Curr Hematol Malig Rep (2012) 7:208–215
DOI 10.1007/s11899-012-0132-3

LYMPHOMAS (J ARMITAGE AND P MCLAUGHLIN, SECTION EDITORS)

Lymphomatoid Granulomatosis and Other Epstein-Barr Virus Associated Lymphoproliferative Processes

Kieron Dunleavy · Mark Roschewski · Wyndham H. Wilson

Published online: 20 July 2012

Abstract We now recognize that the Epstein-Barr virus (EBV), which is a member of the γ- herpesvirus family, plays a pivotal role in the development of several lymphomas and lymphoproliferative disorders that include B-cell, T-cell and NK-cell processes. While over recent years, EBV associated lymphomas that arise in patients with known defects in cellular immunity are relatively well characterized, these diseases are becoming increasingly recognized in patients without overt immunodeficiency. Improved understanding of the biology of these lymphomas including elucidating the role that EBV plays in their pathogenesis has paved the way for improved therapies targeted at critical signaling pathways as well as the development of novel cellular therapies. In this review, we focus on recent progress that has been made in the biology and treatment of the rare EBV-associated disorder lymphomatoid granulomatosis (LYG) and also discuss other EBV-associated processes that occur in both immunocompetent and immunocompromised hosts.

Keywords Lymphomatoid granulomatosis · LYG · Epstein-Barr virus · EBV · Lymphoma · LMP-1 · EBNA-1 · Lymphoproliferative disorders · Cytotoxic T-lymphocyte · Cellular therapy · Interferon

K. Dunleavy · M. Roschewski · W. H. Wilson
Metabolism Branch, Center for Cancer Research,
National Cancer Institute,
Bethesda, MD, USA

W. H. Wilson
e-mail: wilsonw@mail.nih.gov

K. Dunleavy (✉)
Metabolism Branch, National Cancer Institute,
Building 10, Room 4N-115, 9000 Rockville Pike,
Bethesda, MD 20892, USA
e-mail: dunleavk@mail.nih.gov

Introduction

Epstein-Barr virus (EBV) was the very first human tumor virus to be discovered and it was first identified in 1964 in cell lines that had been established from a patient with Burkitt lymphoma (BL) [1]. It is a ubiquitous γ-herpes virus and is epidemiologically important as it asymptomatically infects greater than 90 % of the world's population. Following primary infection, the virus typically remains in a latent state within B lymphocytes during which time it is regulated and controlled by cytotoxic T cells (CTLs)—both $CD8^+$ and $CD4^+$—and natural killer (NK) cells [2]. Failure of the host's cellular immunity can lead to EBV-induced B-cell proliferation and when this occurs, infected carrier B-cells can transform from their latent state into malignant cells and this can lead to the development of lymphoma. The term "EBV-associated lymphomas" encompasses a wide spectrum and heterogeneous group of aggressive B-cell and NK/T-cell lymphomas that arise in patients with and without overt impairments in cellular immunity [3].

During the period of latency, to maintain the viral genome and circumvent the host's immune surveillance, EBV-infected resting memory cells can evade immune recognition by limiting gene expression to specific viral latent proteins. These include 6 nuclear antigens (EBNAs-1, -2, -3a, -3b, -3c, and –LP), 3 latent membrane proteins (LMP-1, -2a, and -2b), 2 small non-coding RNAs (EBER-1 and EBER-2) as well as BamHI-A rightward transcripts (BART) [4, 5•].

Three distinct patterns of latency (types I, II and II) are associated with different types of lymphomas: type I involves selective expression of EBNA 1 in EBV positive Burkitt lymphoma; type II is the expression of EBNA-1, LMP-1 and LMP-2 and is the hallmark of EBV positive Hodgkin lymphoma (HL) and peripheral T/NK cell lymphomas; it is also the pattern seen in DLBCL of the elderly; type III latency,

which is characterized by expression of the entire array of nine EBV latency proteins is seen in EBV-LPD's that occur in severely immunocompromised patients following solid organ and stem-cell transplantation and in human immunodeficiency virus infection (Table 1). The type of latency determines the susceptibility of the infected cells to different immunotherapeutic maneuvers. Mechanisms of EBV lymphomagenesis are reviewed extensively elsewhere [6].

Lymphomatoid Granulomatosis (LYG)

Lymphomatoid granulomatosis (LYG) is a very rare EBV-driven angiocentric and angiodestructive lymphoproliferative process that most commonly affects the lungs of afflicted individuals. Etiologically, while most patients with LYG do not have a history of overt immunodeficiency, the disorder is more commonly diagnosed in patients with immunodeficiency and predisposing conditions include Wiskott-Aldrich syndrome, human immunodeficiency virus infection and allogeneic organ transplantation [7, 3]. The immune characteristics that are associated with LYG are still not completely elucidated or understood but early results suggest that LYG may arise in the setting of a global deficit in CD8 T-cells with selected defects in EBV-specific immunity that resolve with successful therapy [8].

Histologically, LYG lesions are characterized by an angiocentric and angiodestructive lymphoid infiltrate. The infiltrate consists of a small number of EBV positive B-cells and these are admixed with a prominent inflammatory background that is made up of T-cells, plasma cells, and histiocytes. The EBV positive B-cells show some atypia but are typically large in size and express CD20, are variably positive for CD30 and negative for CD15. Vascular changes and angiodestruction are distinctive features. Intimal thickening of blood vessels and accompanying necrosis are seen in many cases.

LYG can be divided into three grades based on the proportion of large atypical EBV positive B-cells and necrosis in relation to the reactive background of T lymphocytes. In grade I lesions, EBV-positive cells are infrequently detected whereas in grade II lesions they are readily detected—and usually number 5–20/high power field—by in situ hybridization [3]. Grade III lesions consist of large atypical B cells and EBV positive cells are very numerous and easily identified. Distinguishing grade III (high grade) from grades I and II (low grade) is an important distinction as grade III lesions are approached therapeutically like diffuse large B-cell lymphoma (DLBCL) and treated with immunochemotherapy.

Clinically, LYG demonstrates a predilection for men in a 2:1 ratio and although it most commonly presents between the fourth and sixth decades of life, it can affect younger patients and children [9]. LYG almost always presents with pulmonary involvement and appearances in the lungs can vary from small pulmonary nodules to large necrotic and sometimes cavitating lesions. Interestingly, disease in the lungs is typically characterized by

Table 1 Various EBV-associated lymphomas and lymphoproliferative disorders and their relationship to EBV

Lymphoma Type	Frequency of EBV (%)	Type of EBV latency
Burkitt lymphoma		
Endemic	100 %	
Sporadic	20–30 %	Type 1
HIV-associated	25–35 %	
Hodgkin lymphoma		
Classical	40 %	Type 2
HIV-associated	80 %	
EBV + DLBCL of the elderly	100 %	Type 2
DLBCL associated with chronic inflammation	70 %	Type 2
Primary Effusion Lymphoma	> 80 %	Type 1
Plasmablastic Lymphoma	70 %	Type 1 or 2
Plasmablastic lymphoma oral type (H IV)	100 %	Type 1
Primary CNS Lymphoma (HIV)	100 %	Type 3
Post-transplant LPD		
B-cell	>90 %	Type 3
T-cell	>70 %	
Extranodal NK/T-cell lymphoma – nasal type	100 %	Type 2
Angloimmunoblastic T-cell lymphoma	>90 %	Type 2
Lymphomatoid Granulomatosis (LYG)	100 %	Type 2

chronic scarring of lung tissue that persists on computed tomography imaging even when the disease is in complete remission. Other common sites of extranodal involvement include the central nervous system and skin in up to 20 % of patients [9]. Many variations of brain involvement have been described and in the largest series that looked at magnetic resonance imaging (MRI) abnormalities in this population, the most frequent findings were multiple focal intraparenchymal lesions and involvement of the leptomeninges and cranial nerves [10•]. Other extranodal sites that may be involved include the kidneys and liver. One striking feature of LYG is that the lymph nodes and spleen are very rarely involved at diagnosis. Patients with LYG typically present with symptoms and signs related to pulmonary involvement such as cough, dyspnea or chest pain. Otherwise, symptoms relate to other sites of disease involvement and many patients present with constitutional symptoms including fever and weight loss.

In the past, therapies that have been utilized with variable success in LYG have included corticosteroids, chemotherapy or observation but the outcome with these approaches was poor with most patients succumbing to the disease after a short period of time [9]. Although patients often respond initially, relapse is very common and the immunosuppressive effects of therapy may actually worsen the condition. At our institution, we have developed a treatment approach based on our understanding that this is an EBV driven process for which we use interferon alpha for grade I and II disease and immunochemotherapy for grade III lesions. The rationale is as follows: as grade I and II diseases are likely polyclonal or oligoclonal and immune dependent, we hypothesized that immunomodulatory therapy like interferon-alpha may be effective. As grade III LYG is monoclonal and immune independent, we approached it like diffuse large B-cell lymphoma and set out to investigate if dose adjusted - etoposide, prednisone, vincristine, cyclophosphamide doxorubicin and rituximab (DA-EPOCH-R) was an effective treatment strategy (Fig. 1).

In grade I and II disease, we tested the efficacy of interferon-alpha at a starting dose of 7.5 million units subcutaneously administered 3 times per week. Then it was dose-escalated to best response or point of complete remission and therapy was continued at that dose for a year beyond that point. There was wide intra-patient variability in the dose of interferon that was required to achieve remission. In the first 31 patients, most of whom had received prior therapy, 60 % achieved a complete remission [8]. Interestingly, 90 % of patients with CNS disease achieved a complete remission with interferon. A total of 21 % of patients progressed on interferon with grade III disease but many of these were successfully treated with immunochemotherapy. There was no predictable time frame for the development of progression. One interesting feature about LYG is that patients with lower grade lesions can after successful treatment relapse with high-grade disease and vice versa—there may also be simultaneous discordant disease at different sites. It is therefore critical to have a low threshold to re-biopsy patients who are progressing on therapy as they may require a switch in treatment strategy. At a median follow-up time of 5 years, the progression-free survival of patients with grade I–II LYG was 56 % with a median time to remission of 9 months. In contrast, we treated all patients with grade III disease at diagnosis with dose-adjusted EPOCH-R chemotherapy. In 24 patients, many of whom had received prior therapy, the PFS was 40 % with a median follow-up of 28 months and 66 % achieved complete remission [11].

Other EBV-Associated Lymphomas and Lymphoproliferative Disorders

EBV plays an important role in several other lymphoproliferative disorders and these can largely be divided into those that occur in immunocompetent hosts and those that occur in immunocompromised hosts.

EBV-Associated B-Cell Lymphomas in Immunocompetent Hosts

EBV in Burkitt Lymphoma (BL)

The presence of EBV varies significantly according to the BL variant. In endemic BL, EBV is found in virtually all tumors. It occurs at a frequency of 20–40 % in sporadic BL and HIV-associated BL [12, 13]. These different variants of BL have distinct clinical presentations with endemic BL often presenting with jaw and other facial bone disease. BL demonstrates a type 1 pattern of latency with expression of EBNA-1 and EBER without expression of latent membrane proteins such as LMP-1 [5•]. Evidence for an oncogenic role of EBV stems from the fact that cell lines that have lost EBV do not induce tumors in mice but re-infection with EBV re-establishes a malignant phenotype [14, 15]. The main role of EBV in endemic BL may be to protect B-cells that already contain a *MYC* translocation from apoptosis and the presence of EBV contributes to telomere dysfunction and genomic instability [16, 17]. There is a strong epidemiological link between endemic BL and holoendemic malaria and *Plasmodium falciparum* infection may play a role in reactivating latently infected memory B-cells [3].

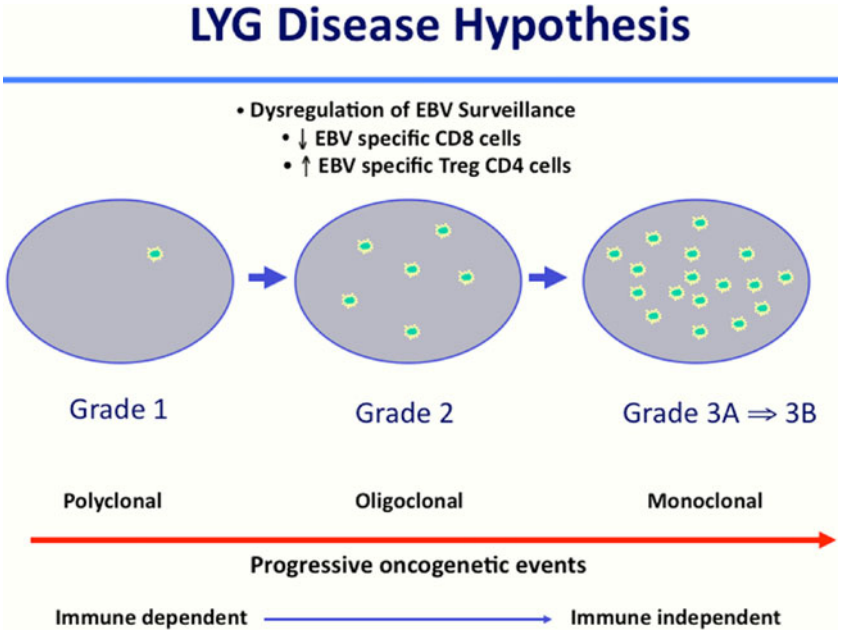

Fig. 1 LYG disease hypothesis. LYG is graded (1, 2, or 3) according to the number of EBV positive B-cells per high power field. We hypothesize that progressive oncogenic events transform lower grade to higher grade disease: grades 1 and 2 are polyclonal or oligoclonal and immune dependent and can be treated with interferon alpha; grade 3 disease is immune independent and is treated with immunochemotherapy

Treatment of BL typically consists of high-intensity, short-duration combination immunochemotherapy regimens and EBV positive BL has not been shown to have a worse outcome and is not approached differently therapeutically. While BL therapy is very effective, toxicity can be problematic especially in older and immunocompromised patients and novel approaches like DA-EPOCH-R have demonstrated excellent efficacy with very low toxicity [18].

EBV Positive Diffuse-Large B-Cell Lymphoma (DLBCL)

While DLBCL in immunocompetent hosts is EBV positive in only 10 % of cases, two distinct types of EBV-associated DLBCL have recently been described and are defined in the current WHO Classification [3]. Firstly, EBV positive DLBCL of the elderly (previously referred to as "senile EBV positive B-cell lymphoproliferative disorder") is an aggressive B-cell neoplasm that occurs in patients with a median age between 70 and 75 years and without overt immunodeficiency [13, 19, 20]. It is commonly associated with elevated LDH, B symptoms, and unusual extranodal sites such as the stomach, lung, skin, and pancreas [20, 21]. EBV likely drives lymphomagenesis in this entity in conjunction with waning immunity that is age related. LMP-1 can be detected in the majority of cases but EBNA-2 is only found in about 25–35 % of cases [19]. Morphologically, it often has varying numbers of giant cells resembling the R-S cells of HL, and there can be diagnostic confusion between this entity and EBV^{+} HL [22]. The clinical course of this disease is aggressive with an inferior outcome compared to EBV negative DLBCL.

The second type of DLBCL associated with EBV is "DLBCL associated with chronic inflammation." This most commonly involves body cavities and is classically associated with pyothorax-associated lymphoma (PAL), which is EBV positive in 70 % of cases [23, 24]. PAL has been most commonly reported in Japan with a striking male predominance of 12.3 to 1 [25]. Patients present with fever, chest/back pain, and cough with a latency period of 10–64 years after the onset of the original inflammatory effusion and are often found to have a very large tumor confined to the thoracic cavity; this tumor mass helps to distinguish PAL from primary effusion lymphoma (PEL). The EBV latency pattern is type III in more than 60 % of cases [3]. DLBCL associated with chronic inflammation is an aggressive lymphoma and also has an inferior outcome compared to EBV negative DLBCL.

EBV in Hodgkin Lymphoma (HL)

Patients with a history of infectious mononucleosis have a 4-fold increase in risk of developing HL and patients with high titers of EBV are at increased risk of developing HL in their lifetime [26, 27]. The malignant cell of HL, the Reed-Sternberg (R-S) cell is EBV positive in 40 % of cases and demonstrates a type II latency pattern [28]. EBV in HL has been reported to negatively affect prognosis, but this observation may be a reflection of its association with certain subtypes and age-related waning immunity. EBV is found in ~75 % of mixed-cellularity cases and in over 95 % of lymphocyte-depleted cases both of which are known to affect older patients and patients who are HIV positive and more commonly present with disseminated disease [29]. EBV is rarely found in nodular-sclerosis HL or lymphocyte-predominant HL which has the best overall prognosis in HL [28]. Detection of EBV DNA in peripheral blood of patients with HL correlates with prognostic factors such as advanced stage, older age, international prognostic score, and CD68+ macrophages and may

serve as a useful biomarker for disease activity in EBV-associated advanced HL [30•, 31]. Therapy for both EBV^+ and EBV^- cases of HL are currently identical and result in long-term remissions in most patients.

EBV in NK/T-Cell Lymphomas

NK- and T-cell lymphomas are also associated with EBV infection in some cases (Table 1). Extranodal NK/T cell lymphoma is a rare condition of NK-cell or cytotoxic T-cell origin that usually affects immunocompetent middle aged men of Asian, Native American or Central/South American descent [32]. It mostly occurs in the nasopharynx and paranasal cavity, but can occur in other sites such as the skin and gastrointestinal tract. Patients with nasal involvement usually present secondary to a mass effect. EBV is associated with virtually all cases of extranodal NK/T cell and exhibits a type II latency pattern [32]. Also, the EBV viral load detected by polymerase chain reaction (PCR) is intimately tied to prognosis, clinical course, and disease relapse [33]. Histologic features include endothelial damage and angioinvasion by medium to large lymphoma cells which are usually positive for CD3 and CD56. There is no consensus on the optimal treatment for extranodal NK/T cell lymphoma but patients with localized disease usually involving the nasal airway should receive therapies that include involved field radiation therapy [34]. Patients with extensive disease typically have a very aggressive clinical course. Many chemotherapy agents are ineffective possibly due to the frequent presence of P-glycoprotein which is associated with the multidrug resistant (MDR) phenotype [34]. L-asparaginase, which is unaffected by MDR status, has recently been shown to have significant activity in combination regimens in relapsed and refractory disease [35].

Angioimmunoblastic T-cell lymphoma (AITL) is a distinct peripheral T-cell lymphoma (PTCL) with a well-characterized association with EBV infection in almost all cases [36]. Curiously, the malignant T-cells are usually negative for EBV and it is the background B-cells that are infected [37]. EBV-positive B-cells typically express a type II latency program with expression of LMP-1 and/or EBNA-2. The median age at diagnosis of AITL is 65 years and it frequently presents with generalized lymphadenopathy in conjunction with features suggestive of an autoimmune disease such as fever, hypereosinophilia, pruritic skin rash, polyclonal hypergammaglobulinemia, arthralgias and circulating immune complexes [38]. Patients also often exhibit some degree of immunodeficiency and are at high risk for infectious complications; a common cause of death. The putative cell of origin in AITL is now recognized to be a $CD4^+$ T-cell of germinal center origin, known as a follicular helper T (T_{FH}) cell [37, 38]. EBV immunoblasts that resemble R-S cells are often found in lymph nodes of patients with AITL early in the disease course, raising the hypothesis that EBV plays a role in T_{FH} cell activation. Reports of expanded monoclonal B-cell clones that give rise to EBV-driven B-cell lymphomas (such as DLBCL) in patients with AITL are not uncommon [37]. Elevated viral load has been associated both with B-cell clonal disorders and higher risk of disease progression [39]. Thus, the exact role of EBV in lymphomagenesis is not completely understood, but it might involve upregulation of the CD28 ligand by EBV^+ B-cells which leads to upregulation and activation of T_{FH} cells and production of chemokines such as CXCL13 [40]. Chronic stimulation of the T_{FH} cells through this mechanism may eventually lead to an antigen-independent clone. The outcome for patients with AITL is disappointing with standard approaches and agents such as cyclosporine and alemtuzumab have demonstrated interesting activity.

EBV-Associated Lymphomas in Immunodeficient Hosts

Patients with congenital, acquired, or iatrogenic defects in cellular immunity are at significantly increased risk for EBV-associated lymphomas and this is especially evident in the post-transplant setting and during the course of HIV infection.

Post-transplantation Lymphoproliferative Disease (PTLD)

PTLDs are defined as a heterogeneous group of lymphoproliferative diseases that occur as a consequence of immunosuppression in the recipient of a solid organ or stem cell allograft and they are associated with EBV infection in 60–70 % of cases [41]. EBV negative cases are more common in adults and tend to occur later than EBV positive cases. The clinical presentation of PTLD varies considerably and involvement is frequently extranodal and includes the transplanted organ itself and sanctuary-sites such as the CNS [41, 42]. Morphologically, PTLDs can be subdivided into monomorphic, polymorphic, plasmacytic, or HL-like variants. They are usually of B-cell origin but 10–15 % of PTLDs are of T/NK-cell origin [43].

The timing of the PTLD varies according to the type of transplant as well as the type, intensity, and duration of immunosuppressive therapy [41]. PTLD is uncommon in kidney transplants, but can be observed in up to 15–20 % of lung transplants. B-cell PTLDs present early with 80 % presenting in the first year and many in the first 6 months whereas PTLDs of T/NK-cell origin are more likely to present late after transplantation [43, 44].

PTLDs develop as a result of EBV-induced transformation of B-cells in the setting of impaired anti-EBV cellular immunity from iatrogenic immunosuppression. Both $CD8^+$ and $CD4^+$ T regulatory cells are required to contain EBV-infected cells and GVHD prevention

strategies that indiscriminately remove T cells from the graft inadvertently increase the risk of PTLD [45]. Thus, risk factors for PTLD after HSCT include the use of a T-cell depleted allograft and use of anti-thymocyte globulin (ATG) or anti-CD3 monoclonal antibody as part of the graft-versus-host disease (GVHD) prevention strategy [46]. Interestingly, agents that deplete both B-cells and T-cells such as the anti-CD52 monoclonal antibody, alemtuzumab, do not appear to increase the risk of PTLD.

Randomized studies that address the optimal management and prevention of PTLDs are lacking and there is much controversy as to how these disorders should be managed. Strategies have been developed to detect EBV reactivation prior to the development of lymphoma such as monitoring PCR viral load and preemptively treating patients with agents like rituximab when EBV DNA levels reach a pre-defined level [47]. Treatment of all PTLDs involves reduction of immunosuppression (RI) to allow for the proliferation of cytotoxic T-cells if feasible, but durable remissions are uncommon with this approach alone and it inherently risks the rejection of the graft. Rituximab alone is not as effective in treating EBV^+ lymphomas as in preventing its occurrence, but can be effective in some patients who fail to respond to RI alone [48]. For patients with aggressive features at diagnosis, combination immunochemotherapy regimens are commonly used with varying success. Response can be achieved in many patients, but treatment related mortality is high due to frequent infectious complications [41, 48]. PTLDs classically display type III latency patterns and immunotherapeutic strategies that generate EBV-specific T-cells have shown promise.

Primary CNS Lymphoma (PCNSL)

Primary CNS lymphoma (PCNSL) is an aggressive B-cell lymphoma that occurs in the intracerebral or intraocular spaces without systemic involvement and is usually morphologically indistinguishable from systemic DLBCL. It once was a major complication after solid organ transplant, but since the routine use of cyclosporine, is rarely encountered in that setting [49]. Increasingly, PCNSL is recognized in patients without a known immunodeficiency, but these tumors are usually not associated with EBV. In patients with a known immunodeficiency such as HIV/AIDS or post-transplantation, the majority of CNS lymphomas are DLBCL, associated with an immunoblastic appearance on histology, and nearly 100 % contain EBV with expression of LMP-1 and EBNA-2 [50]. HIV-related PCNSL tends to be more diffuse and multifocal than in immunocompetent patients and occurs at younger ages [51, 52]. PCNSL does not have a favorable prognosis in any setting, but the presence of HIV may portend an even worse outcome [51]. Treatment is not standardized, but most programs utilize combinations of chemotherapy which include agents that reliably cross the blood-brain barrier such as high-dose methotrexate and cytarabine with or without consolidation with whole brain radiotherapy [52]. The addition of rituximab to chemotherapy regimens is feasible, and may improve survival rates [52].

Primary Effusion Lymphoma (PEL)

Primary effusion lymphoma (PEL) is a large B-cell lymphoma which usually arises in the setting of immunodeficiency such as HIV/AIDS, but not exclusively [53]. It has a strong association with Kaposi sarcoma-associated herpesvirus (KSHV), also known as HHV-8 virus, which is present in virtually every case and EBER is positive in ~70 % of cases [53, 54]. PEL usually presents in body cavities such as the pleura, pericardium, and peritoneum without a corresponding tumor mass. The exact oncogenic role of EBV in the lymphoma is unclear since viral gene expression is limited to EBNA-1 and expression of both LMP-1 and EBNA-2 is absent (latency type I) similar to BL [53]. No effective therapy exists for PEL and patients have a very poor overall prognosis.

Plasmablastic Lymphoma (PBL)

Plasmablastic lymphoma (PBL) is a heterogeneous group of aggressive B-cell lymphomas that arise most often in the setting of immunosuppression such as HIV/AIDS with profoundly low CD4 counts. EBV is variably associated with PBL but nearly 100 % of those in the oral mucosal subtype in HIV/AIDS patients are positive for EBV [55]. Morphologically PBL resembles DLBCL with large immunoblastic cells with a high expression of Ki-67, but the B-cell program is down-regulated and CD45 and CD20 are usually negative. Plasma cell markers such as MUM1, CD38 and CD138 are usually positive and EBER in-situ hybridization may be useful diagnostically [55]. The exact role EBV plays in lymphomagenesis is unclear and LMP-1 and EBNA-2 are rarely expressed (type I latency). MYC rearrangements can be found in up to 50 % of patients with PBL and is more common in cases positive for EBV suggesting a possible mechanism of lymphomagenesis [56]. PBLs tend to be advanced stage at diagnosis and carry a poor prognosis.

Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders

Patients with autoimmune diseases treated with immunosuppressive agents are at an increased risk of developing an EBV-associated lymphoma, particularly DLBCL [57]. Methotrexate (MTX) use in patients with rheumatoid

arthritis (RA) was the first described association, but TNF-α inhibitors used in diseases like RA and inflammatory bowel disease place individuals at increased risk for these lymphomas [58, 59]. The exact etiology of these lymphomas is not entirely clear and may be a direct result of immunosuppression or the ability of these agents to directly stimulate EBV replication. First-line therapy of iatrogenic-induced lymphomas is typically to withdraw the immunosuppressive agent as tumor regressions have been seen with this maneuver [60].

Conclusions and Future Directions

In conclusion, EBV is associated with a wide spectrum of lymphomas and lymphoproliferative disorders and we have gained many interesting insights into their biology in recent years. One of the more uncommon EBV associated disorders is lymphomatoid granulomatosis (LYG) and the outcome for patients with this disease has improved significantly with novel therapies. Overall, though, current standard therapies are ineffective for a large proportion of patients with EBV-related lymphomas and new approaches are needed. In that respect, T-cell therapies such as adoptive cellular immunotherapy have yielded exciting results and may find a defined role in the management of these diseases [61•, 62].

Acknowledgments Supported by the Intramural Research Program of the National Cancer Institute.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Epstein MA, Barr YM. Cultivation in vitro of human lymphoblasts from Burkitt's malignant lymphoma. Lancet. 1964;1(7327):252–3.
2. Cohen JI. Epstein-Barr virus infection. N Engl J Med. 2000;343 (7):481–92.
3. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008.
4. Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. Oncogene. 2003;22(33):5108–21.
5. • Saha A, Robertson ES. Epstein-Barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. Clin Cancer Res. 2011;17(10):3056–63. *This is a well written review that details the pathogenesis and clinical outcome of EBV-associated lymphoproliferative processes*.
6. Roschewski M, Wilson WH. EBV-associated lymphomas in adults. Best Pract Res Clin Haematol. 2012;25(1):75–89.
7. Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES. Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. Blood. 1996;87(11):4531–7.
8. Dunleavy K, Chattopadhyah P, Kawada J, et al. Immune characteristics associated with lymphomatoid granulomatosis and outcome following treatment with interferon-alpha. Blood (ASH Annual Meeting Abstracts). 2010;116:963.
9. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. Canc Surv. 1997;30:233–48.
10. • Patsalides AD, Atac G, Hedge U, et al. Lymphomatoid granulomatosis: abnormalities of the brain at MR imaging. Radiology. 2005;23(1):265–73. *This manuscript describes the appearances of lymphomatoid granulomatosis on neuroimaging from the largest series of these patients*.
11. Bird BH, Grant N, Dunleavy K, et al. Treatment and niology of Lymphomatoid Granulomatosis. *JCO, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Suppl): 8029.*
12. Gulley ML, Raphael M, Lutz CT, Ross DW, Raab-Traub N. Epstein-Barr virus integration in human lymphomas and lymphoid cell lines. Cancer. 1992;70(1):185–91.
13. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. N Engl J Med. 2004;350(13):1328–37.
14. Shimizu N, Tanabe-Tochikura A, Kuroiwa Y, Takada K. Isolation of Epstein-Barr virus (EBV)-negative cell clones from the EBV-positive Burkitt's lymphoma (BL) line Akata: malignant phenotypes of BL cells are dependent on EBV. J Virol. 1994;68(9):6069–73.
15. Komano J, Sugiura M, Takada K. Epstein-Barr virus contributes to the malignant phenotype and to apoptosis resistance in Burkitt's lymphoma cell line Akata. J Virol. 1998;72(11):9150–6.
16. Kamranvar SA, Gruhne B, Szeles A, Masucci MG. Epstein-Barr virus promotes genomic instability in Burkitt's lymphoma. Oncogene. 2007;26(35):5115–23.
17. Kelly GL, Milner AE, Baldwin GS, Bell AI, Rickinson AB. Three restricted forms of Epstein-Barr virus latency counteracting apoptosis in c-myc-expressing Burkitt lymphoma cells. Proc Natl Acad Sci U S A. 2006;103(40):14935–40.
18. Dunleavy K, Pittaluga S, Wayne A, et al. MYC+Aggressive B-cell lymphomas: Novel therapy of untreated Burkitt lymphoma (BL) and MYC+Diffuse Large B-cell lymphoma (DLBCL) with DA-EPOCH-R. Ann Oncol. 2011;22: suppl 4. *Abstract 071.*
19. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+B-cell lymphoproliferative disorders: a clinicopathologic study of 22 patients. Am J Surg Pathol. 2003;27(1):16–26.
20. Shimoyama Y, Oyama T, Asano N, et al. Senile Epstein-Barr virus-associated B-cell lymphoproliferative disorders: a mini review. J Clin Exp Hematop. 2006;46(1):1–4.
21. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. Clin Cancer Res. 2007;13(17):5124–32.
22. Asano N, Yamamoto K, Tamaru J, et al. Age-related Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorders: comparison with EBV-positive classic Hodgkin lymphoma in elderly patients. Blood. 2009;113(12):2629–36.
23. Aozasa K. Pyothorax-associated lymphoma. J Clin Exp Hematop. 2006;46(1):5–10.
24. Fukayama M, Ibuka T, Hayashi Y, Ooba T, Koike M, Mizutani S. Epstein-Barr virus in pyothorax-associated pleural lymphoma. Am J Pathol. 1993;143(4):1044–9.
25. Nakatsuka S, Yao M, Hoshida Y, Yamamoto S, Iuchi K, Aozasa K. Pyothorax-associated lymphoma: a review of 106 cases. J Clin Oncol. 2002;20(20):4255–60.
26. Munoz N, Davidson RJ, Witthoff B, Ericsson JE, De-The G. Infectious mononucleosis and Hodgkin's disease. Int J Cancer. 1978;22(1):10–3.

27. Levine PH, Ablashi DV, Berard CW, Carbone PP, Waggoner DE, Malan L. Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. Cancer. 1971;27(2):416–21.
28. Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. N Engl J Med. 1989;320(8):502–6.
29. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. Clin Cancer Res. 2004;10(3):803–21.
30. • Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med. 2010;362(10):875–85. *In this paper, the authors performed gene expression profiling on cases of Hodgkin lymphoma and identified that a signature of tumor-associated macrophages was associated with a poor outcome*.
31. Hohaus S, Santangelo R, Giachelia M, et al. The viral load of Epstein-Barr virus (EBV) DNA in peripheral blood predicts for biological and clinical characteristics in Hodgkin lymphoma. Clin Cancer Res. 2011;17(9):2885–92.
32. Gualco G, Domeny-Duarte P, Chioato L, Barber G, Natkunam Y, Bacchi CE. Clinicopathologic and molecular features of 122 Brazilian cases of nodal and extranodal NK/T-cell lymphoma, nasal type, with EBV subtyping analysis. Am J Surg Pathol. 2011;35 (8):1195–203.
33. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood. 2009;113(17):3931–7.
34. Jaccard A, Hermine O. Extranodal natural killer/T-cell lymphoma: advances in the management. Curr Opin Oncol. 2011;23(5):429–35.
35. Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood. 2011;117(6):1834–9.
36. Anagnostopoulos I, Hummel M, Finn T, et al. Heterogeneous Epstein-Barr virus infection patterns in peripheral T-cell lymphoma of angioimmunoblastic lymphadenopathy type. Blood. 1992;80(7):1804–12.
37. Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol. 2003;121(5):681–91.
38. Alizadeh AA, Advani RH. Evaluation and management of angioimmunoblastic T-cell lymphoma: a review of current approaches and future strategies. Clin Adv Hematol Oncol. 2008;6(12):899–909.
39. Zhou Y, Attygalle AD, Chuang SS, et al. Angioimmunoblastic T-cell lymphoma: histological progression associates with EBV and HHV6B viral load. Br J Haematol. 2007;138(1):44–53.
40. Dunleavy K, Wilson WH, Jaffe ES. Angioimmunoblastic T cell lymphoma: pathobiological insights and clinical implications. Curr Opin Hematol. 2007;14(4):348–53.
41. Evens AM, Roy R, Sterrenberg D, Moll MZ, Chadburn A, Gordon LI. Post-transplantation lymphoproliferative disorders: diagnosis, prognosis, and current approaches to therapy. Curr Oncol Rep. 2010;12(6):383–94.
42. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. Transplantation. 1999;68 (10):1517–25.
43. Draoua HY, Tsao L, Mancini DM, Addonizio LJ, Bhagat G, Alobeid B. T-cell post-transplantation lymphoproliferative disorders after cardiac transplantation: a single institutional experience. Br J Haematol. 2004;127(4):429–32.
44. Nelson BP, Nalesnik MA, Bahler DW, Locker J, Fung JJ, Swerdlow SH. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? Am J Surg Pathol. 2000;24(3):375–85.
45. Mautner J, Bornkamm GW. The role of virus-specific CD4+ T cells in the control of Epstein-Barr virus infection. Eur J Cell Biol. Mar 31 2011.
46. Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood. 2009;113(20):4992–5001.
47. Peric Z, Cahu X, Chevallier P, et al. Features of Epstein-Barr Virus (EBV) reactivation after reduced intensity conditioning allogeneic hematopoietic stem cell transplantation. Leukemia. 2011;25 (6):932–8.
48. DiNardo CD, Tsai DE. Treatment advances in posttransplant lymphoproliferative disease. Curr Opin Hematol. 2010;17(4):368–74.
49. Ambinder RF. Epstein-Barr virus associated lymphoproliferations in the AIDS setting. Eur J Cancer. 2001;37(10):1209–16.
50. Camilleri-Broet S, Davi F, Feuillard J, et al. High expression of latent membrane protein 1 of Epstein-Barr virus and BCL-2 oncoprotein in acquired immunodeficiency syndrome-related primary brain lymphomas. Blood. 1995;86(2):432–5.
51. Bayraktar S, Bayraktar UD, Ramos JC, Stefanovic A, Lossos IS. Primary CNS lymphoma in HIV positive and negative patients: comparison of clinical characteristics, outcome and prognostic factors. J Neurooncol. 2011;101(2):257–65.
52. Deckert M, Engert A, Bruck W, et al. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. Leukemia. 2011;25(12):1797–807.
53. Fassone L, Bhatia K, Gutierrez M, et al. Molecular profile of Epstein-Barr virus infection in HHV-8-positive primary effusion lymphoma. Leukemia. 2000;14(2):271–7.
54. Nador RG, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood. 1996;88(2):645–56.
55. 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(6):736–47.
56. 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(11):1686–94.
57. Baecklund E, Sundstrom C, Ekbom A, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. Arthritis Rheum. 2003;48(6):1543–50.
58. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007;56(9):2886–95.
59. Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med. 1993;328(18):1317–21.
60. Callan MF. Epstein-Barr virus, arthritis, and the development of lymphoma in arthritis patients. Curr Opin Rheumatol. 2004;16 (4):399–405.
61. • Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. Blood. 2010;115(5):925–35. *In this paper, the authors describe the long-term outcome of 114 patients who received EBV-specific cytotoxic T-lymphocytes to prevent or treat EBV positive lymphoproliferative disease arising after hematopoietic stem cell transplantation*.
62. Bollard CM, Gottschalk S, Leen AM, et al. Complete responses of relapsed lymphoma following genetic modification of tumor-antigen presenting cells and T-lymphocyte transfer. Blood. 2007;110(8):2838–45.