes difficult to distinguish from plasmablastic myeloma [11], especially in the setting of immunodeficiency. However, the presence of monoclonal paraproteinemia, hypercalcemia, anemia, renal dysfunction and/or skeletal lytic lesions might favor a pathological diagnosis of myeloma.

Key molecular markers in PBL include the presence of *MYC* gene rearrangements and EBV-encoded RNA (EBER), which can be identified by *in situ* hybridization techniques. EBER expression has been reported in approximately 80 and 50% of cases with HIV-positive and HIV-negative PBL, respectively, and suggests a role of EBV in the pathogenesis of PBL. *MYC* gene rearrangements can be seen in approximately 40% of cases of HIV-positive PBL and has been associated with a worse prognosis [12]. A smaller study has suggested that EBV-positive PBL cases might be more likely to carry *MYC* gene rearrangements than EBV-negative cases [13].

Clinical presentation

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 (7:1 ratio). The median CD4+ count at diagnosis was less than 200 cells/mm^3 and the median time from HIV infection diagnosis to PBL diagnosis was 5 years [14]. Approximately 50% of the patients presented with advanced disease (stage III or IV) and 50% with primary site of involvement localized in the oral cavity. The second most common site was the GI tract (13%). 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% and 66% achieved complete response (CR) and 6% achieved partial response (PR). These findings have been confirmed by a more recent meta-analysis on approximately 300 patients with PBL [15].

A later systematic review identified 76 HIV-negative patients with a pathological diagnosis of PBL [16]. 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 89% presenting with extranodal involvement. The oral cavity was the most common site of involvement (21%) followed by the GI tract (20%). B symptoms were present in 50% of patients. The large majority (88%) was treated with combination chemotherapy and 43% with CHOP. The ORR was 66%, CR 44% and PR 22%. Another study showed that approximately 30% of HIV-negative PBL patients had some form of immunosuppression such as post-transplantation, concurrent malignancy or autoimmune disorders [17].

A comparative study between 157 HIV-positive and 71 HIV-negative PBL patients has been performed [18]. In this study, HIV-positive PBL patients were younger (39 vs 58 years) with more pronounced male predominance (82 vs 62%) and a higher proportion of oral cavity involvement (58 vs 16%). There were no differences in stage distribution, bone marrow

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

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.

Survival & prognostic factors

The prognosis of patients with PBL remains poor. Systematic reviews have reported median overall survival (OS) times that have ranged between 9 and 15 months [15,16]. More recently, a multicenter study on 50 HIV-positive PBL patients treated in the HAART era reported a median OS of 11 months [12]. Other smaller case series in PBL patients treated in the antiretroviral therapy (ART) era have shown median OS ranging between 5 and 12 months [19,20]. An Italian study has shown better outcomes in PBL patients with 3-year OS of 67% [21]. The reasons for this difference are unclear although the patients in the Italian study had a 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 [15,18]. Intuitively, advanced stage and poor performance status have been shown to be indicators of worse prognosis in PBL [12,20]. Hence, the use of the International Prognostic Index score [22], the most commonly used risk-stratification tool in aggressive lymphomas, might be appropriate in PBL [12,20,21]. Some studies have shown that EBV expression is not associated with outcome in PBL [20]. However, other studies have associated EBV expression by PBL with a better outcome [15]. $CD4^+$ counts <200 cells/mm^3 might be associated with shorter progression-free survival time [12,20]. More recently, the presence of *MYC* gene rearrangements has shown to be associated with worse OS [12,15]. In patients with HIV-positive PBL who are treated with chemotherapy, the attainment of CR has been associated with better outcomes [12,23]. In the HIV-negative setting, concurrent immunosuppression is associated with a worse outcome [17].

Current therapy & emerging options

Current guidelines recommend against the use of CHOP as it is considered inadequate therapy [24]. 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 a benefit from more intensive regimens [12,23]. Based on small retrospective studies and consensus opinion, the following regimens appear to be more appropriate: 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). These regimens could include the administration of intrathecal agents to minimize the risk of 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 include PBL patients [25].

High-dose chemotherapy followed by autologous stem cell support (ASCT) can be an option in patients with PBL. This topic has been recently reviewed [26]. 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 [21,26]. A case series on nine HIV-negative PBL patients suggested longer OS time in patients who received ASCT in CR1 [17]. There are no reports on the use of allogeneic SCT in PBL patients.

The poor results observed with currently available treatments stresses the need to identify novel agents for PBL patients. Given the plasmacytic nature of PBL, the use of agents borrowed from the myeloma armamentarium appears reasonable. The proteasome inhibitor bortezomib alone and in combination with chemotherapy has been used with limited efficacy in patients with relapsed PBL [27–29]. Recently, the combination of bortezomib and infusional dose-adjusted EPOCH has been tried with success in the frontline treatment of three patients with HIV-positive and HIV-negative PBL [30]. In another report, the immunomodulatory drug lenalidomide induced a temporary response in a patient with relapsed PBL [27]. Few studies have shown CD30 expression in approximately 30% of PBL cases [13,31]. Recently, a case report described the antitumor activity of brentuximab vedotin in a patient with CD30-expressing relapsed PBL [32].

Given that 40–50% of patients with PBL would have *MYC* gene rearrangements, targeting *MYC* might be a potential option. The *MYC* gene regulates multiple cellular functions that influence cell division, metabolic adaptation and survival, and is the most commonly altered gene observed in cancer [33]. The *MYC* gene itself is not an easy target as it lacks a ligand-binding domain. However, the transcriptional function of *MYC* can be potentially targetable. *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.

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 [36]. The Kaposi

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

sarcoma-associated herpesvirus or currently named HHV-8 is universally present in tumor cells and its detection is essential for PEL diagnosis [36].

First report

Knowles *et al.* reported the first case of PEL in an HIV-infected patient [37]. Cesarman *et al.* better characterized the disease in 1995. In this series, seven out of eight HIV-positive patients presented with malignant pleural effusion and two patients had concomitant Kaposi sarcoma (KS). The entity was originally called body-cavity-based lymphoma. B-cell lineage was demonstrated by clonal rearrangement as flow cytometry was unable to show typical B-cell markers. The survival was poor with short response and poor tolerance to standard chemotherapy. DNA analysis found sequences of Kaposi sarcoma-associated herpesvirus and EBV genome in the neoplastic cells [38].

Pathological features & cell of origin

The diagnosis of PEL is based on morphological, immunophenotypic and molecular analysis of the affected tissue. In addition, the demonstration of viral infection by HHV-8 is essential. As effusion fluid is universally present, the diagnosis is made on cytological samples such as cell blocks or cytospin. Morphologically, PEL cells are usually large with variable nuclear size and form, with prominent nucleoli. Sometimes PEL cells can resemble plasmablasts, large immunoblasts with eccentric nuclei containing nuclear hof or anaplastic cells with large polygonal cells with pleomorphic nuclei. Some of the anaplastic forms can resemble Reed–Sternberg cells [36].

Immunophenotypic studies in PEL malignant cells reveal a 'null' lymphocyte phenotype with expression of CD45 but no expression of typical B-cell antigens (surface and cytoplasmic immunoglobulin, CD19, CD20, CD79a) and some T-cell markers (CD3, CD4, CD8). PEL cells usually express markers of lymphocyte activation such as CD30, CD38, CD71 and HLA-DR, and the plasma cell-related antigens CD138 and MUM-1/IRF-4 [39]. 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 Figure 2. Rarely, early PEL can occur as germinal center solid tumor in lymph nodes where neoplastic follicles composed of large cells with immunoblastic or plasmablastic features can be recognized in a background of follicular hyperplasia [40]. Early PEL is usually associated with MCD and tumor cells are frequently coinfected by HHV-8 and EBV.

Conventional cytogenetic studies revealed complex cytogenetic abnormalities with trisomy of chromosomes 7, 8 and 12. Recurrent chromosome translocations of *BCL2*, *BCL6*, *CCND1* and *MYC*, typically present in other B-cell lymphomas, are absent in PEL [41,42]. Gene expression profile demonstrated that PEL cells have features of immunoblasts and plasma cells. In addition, immunoglobulin gene rearrangements and somatic hypermutation are present in PEL. These findings suggest that the COO in PEL is a postgerminal B cell that has undergone plasma cell differentiation [43]. Array-based comparative genomic hybridization studies showed gain and losses of several chromosomes, including chromosomes 1, 5, 11, 12 and 17q, among other abnormalities [44].

HHV-8 plays an important role in promoting the development of PEL, and detection of viral infection by HHV-8 in the malignant cells is essential for the diagnosis of PEL. It is also useful to differentiate from other lymphomas complicated by effusions, which are consistently negative for HHV-8 infection [39]. The immunohistochemical staining for HHV-8 latent nuclear antigen 1 is the standard assay performed in PEL cells and tissues. Although not standardized, the detection of HHV-8 viral load by quantitative PCR is also useful; however, its prognostic significance is still under investigation [43,45]. Detection of EBV occurs in approximately 70% of cases and should be pursued using EBER *in situ* hybridization [39].

Clinical presentation

PEL is a rare lymphoma and represents 2–4% of all HIV-associated lymphomas. Cases of PEL have also been observed in the setting of post solid organ transplant and in debilitated elderly patients with chronic comorbidities [46]. 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 [38,47].

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). Approximately one-third of patients have prior diagnosis of KS. It is considered an advanced malignancy as, by definition, PEL is a stage IV disease [48].

Improved diagnostic techniques such as immunophenotype and gene expression profile have described extracavitary (solid) PEL forms of disease with no or minimal clinical evidence of malignant effusions. Extracavitary PEL is otherwise virtually morphologically and genetically identical to classical PEL [49]. The GI tract is most commonly affected in extracavitary PEL; however, there are also reports of involvement of the skin, lungs, lymph nodes and CNS. Extracavitary PEL cases are associated with HHV-8 infection and also with other HHV-8-associated malignancies such as KS and MCD [50,51].

Survival & prognostic factors

The prognosis of PEL is generally poor with few patients being cured from the disease. The median OS ranges from 4 to 9 months and the 1-year survival rate is less than 40% [52,53]. The largest series in a multicenter study of 28 patients showed a median OS of 6.2 months. 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 [53,54].

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

Standard Ann Arbor staging is not relevant as PEL cases are considered stage IV. Whether it has an implication in extracavitary PEL needs to be determined. 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 [55]. Integrating the number and type of body cavities into a prognostic score specific for PEL might warrant further investigation. The International Prognostic Index 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 [56].

Current therapy & emerging options

There is no standard treatment for PEL. Response rates with CHOP are approximately 40% with a median OS of 6 months [52]. 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 [53,57]. Dose-adjusted EPOCH has been reported in individual cases as well [58]. Recently, EPOCH has been associated with better outcomes than CHOP in patients with HIV-associated lymphomas [59]. Combination of CHOP with high-dose methotrexate can also be considered, but should be used with caution as methotrexate could accumulate in effusions and lead to increased toxicity [53]. It is unclear if more intense regimens will offer better outcomes and larger studies are needed.

Initiation of HAART is essential at PEL diagnosis as improved survival has been demonstrated. In some cases, prolonged remissions and lymphoma regression have been reported with HAART alone [53,60]. The experience of autologous or allogeneic SCT in PEL is limited to case reports, and considerations for the procedure should be based on individual cases [61,62]. Provided the poor prognosis associated with PEL, SCT constitutes an attractive option, but larger studies are needed to assess efficacy and toxicity.

Increased constitutive activation of the NF-kB pathway has been demonstrated to be critical for the survival of PEL cells [63]. Inhibition of the NF-kB pathway by bortezomib induced apoptosis in PEL cell lines [64]. Despite these promising findings, the activity of bortezomib has not been translated into clinical efficacy [65]. However, it appears that combination therapy could be promising [66]. 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 the G2/M cell cycle phase. The preclinical activity of brentuximab is yet to be translated into clinical practice [67].

Immunotherapy has emerged as a potential target for B-cell malignancies. Multiple targets have been identified with immunomodulatory properties. One of the more attractive molecules is the programmed cell death ligand-1 (PD-L1). Approximately 50% of HHV-8-associated PEL cases express PD-L1. Thus, anti-PD-L1 therapy could be a potential alternative for PEL, although preclinical activity has not been demonstrated yet [68]. Another interesting therapeutic option is the gamma secretase inhibitors that target NOTCH1-mutated tumor cells. NOTCH1 expression has been demonstrated in almost 80% of PEL cases [69].

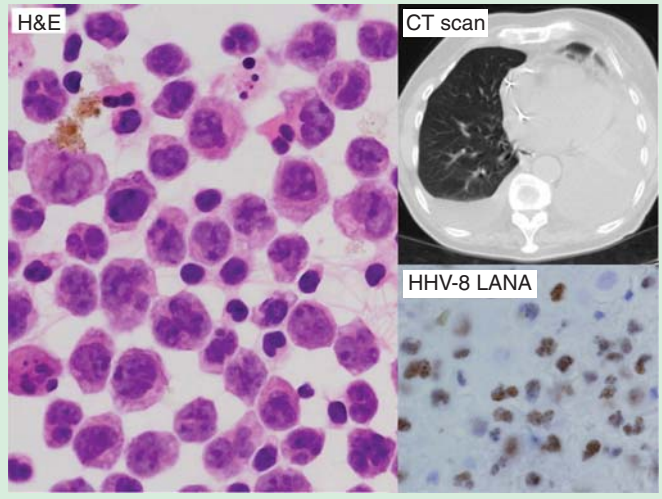

Figure 2. Representative case of primary effusion lymphoma. H&E (400×) staining from a pleural effusion cytoprep in a typical case of PEL is shown here. CT scan shows a left-sided pleural effusion. HHV-8 infection can be demonstrated by the expression of LANA (400×) in these cases. PEL: Primary effusion lymphoma.

Large B-cell lymphoma arising in HHV-8-associated MCD

First report

Dupin *et al.* reported the first case of this rare condition [70]. The authors described patients with HHV-8-associated MCD who later developed 'plasmablastic' lymphoma and one additional case who developed a plasmablastic leukemic picture. Most of these patients died within months of MCD diagnosis and some within weeks of overt lymphoma diagnosis.

Pathological features & cell of origin

Patients with HIV and MCD have a 15-fold greater risk of developing different types of lymphoma than the general HIV-positive population [71]. Specific lymphoma types associated with HHV-8 infection are cavitary and extracavitary PELs and large B-cell lymphomas with plasmablastic differentiation arising in HHV-8-associated MCD [70–72], according to WHO classification [73]. While PELs show typically hypermutated immunoglobulin and absence or dim expression of surface and cytoplasmic immunoglobulin, large B-cell lymphomas in MCD show unmutated immunoglobulin and expression of IgM and λ-chain restriction suggesting that these lymphomas derive from HHV-8-positive plasmablasts [72]. However, the molecular events leading from polyclonal HHV-8-positive plasmablastic expansions in MCD to

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

monoclonal HHV-8-positive large cell lymphoma are unresolved and surely act in concert with both HIV coinfection and the immunosuppression status of the patient to trigger the development of overt lymphoma in most instances.

Thus, large B-cell lymphoma arising in HHV-8-associated MCD is histopathologically defined by large confluent sheets of plasmablasts with HHV-8 expression [73]. These blasts are not coinfected with EBV, show cytoplasmic IgM with λ-chain restriction and have a phenotypic profile equivalent to other PBLs with loss of B-cell differentiation markers such as downregulation of 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 [10,71,74]. A representative case of large B-cell lymphoma arising from HHV-8-associated MCD is shown in Figure 3.

Of note, the histopathological differences between overt lymphoma and so-called plasmablastic microlymphoma are not well defined, and the latter situation might represent an intermediate step in the progression from conventional MCD to large B-cell lymphoma. Clonality analysis has yielded conflicting results in this regard. While usual MCD is polyclonal in nature and overt lymphoma is monoclonal, plasmablastic microlymphomas in the lymph node have been found to be monoclonal in only two of eight cases so far published, with subsequent development of lymphoma in one of these cases. However, another case with associated polyclonal microlymphoma also developed overt lymphoma [72]. A similar picture is found in three cases reported as severe MCD with polyclonal IgMλ plasmablastic lymphocytosis successfully treated with combined chemotherapy [75].

Clinical features

MCD is a distinct type of lymphoproliferative disorder associated with IL-6 dysregulation [71]. 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 [76]. In contrast, cases of idiopathic MCD are typically HHV-8 negative. HHV-8 replicates in immunoblasts and plasmablasts and signals the release of viral- and human-derived IL-6 and other inflammatory cytokines [77], which induce B-cell and plasma cell proliferation, VEGF secretion and angiogenesis, and an acute phase reaction [78]. B-cell proliferation leads to the accumulation in the lymph nodes of clusters of HHV-8+, IgM+, λ-chain restricted but polyclonal plasmablasts [70,79]. These plasmablasts were found to be polyclonal/multiclonal in nature when immunoglobulin clonality analyses were performed [70–72] and do not fulfill the current histopathological criteria to be considered DLBCL (i.e., diffuse pattern of growth or tissue effacement and immunoglobulin monoclonality) [79].

Prognosis, preventive & therapeutic options

The outcome of patients with HHV-8-associated MCD is poor and is measured within few to several months from the development of MCD [70,71]. The median OS is shorter at 1 month in patients who develop overt lymphoma and extremely poor (1–2 weeks) in cases of leukemic phase. Patients with so-called plasmablastic microscopic lymphomas should be treated as high-risk MCD [72,75,80]. Given there is a definite risk of developing overt lymphoma in patients with HHV-8-positive MCD, higher in those coinfected with HIV, control of HHV-8-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 [59]. In one prospective study, the incidence of lymphoma was significantly reduced (>90% reduction) in patients receiving rituximab with an incidence rate of 4.2/1000 person-years versus 69.6/1000 person-years in untreated patients [81].

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 the time of relapse or if the patient is refractory to initial therapy.

Other agents to consider in the MCD relapsed setting are the proteasome inhibitor bortezomib and the anti-IL-6 monoclonal antibody siltuximab. Experimental use of bortezomib in a preclinical xenograft mouse model of HHV-8-positive PEL demonstrates that the drug induces apoptosis and lytic reactivation of HHV-8 in lymphoma cells, suggesting a possible rationale for the use of the combination of bortezomib and ganciclovir in patients with HHV-8-positive lymphomas [82]. Siltuximab has been shown to be safe and efficacious in a randomized study in patients with HIV-negative, HHV-8-negative MCD [83,84]. As stated above, the development of HHV-8-positive large B-cell lymphoma is fatal in most instances and no standard therapy is available. Our recommendation is to consider dose-adjusted EPOCH in patients who have not received chemotherapy previously for the treatment of MCD. Otherwise, the goal of therapy should be largely palliative.

ALK+ diffuse large B-cell lymphoma

First report

ALK-associated hematological malignancies are characterized by the chromosomal translocation of the ALK gene to other partner genes. ALK is a receptor tyrosine kinase that was originally described at the breakpoint of the t(2:5)(p23;q35) translocation observed in patients with anaplastic large cell lymphoma (ALCL) [85]. Such translocation fuses the ALK with the nucleophosmin (NPM) gene leading to a constitutive transcription of the NPM–ALK hybrid gene. Other studies identified NPM–ALK as one of the first proto-oncogenes driving certain types of lymphoid malignancies. Since then, additional gene partners

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

to ALK had been identified [86]. ALK+ DLBCL is an extremely rare subtype of DLBCL. In contrast to ALCL, ALK+ DLBCL is commonly associated with t(2;17)(p23;q23) in which the ALK gene is juxtaposed to the clathrin (CLTC) gene. ALK+ DLBCL was originally described by Delsol *et al.* in a case series describing the pathological characteristics of seven patients with aggressive lymphoma [87]. Since then, fewer than 60 cases of ALK+ DLBCL had been reported in the literature [88–90].

Pathological features

Pathologically, ALK+ DLBCL is comprised of monomorphic large immunoblastic or plasmablastic cells containing large central nucleoli that tend to invade lymphatic sinuses. The cells exhibit a high proliferative index, perhaps related to MYC overexpression. In contrast to ALCL, ALK+ DLBCL does not express CD30 [87]. The immunophenotype of ALK+ DLBCL is characterized by the expression of CD138, CD38, EMA and cytoplasmic immunoglobulin (commonly IgA isotype) and the absence of CD20 and CD79a [87]. In addition, ALK+ DLBCL expresses other plasma cell differentiation antigens such as BLIMP1 and XBP1 [88]. The t(2:17)(p23;q23) 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)(p23;q35) (NMP–ALK) or the rare cryptic insertion of 3′ALK gene sequences into chromosome 4 [91]. Of interest, ALK+ DLBCL does not carry MYC translocations [92,93]. A representative case of ALK+ DLBCL is shown in Figure 4.

The precise mechanism(s) by which ALK fusion genes induce the oncological transformation of lymphoid cells remains to be elucidated. However, laboratory studies suggest that both NPM–ALK and, to a lesser degree, CLTC–ALK activate the signal transducer and activator of transcription (STAT) family proteins, specifically STAT3 and STAT5 [94–96]. Laboratory studies demonstrated that STAT3 activation was induced by the NPM–ALK fusion gene and was necessary for NPM–ALK lymphomagenesis. On the other hand, the degree of STAT phosphorylation varies between the different ALK fusion proteins identified. In particular, the CLTC–ALK, observed in most cases of ALK+ DLBCL, induces the lowest level of STAT3 phosphorylation. STAT3 and STAT5 activation is associated with the upregulation of antiapoptotic proteins (i.e., survivin and Bcl-XL) that may contribute to the poor clinical outcome observed in this subgroup of B-cell lymphoma patients [97]. In addition, STAT3 activation observed in ALK+ DLBCL results in the upregulation of BLIMP1 and c-MYC accounting for plasmacytic differentiation and increase in cell proliferation observed, respectively [93].

Clinical features

Clinically, there is a male predominance (5:1), pediatric and adult patients can be affected, and it appears that there is no relation with viral infections [98]. Patients present with advanced-stage disease in 60% of the cases and bone marrow involvement in 25%. In a retrospective study on 38 patients with ALK+ DLBCL, the survival rates were poor with a 5-year OS of 25%.

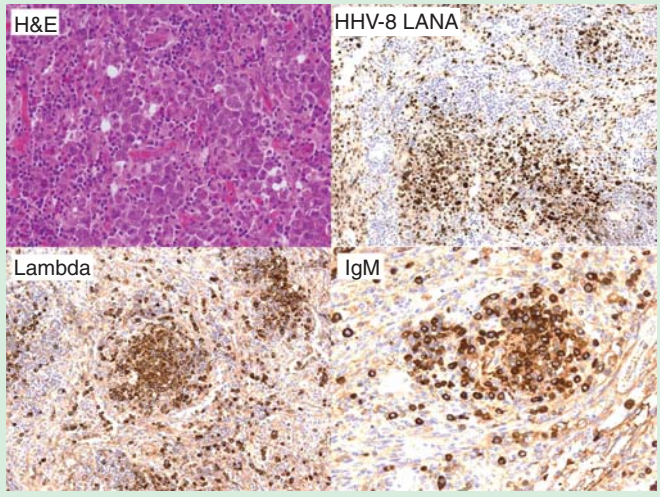

Figure 3. Representative case of a large B-cell lymphoma arising from HHV-8-associated multicentric Castleman disease. H&E (200×) staining from a lymph node biopsy shows large cells with plasmablastic morphology. HHV-8 LANA (200×) immunohistochemical staining demonstrates HHV-8 infection in a case of so-called plasmablastic microlymphoma and Kaposi sarcoma (KS) in the lymph node. Note nuclear staining in round large cells and spindle KS cells. Lambda chain restriction (200×) is the rule in these cases along with IgM expression (200×).

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%.

Therapy & future directions

In general and based on peer-reviewed literature, ALK+ DLBCL represents a rare subgroup of DLBCL with poor clinical outcome despite currently available therapies that include systemic multiagent chemotherapy and ASCT or allogeneic SCT. Targeted agents against CD20 or CD30 are unlikely to produce clinical benefit in ALK+ DLBCL given the lack of expression of these surface receptors. There is a desperate need to develop and incorporate novel therapeutic agents with proven antitumor activity in the management of patients with ALK+ DLBCL.

The current management of patients with ALK+ DLBCL consists of 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 with median OS ranging from 10 to 20 months, there is a need to develop novel therapeutic approaches.

Preclinical studies suggest that pharmacological inhibition of STAT3 or CLTC–ALK fusion protein results in antitumor activity against lymphoma cell lines or lymphoma xenograft murine models [99,100]. Crizotinib is the only ALK inhibitor approved by the US 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

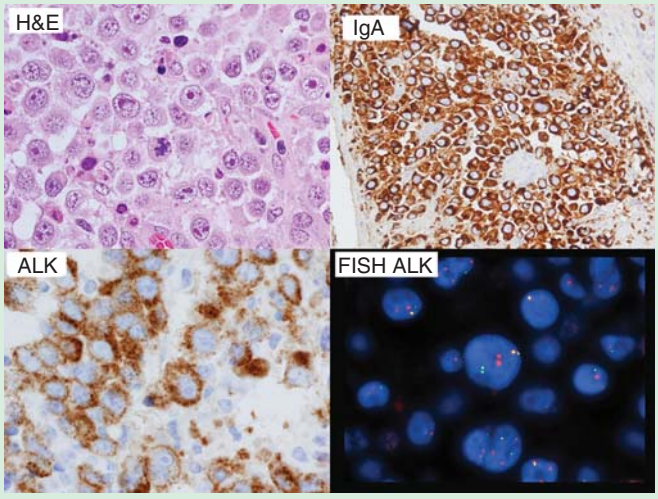

Figure 4. Representative case of ALK+ diffuse large B-cell lymphoma. H&E (400×) staining from a lymph node biopsy shows large plasmablastic cells. IgA expression (200×) is found in a percentage of the cases. ALK cytoplasmic granular immunoreactivity is a surrogate of the ALK–CLTC fusion gene (400×). ALK gene rearrangement can be demonstrated by FISH (1000×). ALK: Anaplastic lymphoma kinase.

activity in a refractory ALK+ DLBCL patient treated with crizotinib single agent. However, the patient experienced a very short duration of response [101].

Expert commentary

CD20-negative lymphomas are rare but aggressive lymphoproliferative disorders. In general, they pose a significant diagnostic challenge given their atypical morphology and protean presentation. Additionally, CD20-negative lymphomas are associated with clinical courses characterized by primary chemoresistance, early relapse and the obvious lack of benefit from CD20-directed monoclonal antibody therapy. Overall, the outcomes of patients with CD20-negative lymphomas are poor and can be 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 occur mainly in immunosuppressed patients with chronic viral infections. The relationship between distinct variants of CD20-negative DLBCL and viral infections are shown in Table 1. Given the rarity associated with these conditions, therapeutic standards of care have not been established and large prospective studies are unlikely to be performed. However, we advocate for their inclusion in larger clinical trials for aggressive B-cell lymphomas. It is encouraging to see that PBL, for example, will be included in the CTSU-1977 study evaluating the use of infusional EPOCH in high-risk DLBCL.

Table 1. Relationship between distinct types of CD20-negative DLBCL and viral infection.

Entity	HIV	EBV	HHV-8
Plasmablastic lymphoma	+++	+++	–
Primary effusion lymphoma	+++	++	+++
Large cell lymphoma in MCD	+++	–	+++
ALK+ DLBCL	–	–	–

ALK: Anaplastic lymphoma kinase; DLBCL: Diffuse large B-cell lymphoma; MCD: Multicentric Castleman disease.

It is also encouraging to see preclinical and clinical data showing that novel compounds such as bortezomib have activity in PEL and PBL patients. Also, anti-CD30 therapy appears to be of benefit in a small fraction of patients with CD20-negative but CD30-positive DLBCL. Similarly, the use of BET inhibitors could be of value in *MYC*-positive PBL. Given the close relation between *MYC* and EBV, it would be reasonable to investigate *MYC* and/or BET inhibitors in other EBV-mediated or *MYC*-driven CD20-negative lymphomas such as PEL. A study will evaluate crizotinib in patients with ALK-positive tumors excluding lung cancer [102]. Hopefully, cases of ALK+ DLBCL will be included in this study.

Given the aggressive nature of CD20-negative DLBCL, it is unlikely that molecular or targeted agents used alone would be able to induce durable responses or be curative. In that sense, the combination of novel agents and chemotherapy such as dose-adjusted EPOCH might be reasonable. From the practical perspective, practicing oncologists and pathologists need to identify this subgroup of DLBCL patients so they can be referred to tertiary institutions and receive early access to more promising treatments than standard chemotherapy.

Five-year view

Based on the information presented in this review, CD20-negative DLBCL is a group of aggressive lymphomas with poorly understood pathobiology and poor outcomes with standard regimens. One of our objectives was to increase the awareness on these rare disorders among clinicians and pathologists to promote multi-institutional collaboration in the basic and clinical research realms. If indeed a foundation or research network focusing on CD20-negative aggressive lymphomas is formed and adequately funded, then the design and execution of clinical trials would be possible. This approach would promote the enrollment of patients with CD20-negative DLBCL in prospective studies evaluating novel agents in academic settings. Such clinical studies would need to be supported by strong correlative basic research such as genomic and molecular profiling and transcriptome analysis, just to name a few. Within a few years of tenacious work, specific targets would be identified promoting studies designed at evaluating specific inhibitory molecules in combination with chemotherapy. Since the median survival of these conditions is measured in few to several months, the improved outcomes with novel approaches should be evident relatively quickly, motivating the establishment of a therapeutic standard of care. It is likely, however, that not all the CD20-negative DLBCL variants will have similar response and survival rates to the same standard of care. This initial effort would have to be followed by a more refined approach in

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

terms of diagnosis as well as predictive and prognostic factors. Studies would then have to focus on separate CD20-negative DLBCL entities to further improve therapies and outcomes.

Acknowledgements

JJ Castillo designed the review. JJ Castillo, JC Chavez, FJ Hernandez-Ilizaliturri and S Montes-Moreno gathered and analyzed the data and wrote the manuscript. S Montes-Moreno provided the pictures.

Financial & competing interests disclosure

JJ Castillo is a consultant for Otsuka Pharmaceuticals. JC Chavez, FJ Hernandez-Ilizaliturri and S Montes-Moreno have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Key issues

- CD20-negative diffuse large B-cell lymphoma (DLBCL) is rare and aggressive and represents a diagnostic and therapeutic challenge.
- Known variants of CD20-negative DLBCL include plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising from HHV-8-associated multicentric Castleman disease and ALK+ DLBCL.
- Plasmablastic lymphoma is strongly associated with HIV and EBV infections, presents in the oral cavity and other extralymphatic sites and has a poor prognosis with a median survival of 6–15 months.
- Primary effusion lymphoma is associated with HIV, EBV and HHV-8 infections; presents as a malignant effusion, rarely as a solid extracavitary lesion; and has a poor survival ranging between 4 and 9 months.
- Large B-cell lymphomas arising from multicentric Castleman disease is associated with HIV and HHV-8 infections and has a short survival of 1 month. Its development can be prevented by the use of rituximab.
- ALK+ DLBCL is characterized by the expression of ALK, can present with nodal and extranodal involvement, and has a poor prognosis between 10 and 20 months. It does not seem to be associated with viral infections.
- CD20-negative DLBCL patients should be treated with combination chemotherapy in academic centers. Antiretroviral therapy should be started or optimized in HIV-positive patients. Stem cell transplantation in first remission should be considered in special cases.
- Potential therapies include drugs directed against targets such as the proteasome, CD30, BET, MYC, EBV, HHV-8, PD-L1, NOTCH, IL-6 and ALK.

References

References of special note have been highlighted as:
• of interest
•• of considerable interest

1. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-26

•• **A randomized study showing response and survival benefit of the addition of rituximab to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL).**

2. Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013-22

•• **A randomized study showing response and survival benefit of the addition of rituximab to chemotherapy in young patients with DLBCL.**

3. Garg M, Lee BE, McGarry K, et al. CD20-negative diffuse large B-cell lymphoma presenting with lactic acidosis. Am J Hematol 2014. [Epub ahead of print]

4. Gaur S, Padilla O, Nahleh Z. Clinical features and prognosis of CD20 negative aggressive B-cell non-Hodgkins lymphoma. Lymphoma 2013;2013:290585

5. Li YJ, Li ZM, Rao HL, et al. CD20-negative de novo diffuse large B-cell lymphoma in HIV-negative patients: a matched case-control analysis in a single institution. J Transl Med 2012;10:84

6. Hiraga J, Tomita A, Sugimoto T, et al. Down-regulation of CD20 expression in B-cell lymphoma cells after treatment with rituximab-containing combination chemotherapies: its prevalence and clinical significance. Blood 2009;113:4885-93

7. Maeshima AM, Taniguchi H, Fukuhara S, et al. Follow-up data of 10 patients with B-cell non-Hodgkin lymphoma with a CD20-negative phenotypic change after rituximab-containing therapy. Am J Surg Pathol 2013;37:563-70

8. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413-20

• **The first report on plasmablastic lymphoma (PBL).**

9. Stein H, Harris N, Campo E. Plasmablastic lymphoma. In: Swerdlow S, Campo E, Harris N, et al. editors. WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues, 4th Edition. IARC, Lyon 2008;256-7

10. Montes-Moreno S, Gonzalez-Medina AR, Rodriguez-Pinilla SM, et al. Aggressive large B-cell lymphoma with plasma cell differentiation: immunohistochemical characterization of plasmablastic lymphoma and diffuse large B-cell lymphoma with partial plasmablastic phenotype. Haematologica 2010;95:1342-9

11. Vega F, Chang CC, Medeiros LJ, et al. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol 2005;18:806-15

12. Castillo JJ, Furman M, Beltran BE, et al. Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

the era of highly active antiretroviral therapy. Cancer 2012;118:5270-7

• **The largest case series on HIV-associated PBL.**

13. Valera A, Balague O, Colomo L, et al. IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas. Am J Surg Pathol 2010;34:1686-94
14. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. Am J Hematol 2008;83:804-9
15. Morscio J, Dierickx D, Nijs J, et al. Clinicopathologic comparison of plasmablastic lymphoma in HIV-positive, immunocompetent, and posttransplant patients: single-center series of 25 cases and meta-analysis of 277 reported cases. Am J Surg Pathol 2014;38:875-86

• **The largest literature review on PBL.**

16. Castillo JJ, Winer ES, Stachurski D, et al. HIV-negative plasmablastic lymphoma: not in the mouth. Clin Lymphoma Myeloma Leuk 2011;11:185-9
17. Liu JJ, Zhang L, Ayala E, et al. Human immunodeficiency virus (HIV)-negative plasmablastic lymphoma: a single institutional experience and literature review. Leuk Res 2011;35:1571-7
18. Castillo JJ, Winer ES, Stachurski D, et al. Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma. Leuk Lymphoma 2010;51:2047-53
19. Noy A, Chadburn A, Lensing SY, Moore P. Plasmablastic Lymphoma Is Curable The HAART Era. A 10 Year Retrospective By The AIDS Malignancy Consortium (AMC). 2013;122:1801-1
20. Schommers P, Wyen C, Hentrich M, et al. Poor outcome of HIV-infected patients with plasmablastic lymphoma: results from the German AIDS-related lymphoma cohort study. AIDS 2013;27:842-5
21. Cattaneo C, Re A, Ungari M, et al. Plasmablastic lymphoma among human immunodeficiency virus-positive patients: results of a single center's experience. Leuk Lymphoma 2014. [Epub ahead of print]
22. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-94

•• **A report on the International Prognostic Index score, the most commonly used risk-stratification tool in aggressive lymphomas.**

23. Castillo JJ, Winer ES, Stachurski D, et al. Prognostic factors in chemotherapy-treated patients with HIV-associated Plasmablastic lymphoma. Oncologist 2010;15:293-9
24. NCCN Guidelines Version 4.2014. AIDS-Related B-Cell Lymphomas. Available from: www.nccn.org/professionals/physician_gls/pdf/nhl.pdf [Last Accessed on 18 September 2014]
25. Phase II Study of Dose-Adjusted EPOCH-Rituximab in Adults With Untreated Burkitt Lymphoma and c-MYC+ Diffuse Large B-Cell Lymphoma. Available from: https://clinicaltrials.gov/ct2/show/NCT01092182
26. Al-Malki MM, Castillo JJ, Sloan JM, Re A. Hematopoietic Cell Transplantation for Plasmablastic Lymphoma: a Review. Biol Blood Marrow Transplant 2014. [Epub ahead of print]
27. Bibas M, Grisetti S, Alba L, et al. Patient with HIV-associated plasmablastic lymphoma responding to bortezomib alone and in combination with dexamethasone, gemcitabine, oxaliplatin, cytarabine, and pegfilgrastim chemotherapy and lenalidomide alone. J Clin Oncol 2010;28:e704-8
28. Dasanu CA, Bauer F, Codreanu I, et al. Plasmablastic haemato-lymphoid neoplasm with a complex genetic signature of Burkitt lymphoma responding to bortezomib. Hematol Oncol 2013;31:164-6
29. Yan M, Dong Z, Zhao F, et al. CD20-positive plasmablastic lymphoma with excellent response to bortezomib combined with rituximab. Eur J Haematol 2014;93:77-80
30. Castillo JJ, Reagan JL, Sikov WM, Winer ES. Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma. Br J Haematol 2014; In press
31. Colomo L, Loong F, Rives S, et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 2004;28:736-47
32. Holderness BM, Malhotra S, Levy NB, Danilov AV. Brentuximab vedotin demonstrates activity in a patient with plasmablastic lymphoma arising from a background of chronic lymphocytic leukemia. J Clin Oncol 2013;31:e197-9
33. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature 2010;463:899-905
34. Rahl PB, Lin CY, Seila AC, et al. c-Myc regulates transcriptional pause release. Cell 2010;141:432-45
35. Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011;146:904-17
36. Banks P, Warnke R. Primary effusion lymphoma. In: Jaffe E, Harris N, Stein H, et al. editors. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues edition 3. IARC WHO Classification of Tumours, Lyon, France; 2001:179-80
37. Knowles DM, Inghirami G, Ubriaco A, Dalla-Favera R. Molecular genetic analysis of three AIDS-associated neoplasms of uncertain lineage demonstrates their B-cell derivation and the possible pathogenetic role of the Epstein-Barr virus. Blood 1989;73:792-9
38. Cesarman E, Chang Y, Moore PS, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995;332:1186-91

• **The first report on the association between HHV-8 and primary effusion lymphoma (PEL).**

39. Said J, Cesarman E. Primary effusion lymphoma. In: Swerdlow S, Campo E, Harris N, et al. editors. WHO classification of tumours of haematopoietic and lymphoid tissues, 4th Edition. IARC, Lyon 2008;260-1
40. Gloghini A, Dolcetti R, Carbone A. Lymphomas occurring specifically in HIV-infected patients: from pathogenesis to pathology. Semin Cancer Biol 2013;23:457-67
41. Wilson KS, McKenna RW, Kroft SH, et al. Primary effusion lymphomas exhibit complex and recurrent cytogenetic abnormalities. Br J Haematol 2002;116:113-21
42. Boulanger E, Agbalika F, Maarek O, et al. A clinical, molecular and cytogenetic study of 12 cases of human herpesvirus 8 associated primary effusion lymphoma in HIV-infected patients. Hematol J 2001;2:172-9
43. Kim Y, Park CJ, Roh J, Huh J. Current concepts in primary effusion lymphoma and other effusion-based lymphomas. Korean J Pathol 2014;48:81-90
44. Luan SL, Boulanger E, Ye H, et al. Primary effusion lymphoma: genomic profiling

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

revealed amplification of SELPLG and CORO1C encoding for proteins important for cell migration. J Pathol 2010;222: 166-79

45. Gantt S, Casper C. Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. Curr Opin Infect Dis 2011;24:295-301

46. Shi Y, Hou Y, Hu Q, et al. A rare case of HHV-8-positive/HIV-negative/EBV-negative primary effusion lymphoma in a renal transplant recipient. Cytopathology 2012;23:137-9

47. Matsumoto Y, Nomura K, Ueda K, et al. Human herpesvirus 8-negative malignant effusion lymphoma: a distinct clinical entity and successful treatment with rituximab. Leuk Lymphoma 2005;46:415-19

48. Kaplan LD. Human herpesvirus-8: kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. Hematology Am Soc Hematol Educ Program 2013;2013:103-8

49. Carbone A, Gloghini A, Vaccher E, et al. Kaposi's sarcoma-associated herpesvirus/human herpesvirus type 8-positive solid lymphomas: a tissue-based variant of primary effusion lymphoma. J Mol Diagn 2005;7:17-27

50. Chadburn A, Hyjek E, Mathew S, et al. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. Am J Surg Pathol 2004;28: 1401-16

51. Pan ZG, Zhang QY, Lu ZB, et al. Extracavitary KSHV-associated large B-Cell lymphoma: a distinct entity or a subtype of primary effusion lymphoma? Study of 9 cases and review of an additional 43 cases. Am J Surg Pathol 2012;36:1129-40

52. Simonelli C, Spina M, Cinelli R, et al. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. J Clin Oncol 2003;21:3948-54

53. Boulanger E, Gerard L, Gabarre J, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. J Clin Oncol 2005;23:4372-80

• **The largest case series on PEL.**

54. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. J Clin Oncol 2005;23: 4430-8

•• **An important study on the effect of antiretroviral therapy on the outcome of patients with HIV-associated lymphomas.**

55. Castillo JJ, Shum H, Lahijani M, et al. Prognosis in primary effusion lymphoma is associated with the number of body cavities involved. Leuk Lymphoma 2012;53: 2378-82

• **The largest literature review on PEL.**

56. Simonelli C, Tedeschi R, Gloghini A, et al. Characterization of immunologic and virological parameters in HIV-infected patients with primary effusion lymphoma during antiblastic therapy and highly active antiretroviral therapy. Clin Infect Dis 2005;40:1022-7

57. Boulanger E, Daniel MT, Agbalika F, Oksenhendler E. Combined chemotherapy including high-dose methotrexate in KSHV/HHV8-associated primary effusion lymphoma. Am J Hematol 2003;73:143-8

58. El-Ayass W, Yu EM, Karcher DS, Aragon-Ching JB. Complete response to EPOCH in a patient with HIV and extracavitary primary effusion lymphoma involving the colon: a case report and review of literature. Clin Lymphoma Myeloma Leuk 2012;12:144-7

59. Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-83

•• **The largest patient-level meta-analysis evaluating the role of rituximab and infusional chemotherapy regimens in HIV-associated lymphoma.**

60. Ripamonti D, Marini B, Rambaldi A, Suter F. Treatment of primary effusion lymphoma with highly active antiviral therapy in the setting of HIV infection. AIDS 2008;22:1236-7

61. Won JH, Han SH, Bae SB, et al. Successful eradication of relapsed primary effusion lymphoma with high-dose chemotherapy and autologous stem cell transplantation in a patient seronegative for human immunodeficiency virus. Int J Hematol 2006;83:328-30

62. Bryant A, Milliken S. Successful reduced-intensity conditioning allogeneic HSCT for HIV-related primary effusion lymphoma. Biol Blood Marrow Transplant 2008;14:601-2

63. Keller SA, Schattner EJ, Cesarman E. Inhibition of NF-kappaB induces apoptosis of KSHV-infected primary effusion lymphoma cells. Blood 2000;96:2537-42

64. An J, Sun Y, Fisher M, Rettig MB. Antitumor effects of bortezomib (PS-341) on primary effusion lymphomas. Leukemia 2004;18:1699-704

65. Boulanger E, Meignin V, Oksenhendler E. Bortezomib (PS-341) in patients with human herpesvirus 8-associated primary effusion lymphoma. Br J Haematol 2008;141:559-61

66. Bhatt S, Ashlock BM, Toomey NL, et al. Efficacious proteasome/HDAC inhibitor combination therapy for primary effusion lymphoma. J Clin Invest 2013;123:2616-28

67. Bhatt S, Ashlock BM, Natkunam Y, et al. CD30 targeting with brentuximab vedotin: a novel therapeutic approach to primary effusion lymphoma. Blood 2013;122: 1233-42

68. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res 2013;19:3462-73

69. Wang HY, Fuda FS, Chen W, Karandikar NJ. Notch1 in primary effusion lymphoma: a clinicopathological study. Mod Pathol 2010;23:773-80

70. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood 2000;95:1406-12

• **The first report on the association between HHV-8 and multicentric Castleman disease (MCD) in HIV-infected patients.**

71. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Blood 2002;99:2331-6

72. Du MQ, Liu H, Diss TC, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood 2001;97:2130-6

73. Issacson P, Campo E, Harris NL. Large B-cell lymphoma arising in HHV8-associated multicentric Castlemans disease. In: Swerdlow S, Campo E, Harris N, et al. editors. WHO classification of tumours of haematopoietic and lymphoid

Downloaded by [North Shore Med Ctr], [Jorge Castillo] at 07:44 16 March 2016

tissues, 4th Edition. IARC, Lyon; 2008; 258-9

74. Montes-Moreno S, Montalban C, Piris MA. Large B-cell lymphomas with plasmablastic differentiation: a biological and therapeutic challenge. Leuk Lymphoma 2012;53:185-94

75. Oksenhendler E, Boutboul D, Beldjord K, et al. Human herpesvirus 8+ polyclonal IgMlambda B-cell lymphocytosis mimicking plasmablastic leukemia/lymphoma in HIV-infected patients. Eur J Haematol 2013;91:497-503

76. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 2001;51: 671-9

77. Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 2009;16:236-46

78. Kishimoto T. IL-6: from its discovery to clinical applications. Int Immunol 2010;22: 347-52

79. Hsi ED, Lorsbach RB, Fend F, Dogan A. Plasmablastic lymphoma and related disorders. Am J Clin Pathol 2011;136: 183-94

80. Pagni F, Bosisio FM, Sala E, et al. The plasmablasts in Castleman disease. Am J Clin Pathol 2013;139:555-9

81. Gerard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood 2012;119:2228-33

- **A study showing the efficacy of rituximab on reducing the risk of developing overt lymphoma in patients with HIV-associated MCD.**

82. Sarosiek KA, Cavallin LE, Bhatt S, et al. Efficacy of bortezomib in a direct xenograft model of primary effusion lymphoma. Proc Natl Acad Sci USA 2010;107:13069-74

83. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood 2014;123:2924-33

84. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-74

- **A randomized study on the use of siltuximab, an IL-6 inhibitor, in MCD.**

85. Rimokh R, Magaud JP, Berger F, et al. A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of anaplastic large cell lymphoma ('Ki-1 lymphoma'). Br J Haematol 1989;71:31-6

86. Stein H, Foss HD, Durkop H, et al. CD30 (+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96:3681-95

87. Delsol G, Lamant L, Mariame B, et al. A new subtype of large B-cell lymphoma expressing the ALK kinase and lacking the 2;5 translocation. Blood 1997;89:1483-90

- **The first report on ALK+ DLBCL.**

88. Momose S, Tamaru J, Kishi H, et al. Hyperactivated STAT3 in ALK-positive diffuse large B-cell lymphoma with clathrin-ALK fusion. Hum Pathol 2009;40: 75-82

89. Beltran B, Castillo J, Salas R, et al. ALK-positive diffuse large B-cell lymphoma: report of four cases and review of the literature. J Hematol Oncol 2009;2:11

90. Sachdev R, Goel S, Gupta S, Sood N. Anaplastic lymphoma kinase (ALK) positive diffuse large B cell lymphoma in a 20 year old: a rare entity. Indian J Pathol Microbiol 2014;57:157-8

91. Stachurski D, Miron PM, Al-Homsi S, et al. Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma with a complex karyotype and cryptic 3' ALK gene insertion to chromosome 4 q22-24. Hum Pathol 2007;38:940-5

92. Ott G, Rosenwald A, Campo E. Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification. Hematology Am Soc Hematol Educ Program 2013;2013:575-83

93. Valera A, Colomo L, Martinez A, et al. ALK-positive large B-cell lymphomas express a terminal B-cell differentiation program and activated STAT3 but lack MYC rearrangements. Mod Pathol 2013;26: 1329-37

94. Nieborowska-Skorska M, Slupianek A, Xue L, et al. Role of signal transducer and activator of transcription 5 in nucleophosmin/anaplastic lymphoma kinase-mediated malignant transformation of lymphoid cells. Cancer Res 2001;61: 6517-23

95. Zamo A, Chiarle R, Piva R, et al. Anaplastic lymphoma kinase (ALK) activates Stat3 and protects hematopoietic cells from cell death. Oncogene 2002;21:1038-47

96. Zhang Q, Wang HY, Liu X, Wasik MA. STAT5A is epigenetically silenced by the tyrosine kinase NPM1-ALK and acts as a tumor suppressor by reciprocally inhibiting NPM1-ALK expression. Nat Med 2007;13: 1341-8

97. Bai RY, Ouyang T, Miething C, et al. Nucleophosmin-anaplastic lymphoma kinase associated with anaplastic large-cell lymphoma activates the phosphatidylinositol 3-kinase/Akt antiapoptotic signaling pathway. Blood 2000;96:4319-27

98. Laurent C, Do C, Gascoyne RD, et al. Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma: a rare clinicopathologic entity with poor prognosis. J Clin Oncol 2009;27:4211-16

- **The largest retrospective case series on ALK+ DLBCL.**

99. Cerchietti L, Damm-Welk C, Vater I, et al. Inhibition of anaplastic lymphoma kinase (ALK) activity provides a therapeutic approach for CLTC-ALK-positive human diffuse large B cell lymphomas. PLoS ONE 2011;6:e18436

100. Amin HM, McDonnell TJ, Ma Y, et al. Selective inhibition of STAT3 induces apoptosis and G(1) cell cycle arrest in ALK-positive anaplastic large cell lymphoma. Oncogene 2004;23:5426-34

101. Wass M, Behlendorf T, Schadlich B, et al. Crizotinib in refractory ALK-positive diffuse large B-cell lymphoma: a case report with a short-term response. Eur J Haematol 2014;92:268-70

102. An Investigational Drug, Crizotinib (PF-02341066), is being studied in tumors, except non-small cell lung cancer, that are positive for anaplastic lymphoma kinase (ALK). Available from: https://clinicaltrials.gov/ct2/show/NCT01121588