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EBV-associated lymphomas in adults

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Abstract

Epstein-Barr virus (EBV) is a ubiquitous γ-herpes virus that infects most people but results in life-threatening diseases in only a small subset. Persons who are unable to maintain the virus in its latent state can develop uncontrolled EBV-driven lymphoproliferative disorders and lymphomas. EBV-associated lymphomas are well-characterized in patients with known defects in cellular immunity as occurs post-transplantation or HIV/AIDS but are increasingly recognized in patients without overt immunodeficiencies. Improved understanding of the biology of these lymphomas and the role EBV plays in lymphomagenesis offers the opportunity for improved therapies targeted at important signaling pathways and immunotherapy specific against EBV viral antigens.

Keywords

LMP-1; EBNA-1; Epstein-Barr Virus; lymphoma; lymphoproliferative disorders; cytotoxic T-Lymphocyte

I. Introduction

Epstein-Barr virus (EBV) is a ubiquitous γ-herpes virus that infects > 90% of normal adults through contact with oral secretions. After primary infection, the virus remains in an asymptomatic latent state within resting B-cells for the lifetime of the host and cytotoxic T cells (CTLs), both $CD8^+$ and $CD4^+$, and natural killer (NK) cells are primarily responsible for containing the infection.[1] Under circumstances in which the host's cellular immune system fails to control EBV-induced B-cell proliferation, infected carrier B-cells can transform from their latent state into malignant cells. The type and duration of the host's defect in EBV immune surveillance determines the clinical presentation, which is usually

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aggressive. Thus, the term “EBV-associated lymphomas” encompasses a heterogeneous group of aggressive B-cell and NK/T-cell lymphomas which arise in patients with and without overt impairments in cellular immunity. [2] Management of EBV-associated lymphomas involves restoration of the host’s immune response to EBV whenever possible in addition to therapy directed at the malignant cells. Despite improved understanding of the molecular mechanisms that underpin EBV-driven lymphomagenesis, management of these conditions is largely unsatisfactory and novel therapeutic approaches are necessary.

II. Latency patterns of EBV infection

In vitro, EBV can transform B-lymphocytes into cells that proliferate in an unregulated fashion. [3] *In vivo*, EBV preferentially infects B-lymphocytes by binding to the cell surface CD21 receptor and HLA class II molecules as a co-receptor. After primary infection, the EBV episome largely remains in a latent cycle in resting memory B cells in most patients. While perpetually present within the host, EBV has deftly developed strategies to evade the host’s CTLs by altering its pattern of gene expression. The EBV genome normally codes for nearly 100 viral proteins, but EBV-infected resting memory cells evade immune recognition by limiting the gene expression to nine viral latent proteins in varying patterns. The six nuclear antigens EBNAs-1, -2, -3a, -3b, -3c, and -LP are responsible for maintaining the viral genome as well as controlling the expression of three latent membrane proteins: LMP-1, -2a, and -2b. Also expressed are 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 programs are associated with different types of lymphomas. The first pattern of latency (type I) is selective expression of EBNA 1 only which is seen in Burkitt’s lymphoma (BL). A second pattern of latency (type II) is the expression of EBNA-1 along with LMP-1 and LMP-2 and is found in Hodgkin’s lymphoma (HL) and peripheral T-cell lymphoma (PTCL). The third pattern of latency (type III), also known as the “growth program,” is commonly found in post-transplantation lymphoproliferative disorders (PTLD) and is characterized by the expression of all nine latent-cycle EBV antigens (Table 1). The latency pattern determines the susceptibility of the infected cells to immunotherapeutic maneuvers as will be discussed later in greater detail.

III. EBV and lymphomagenesis

EBV was originally discovered in cultured lymphoblasts from Burkitt’s lymphoma patients in 1964. [6] It has been defined as a “carcinogenic agent” by the World Health Organization (WHO) since 1997 and its primary role in lymphomagenesis in immunosuppressed patients (type III latency) is well characterized. However, its oncogenic role in immunocompetent patients is less clear and it may simply be a passenger virus and/or be acting as a co-factor. The latent gene expression program is directly responsible for inducing B-cell transformation through its interactions with the host and utilizes numerous mechanisms to control the activation and differentiation of B-cells, alter cellular gene transcription, and constitutively activate key cell-signaling pathways.

LMP-1 is the main transforming protein of EBV and can act as an oncogene as evidenced by its ability to induce B-cell lymphomas in transgenic mice. [7] It structurally mimics the CD40 ligand and can bind to the CD40 receptor which is normally found on the surface of B-cells. [8] In this way, LMP-1 expression results in ligand-independent constitutive activation of the nuclear factor-κB (NFκB) pathway and provides a growth signal to B-cells. Other signaling pathways that are modulated by LMP-1 include JAK/STAT, extracellular signal regulated kinase (ERK), mitogen activated protein kinase (MAPK), interferon-regulatory factor 4 (IRF4), and Wnt pathways which are essential for B-cell immortalization. [9–12] LMP-1 also can block p53-mediated apoptosis in B-cells by

upregulating the expression of anti-apoptotic proteins such as Bcl-2 and A20 and triggers B-cell proliferation through the stimulation of cytokines such as IL-10. [5, 7] LMP-1 also appears to prevent the plasma cell differentiation of B-cells by downregulating BLIMP1α; this action may contribute to lymphomagenesis by preventing the EBV-infected cell from entering its replicative cycle and being removed by the immune system. [13] In cases where LMP-1 is absent, the loss of A20 may be an alternative mechanism of NFκB pathway activation as has been recently described in a subset of AIDS-related lymphomas. [14]

LMP-2 is not required for B-cell transformation, but plays a role in the persistent infection of B-cells. It maintains the episome and prevents reactivation of EBV from latently infected cells by blocking tyrosine kinase phosphorylation of Lyn and Syk [1, 5]. Its expression allows B-cells to survive independent of B-cell receptor (BCR) signaling. EBNA-1 also does not appear to be directly crucial to lymphomagenesis but is the only antigen expressed in all EBV-associated tumors [15]. It is essential for replication and stable persistence of episomes in EBV-infected proliferating cells through its interactions with viral promoters. It can promote genomic instability in Burkitt's lymphoma cells via induction of oxidative stress and has recently been demonstrated to cause uncapping and shortening of telomeres in lymphoma cell lines [16, 17]. Other lines of evidence suggest that EBNA-1 is necessary for survival of EBV-positive cancer cells possibly by inhibiting apoptosis [5]. EBNA-2 is the first latent antigen detected after primary EBV infection and acts as the master transcription factor to control expression of LMP-1 and LMP-2 [2]. It also controls the expression of other cellular genes, such as CD21, CD23, and c-myc which are important for B-cell activation and growth [1].

IV. EBV-associated B-cell lymphomas in immunocompetent hosts

In some patients without an overt immunodeficiency, primary EBV infection is not contained by the cellular immune system, and an EBV-associated B-cell lymphoma occurs (Table 2). In some, EBV is "driving" the process and, in others, the role of EBV is unknown.

a. EBV in Burkitt's lymphoma (BL)

Burkitt's lymphoma (BL) is a highly aggressive lymphoma associated with MYC overexpression as a result of the translocation between chromosome 8 and one of the immunoglobulin genes on chromosomes 2, 14, and 22. BL can be subdivided into three clinical variants; endemic BL, sporadic BL, and immunodeficiency-associated BL with important differences in epidemiology, clinical presentation, and biology. In endemic BL, which occurs in developing countries such as equatorial Africa and Papa New Guinea, the jaw is a frequent site of involvement and clonal EBV is found in the neoplastic cells in virtually all patients [18]. Contrastingly, EBV is only seen in 20–30% of the sporadic BL cases and 25% of cases of BL occur in the setting of HIV in developed countries with abdominal tumors predominating [3]. Patients with lower socioeconomic status and early EBV infection are more likely to be positive for EBV in sporadic BL.

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 [19, 20]. The main role of EBV in endemic BL may be to protect B-cells that already contain a c-myc translocation from apoptosis and the presence of EBV contributes to telomere dysfunction and genomic instability [16, 21]. Thus, EBV may increase the likelihood of genetic accidents giving rise to the translocation, or by complementing the activity of c-myc. It is also possible that endemic BL is a polymicrobial disease and the chronic immune stimulation provided by

both holoendemic *Plasmodium falciparum* infection and EBV co-operate in lymphomagenesis. EBV viral load is increased in patients with acute malarial infection likely due to viral reactivation driven by malarial antigens. The immunophenotype of BL is that of a germinal center cell ($BCL6^+$, $CD10^+$) and persistent malarial infection could promote the hyperactivation of these germinal centers thereby increasing the risk of somatic hypermutation and c-myc translocations [22].

The therapy of both EBV^+ and EBV^- BL are highly effective and currently do not routinely employ EBV-specific therapy. High-intensity, short-duration combination chemotherapy regimens with/without the anti-CD20 monoclonal antibody, Rituximab, achieve remissions in > 85% of younger patients but at the cost of significant myelosuppressive toxicity [23, 24]. Early results from less intense outpatient regimens such as dose-adjusted EPOCH-R show a 100% complete response rate with much less toxicity but require further validation (Dunleavy Lugano 2011). Thus, the finding of EBV in BL does not have an established effect on prognosis or therapy.

b. EBV positive diffuse-large B-cell lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most common B-cell lymphoid neoplasm and EBV infection is only associated with DLBCL in about 10% of cases among immunocompetent hosts. However, recently described specific clinical situations exist in which subsets of DLBCL cases are frequently associated with EBV infection. Two considered in this section are DLBCL associated with chronic inflammation and the provisional entity, EBV positive DLBCL of the elderly.

DLBCL associated with chronic inflammation most commonly involves body cavities and is classically associated with pyothorax-associated lymphoma (PAL). PAL was first reported in 1987 in patients who were treated for tuberculosis with the induction of an artificial pneumothorax and is EBV positive about 70% of the time [25, 26]. PAL is most commonly reported in Japan with a striking male predominance of 12.3 to 1 [27]. 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 (often > 10cm) confined to the thoracic cavity; this tumor mass helps to distinguish PAL from primary effusion lymphoma (PEL). Other cases of DLBCL occurring in the setting chronic inflammation (such as chronic skin ulcers or osteomyelitis) are also frequently positive for EBV.

PAL cell lines have mutated and crippled IgVH genes and express the immunosuppressive cytokine IL-10 more than cell lines without EBNA-2 [28, 29]. Also, interferon-inducible (IFI) protein 27 is differentially expressed in PAL cell lines compared to bystander cells [25]. The function of IFI27 is not known, but it can be induced in B-cells by the stimulation of interferon. Taken together, these findings suggest that the presence of inflammation itself plays a dual role in PAL with EBV inducing B-cell transformation and escape from cytotoxic T-cells.

EBV positive DLBCL of the elderly is an aggressive B-cell neoplasm that occurs in patients without overt immunodeficiency and usually over the age of 50, although not exclusively [3]. It was first called “senile EBV^+ B-cell lymphoproliferative disorder” and has a median age between 70 and 75 years [30, 31]. This lymphoma is commonly associated with elevated LDH, B symptoms, and unusual extranodal sites such as the stomach, lung, skin, and pancreas [31, 32]. Characterization of this entity in elderly patients in the West described a wider spectrum of conditions including cases with localized extranodal involvement of mucocutaneous ulcers [33].

EBV infection is suspected to drive lymphomagenesis in this entity in conjunction with waning immunity that is part of the aging process. LMP-1 can be detected in the majority of cases but EBNA-2 is only found in about 25–35% of cases [30]. 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. EBV^+ DLBCL of the elderly usually has more R-S cells than HL and is almost always positive for B-cell markers such as CD20 and CD79a on the surface [34]. Since an increasingly recognized number of HL patients can have CD20 expression on their tumor cells, however, expert hematopathologic review is required to differentiate these two entities in many cases.

EBV positivity in subsets of DLBCL has an adverse effect on prognosis but does not currently alter therapy recommendations [35]. The 5 year overall survival of PAL is reportedly only 21.6% with treatment consisting of surgical resection, chemotherapy, and radiotherapy before the advent of Rituximab [27]. Similarly, the prognosis of EBV^+ DLBCL of the elderly is poorer compared to EBV^- DLBCL, but the interplay between patient characteristics and tumor biology need further clarification in the modern era. Since most patients with EBV^+ DLBCL of the elderly will be over the age of 70 and often unable to tolerate aggressive chemotherapy, the development of adoptive immunotherapy with CTLs directed against EBV latency antigens holds intuitive promise.

- EBV^+ subsets of DLBCL do poorly with conventional therapy and should be considered for novel treatment strategies

c. EBV in Hodgkin's 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 serologic studies are at increased risk to develop HL in their lifetime [36, 37]. The malignant cell of HL, the Reed-Sternberg (R-S) cell is EBV positive 40% of the time and demonstrates a type 2 pattern of latency [38]. The pathogenesis of R-S cells show constitutive activity of both the canonical and alternative non-canonical NF-κB signaling pathways, and LMP-1 can activate this pathway through its mimicry of CD40 as previously discussed [39].

EBV in HL has been reported to negatively affect prognosis, but this observation may be a reflection of its association with certain subtypes and waning immunity associated with aging. EBV can be found in ~75% of mixed-cellularity cases and > 95% of lymphocyte-depleted cases both of which are known to affect older patients and more commonly present with disseminated disease [40]. Contrastingly, it is infrequently found in nodular-sclerosis HL and it is almost never seen in lymphocyte-predominant HL which has the best overall prognosis in HL [38]. 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 [41, 42].

Therapy for both EBV^+ and EBV^- cases of HL are currently identical and result in long-term remissions in most patients. In the minority of patients with EBV^+ HL who relapse, however, prognosis is worse and therapies which target the NF-κB signaling pathways or infusion of cytotoxic T-cells specific to EBV might provide novel therapeutic avenues.

- Agents targeting the NF-κB signaling pathways deserve study in EBV^+ cases of relapsed Hodgkin's lymphoma

d. Lymphomatoid granulomatosis (LYG)

Lymphomatoid granulomatosis (LYG) is a rare angiodestructive EBV-driven lymphoproliferative disease comprised of atypical clonal EBV^+ B-cells in an inflammatory background. Patients usually do not have an overt immunodeficiency prior to diagnosis, but evidence of immune dysregulation can be found in many patients and patients with known immunodeficiency are at increased risk [43]. LYG's relationship with lymphoma was uncertain until modern techniques were able to demonstrate the malignant cell to be of B-cell lineage and positive for EBV DNA in most cases [44]. EBV transformation of B-cells and chemokine induction is currently believed to be at the center of all the pathological and clinical features of LYG [45].

Histologically, LYG is comprised of a small number of EBV^+ B-cells admixed with a prominent inflammatory background comprised of T-cells, plasma cells, and histiocytes. The malignant B-cells usually are large in size and express CD20, LMP-1, and EBER by in-situ hybridization. They are variably positive for CD30 and usually negative for CD15. Vascular changes and angiodestruction are distinctive features with intimal thickening of blood vessels and accompanying necrosis in many cases. LYG can be divided into three grades on the basis of the proportion of large atypical EBV^+ B-cells and necrosis. Low grade (Grades I–II) cases have different prognosis and treatment strategies than high-grade (Grade III) lesions which share overlapping features with aggressive lymphomas.

LYG mostly involves extranodal sites with the lung virtually always being involved. Patients present with multiple bilateral pulmonary nodules of varying size in the mid and lower lung fields; often with evidence of central necrosis and/or cavitation. Other common sites of extranodal involvement include the CNS and skin in up to 20% of patients [45]. One striking feature of LYG is that lymph nodes and spleen are almost always spared at initial diagnosis and only involved at late stages of disease. LYG demonstrates a predilection for men in a 2:1 ratio and most commonly presents between the fourth and sixth decades of life, although there is a wide age range to include children [45]. Patients with low-grade lesions may experience occasional spontaneous remissions without therapy, but patients with high-grade LYG usually experience an aggressive disease course with a poor prognosis and should be managed accordingly. The most common cause of death is progressive pulmonary involvement [45].

Therapies that have been utilized with variable success include corticosteroids, chemotherapy or observation, respectively, without demonstrable effects on the natural history of the disease [45]. 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 employed a treatment approach based from the understanding that LYG is an EBV-driven disease. We have tested the efficacy of interferon-a2b (IFN) in grade I-II LYG started at a dose of 7.5 million units subcutaneously 3 times weekly and dose-escalated to best response with treatment duration of up to 1–2 years. In the first 31 patients, most of whom had received prior therapy, 60% achieved a complete remission and 21% patients rapidly progressed on interferon with grade III disease suggesting it was present prior to beginning treatment. At a median follow-up time of 5 years, the progression-free survival of grade I–II LYG was 56% with a median time to remission of 9 months. All patients with grade III disease at diagnosis receive combination dose-adjusted EPOCH-R chemotherapy. In these patients, PFS is 40% with a median follow-up of 28 months and 66% achieved complete remission. At a median of 4 years, the overall survival of all patients with LYG treated with this strategy is 68% (Dunleavy ASH 2010 presentation). Preliminary results suggest that IFN is potentially curative in patients with grade I or II disease, but there remains a high rate of relapse among patients treated with chemotherapy.

- Patients with LYG often have subtle evidence of immune dysregulation and combination chemotherapy may worsen the immune defect

V. EBV-associated T-cell lymphomas in immunocompetent hosts

NK- and T-cell lymphomas are also associated with EBV infection in select cases (Table 3). Individual characterization of two EBV-associated T-cell lymphomas: angioimmunoblastic Tcell lymphoma (AITL) and Extranodal T/NK-cell lymphoma, nasal type will be reviewed.

a. Angioimmunoblastic T-cell lymphoma (AITL)

Angioimmunoblastic T-cell lymphoma (AITL) was first described in the 1970s and was originally known as ‘angioimmunoblastic lymphadenopathy with dysproteinemia’ [46]. It is now characterized as a distinct peripheral T-cell lymphoma (PTCL) with a well-characterized association with EBV infection in almost all cases [47]. Curiously, the malignant T-cells are usually negative for EBV and it is the background B-cells that are infected [48]. EBV-positive B-cells typically express a type II latency program with expression of LMP-1 and/or EBNA-2. AITL is the second most common PTCL in North America and the most common subtype diagnosed in Europe [49]. The median age at diagnosis 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 [50]. Paradoxically, 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[48, 50]. 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 [48]. Elevated viral load has been associated both with B-cell clonal disorders and higher risk of disease progression [51]. 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 [52]. Chronic stimulation of the T_{FH} cells through this mechanism may eventually lead to antigen-independent clone.

The treatment of AITL is not standardized but typical lymphoma chemotherapy regimens results in disappointing outcomes due to frequent relapses and a high incidence of opportunistic infections [48, 50]. Investigators have retrospectively reported their collective experience with cyclosporine which was found to have high initial response rates of 67%, with a median duration of 13 months, but needs confirmation in a controlled fashion [53]. The occurrence of B-cell dysregulation in AITL suggests a possible role for immunotherapy aimed at the EBV positive B-cells such as Rituximab or the anti-CD52 monoclonal antibody, alemtuzumab added to chemotherapy. At this point these therapies should be considered experimental as they have not yet demonstrated a clear effect on the natural history of AITL.

- AITL is a disorder of both B-cell and T-cell clones in many cases. Strategies that target the microenvironment have shown unclear benefit to this point.

b. Extranodal NK/T cell lymphoma, nasal type

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 [54]. As the name implies, it mostly occurs in the upper aerodigestive tract such as the nasopharynx and paranasal cavity, but can occur in other sites as well such as the skin and gastrointestinal tract. Patients with nasal involvement usually present secondary to mass effect and commonly have significant associated facial destruction and tissue necrosis. EBV is associated with virtually all cases of extranodal NK/T cell exhibiting a type II latency pattern with expression of LMP-1 and EBNA-1 but negative for EBNA-2 [54]. In fact, if in-situ hybridization for EBV is negative, one should question the accuracy of diagnosis. Also, the EBV viral load detected by polymerase chain reaction (PCR) is intimately tied to prognosis, clinical course, and disease relapse [55, 56]. Histologic features include endothelial damage and angioinvasion by medium-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 immediately be offered involved field radiation therapy with 50Gy with curative intent [57] Patients with extensive disease, however, usually experience an aggressive clinical course often accompanied by hemophagocytic syndrome. Typical lymphoma chemotherapy programs are not very effective possibly due to the frequent presence of P-glycoprotein which is, in part, associated with the multidrug resistant (MDR) phenotype [57]. L-asparaginase, which is unaffected by MDR status, has recently been shown to have significant activity in combination regimens in relapsed and refractory disease. L-asparaginase combined with methotrexate and dexamethasone was prospectively studied in 18 patients and found to have an overall response rate (ORR) of 78% with 61% complete remission rate [56]. L-asparaginase, methotrexate, dexamethasone, etoposide, and ifosfamide (SMILE) was also recently tested in untreated and relapsed patients and demonstrated an ORR of 74% with a complete remission rate of 38% (Yamaguchi ASCO 2010 abstract #8044). In patients with relapsed disease, stem cell transplantation (either autologous or allogeneic) should be strongly considered; its feasibility has been established in patients who respond to induction therapy and there appears to be a graft-versus-lymphoma effect [58].

VI. EBV-associated lymphomas in immunodeficient hosts

Patients with congenital, acquired, or iatrogenic defects in cellular immunity are at risk for EBV-associated lymphomas (Table 4). AIDS patients have 10–20 times more EBV-infected B-cells as healthy counterparts and the risk of NHL is 60–200 times higher in HIV-positive patients [3]. Since the widespread use of highly active anti-retroviral therapy (HAART), the incidence of AIDS-related lymphomas has decreased and outcomes have improved, but these lymphomas are usually aggressive in nature and a frequent cause of morbidity and mortality in immunodeficient hosts.

a. Post-transplantation lymphoproliferative disease (PTLD)

PTLDs are broadly defined as a heterogeneous group of lymphoproliferative diseases that occur in the setting of acquired immune deficiency after allogeneic transplantation of either solid organs (SOT) or hematopoetic stem cells (HSCT). PTLDs therefore refer to a spectrum

of lymphoproliferative disorders which are associated with EBV reactivation in 60–70% of cases ranging from benign hyperplasia to life-threatening aggressive lymphomas [59]. The clinical presentation of PTLD varies considerably and can be disseminated or localized. Involvement is frequently extranodal and includes the transplanted organ itself and sanctuary-sites such as the CNS [59, 60]. 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 will be identified of T/NK-cell origin [61].

PTLD after SOT occurs between 36–40 months after transplant with a frequency that varies with the type of solid organ graft as well as the type, intensity, and duration of immunosuppressive therapy utilized [59]. PTLD is uncommon in kidney transplants, but can be seen in up to 15–20% of lung transplants which involve transplantation of greater amounts of lymphoid tissue and the malignant cells are typically of host origin. Thus, another major risk factor for development of PTLD is EBV seronegative status of the host who receives an organ from an EBV^+ donor [60]. Regarding cell of origin, 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 [61, 62].

The pathogenesis of PTLDs is 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 indiscriminantly remove T cells from the graft inadvertently increase the risk of PTLD [63]. 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 [64]. 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 largely lacking. Strategies have been developed to detect EBV reactivation prior to the development of lymphoma such as monitoring PCR viral load and preemptively treating with Rituximab when EBV DNA levels reach a pre-defined level [65]. The incidence of EBV reactivation monitored in this fashion can be as high as 15% but, unfortunately, not all PTLDs are heralded by a rise in the viral load [65, 66]. Nonetheless, pre-emptive treatment strategies are becoming increasingly common in the era of reduced intensity condition HSCT given its greater reliance on immunosuppression relative to conventional myeloablative HSCT procedures.

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. Localized disease may respond durably to surgical resection alone. Rituximab alone is not as effective in treating EBV^+ lymphomas as in preventing its occurrence, but can achieve responses in 35–70% of patients who fail to respond to RI alone [67]. For patients with aggressive features at diagnosis, combination chemotherapy regimens such as R-CHOP are commonly used with varying success. Response can be achieved in many patients, but treatment related mortality has been reported as high as 50% due to frequent infectious complications [59, 67]. PTLDs classically display type III latency patterns and immunotherapeutic strategies that generate EBV-specific T-cells have shown tremendous promise and will be discussed in more detail later.

- Randomized trials to address pre-emptive strategies to prevent post-transplantation lymphoproliferative disorders are needed

b. 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 used to be a major complication after SOT, but since the routine use of cyclosporine, is rarely encountered in that setting [68]. 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 [69]. In fact, the finding of EBV DNA in the cerebrospinal fluid is virtually diagnostic of CNS involvement by lymphoma. Additionally, the presence of EBV in systemic HIV-related lymphomas correlates with an increased risk of CNS involvement during the course of the disease [70]. HIV-related PCNSL tends to be more diffuse and multifocal than in immunocompetent patients and occurs at younger ages [71, 72].

PCNSL does not have a favorable prognosis in any setting with 5 year survival rates in the 20–30% range, but the presence of HIV may portend an even worse outcome [71]. 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 [72]. The addition of Rituximab to chemotherapy regimens is feasible, but its effect on outcomes is unproven [72]. HAART is frequently initiated or modified at the time of diagnosis of HIV-associated PCNSL, but the effect of immune reconstitution on lymphoma outcomes is not yet clear and requires prospective investigation [71]. No EBV-specific therapies are typically included in the treatment of patients with HIV-associated PCNSL.

c. 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 [73]. It has a strong association with Kaposi sarcoma-associated herpesvirus (KSHV), formerly known as HHV-8 virus, which is present in virtually every case and EBER is positive in ~70% of cases [73, 74]. PEL usually presents in body cavities such as pleural, pericardial, and peritoneal 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 [73]. The surface B-cell markers CD20 and CD79a are down-regulated in PEL and gene expression profiling of PEL demonstrates features similar to EBV-transformed cell lines and plasmablastic lymphomas [74]. Recent characterization of PEL cell lines by gene expression analysis suggests the loss of tumor suppressor genes WWOX and FHIT might play a role in lymphomagenesis. Less genomic complexity was observed in EBV^+ cell lines as compared to those negative for EBV [75]. No effective therapy exists for PEL and patients have a very poor overall prognosis.

d. Plasmablastic lymphoma (PBL)

Plasmablastic lymphoma (PBL) is a heterogeneous group of very aggressive B-cell lymphomas that arise most often in the setting of immunosuppression such as HIV/AIDS

with profoundly low CD4 counts. PBL was first described in AIDS patients with lesions that arose in the oral cavity and has a strong predilection for the sinonasal cavity, orbit, and other extranodal sites [76]. EBV is variably associated with PBL but nearly 100% of those in the oral mucosal subtype in HIV/AIDS patients are positive for EBV [77]. 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 [77]. 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 [78]. PBLs tend to be advanced stage at diagnosis and carry a poor prognosis compared to other aggressive lymphomas.

> Given the association with profoundly low CD4 counts, institution of HAART should be started at the time of diagnosis in plasmablastic lymphomas.

e. HIV-related Hodgkin's lymphoma (HIV-HL)

HL that occurs in the setting of HIV (HIV-HL) is not considered an AIDS-defining illness but has actually increased in incidence since the widespread use of HAART [79]. It is widespread at presentation, demonstrates aggressive features, and more commonly has associated "B" symptoms than HL in the general population. HIV-HL does not always spread via contiguous nodal regions as is classically seen in HL and up to 50% of patients will exhibit bone marrow involvement [80]. Subtypes such as mixed-cellularity and lymphocyte-depleted classical HL are more common in HIV-HL and the nodular-sclerosing subtype is less common. R-S cells tend to be more concentrated in HIV-HL and clonal EBV episomes can be detected in 80–100% of cases [80]. The oncogene LMP-1 (but not EBNA-2) is virtually always expressed and the CD4/CD8 ratio is typically inverted, but CD40 ligand is rarely expressed [80]. Despite the more aggressive nature of HIV-HL, there is little consensus on optimal therapy and most patients are treated similarly to HL that arises in the general population with ABVD supported by growth factors and anti-infectious prophylaxis [79]. More intense regimens such as BEACOPP are feasible in HIV-HL but carry a greater risk of infection [81]. HAART can be initiated at diagnosis or at the completion of chemotherapy [82].

f. Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Patients with autoimmune diseases treated with immunosuppressive agents are at an elevated risk of developing an EBV-associated lymphoma. The exact incidence is unknown but the most common subtype appears to be DLBCL [83]. The risk of developing lymphoma is not restricted to patients undergoing treatment with immunosuppression agents, however, since these patients have a baseline defect in controlling EBV infection and development of lymphomas [83, 84]. Methotrexate (MTX) use in patients with rheumatoid arthritis (RA) was the first described association, but TNF-α inhibitors used in RA, psoriasis, inflammatory bowel disease, and dermatologic diseases also place individuals at risk for these lymphomas [85, 86]. 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 to withdraw the immunosuppressive agent if possible as spontaneous regression has been seen with this maneuver alone but is less common in cases negative for EBV [84].

VII. Immunotherapeutic approaches to management

As discussed, EBV-associated lymphomas typically arise in patients with congenital or acquired defects in cellular immunity, which allows EBV^+ cells to proliferate in an unregulated fashion. Lymphomas associated with a type III latency program (such as PTLD) express multiple latency proteins making them the most immunogenic and amenable to adoptive immunotherapy strategies. $CD8^+$ HLA-class-I-restricted, EBV-specific T-cells typically target EBNA-3, -4, and -6 and only occasionally LMP-2. EBNA-2 and LMP-1 are only rarely recognized and EBNA-1 is not targeted by cytotoxic $CD8^+$ T-cells [87]. Thus, lymphomas (such as BL) associated with a type I latency program and only express EBNA-1 are not very susceptible to the same immunotherapeutic strategies using $CD8^+$ CTLs.

The first clinical studies testing this strategy were performed by infusing small amounts of donor-derived peripheral blood mononuclear cells (PBMC) to treat EBV-associated lymphomas that developed shortly after a bone marrow allograft [88]. Sustained remissions were achieved in both monoclonal and polyclonal lymphomas in the majority of these patients, but the use of PBMC risks infusing alloreactive T-cells that are not specific for EBV, which could induce or worsen GVHD.

In an effort to avoid inducing GVHD, EBV-specific T-cells were first reported to be effective in the treatment EBV-associated lymphomas after marrow allografts by Rooney et al. in 1995. The T-cell lines were generated from donor-derived T-cells sensitized to EBV-transformed host B-cells and then expanded in vitro for 21–28 days to allow proliferation of the EBV-reactive T-cells and to deplete other alloreactive T-cells [89]. Infusions of EBV-specific T-cells (both $CD4^+$ and $CD8^+$) have since been found to be 100% effective as prophylaxis and 80% effective in the treatment of EBV-associated lymphomas in patients considered high risk for EBV-associated lymphomas after allograft [90]. These adoptively transferred T-cells can be found in the recipients up to 9 years after initial infusion.

- Cellular therapy with infusions of EBV-specific CTLs is a highly effective therapy in preventing and treating EBV-associated lymphomas with a type III latency program
- One drawback to current approaches is the time required to develop CTL cell lines

EBV-associated lymphomas with type 1 latency expression such as BL, however, would not be expected to respond to infusions of CTLs of the CD8 phenotype. BL cell lines are recognized by EBNA1-specific $CD4^+$ CTLs, which offers an attractive therapeutic strategy, but its clinical utility is currently underexplored [91].

LMP-2 is a possible target in lymphomas with a type II latency pattern and has been explored in relapsed HL patients but is only weakly immunogenic [92]. Although viral load responses were observed and some patients achieved remission, the results were not as effective as in the PTLD setting [93]. The same group then modified the antigen-presenting cells (APCs) to augment the expression and immunogenicity of LMP2 which resulted in better clinical responses [94]. Side populations of tumor cells from HL patients that are resistant to chemotherapy do express tumor-associated antigens and can, thus, be targeted by adoptive immunotherapy strategies [95].

VIII. Summary

EBV is associated with a heterogeneous group of lymphomas and occurs in hosts with both overt and subtle defects in the cellular immune system. The exact role that EBV plays in lymphomagenesis remains unclear and likely varies with the clinical scenario and subtype of lymphoma. Treatment of most EBV-associated lymphomas is currently unsatisfactory and therapies with novel mechanisms that target important signaling pathways are needed. Adoptive cellular immunotherapy has been very successful in some circumstances and offers the potential of overcoming cellular resistance to chemotherapy. Well-designed clinical trials constructed to clarify the prognostic impact of EBV positivity in immunocompetent hosts are needed and patients with EBV-associated lymphomas should be enrolled on clinical trials that offer novel therapies whenever possible.

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Table 1

EBV latency programs and associated lymphomas

Program	EBER	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	Lymphoma
Type 1	+	+	−	−	−	−	BL, plasmablastic
Type 2	+	+	−	−	+	+	HL, AITL, Extranodal T/NK cell
Type 3	+	+	+	+	+	+	PTLD, AIDS-related

Table 2

EBV-associated B-cell lymphomas in immunocompetent hosts

Lymphoma	EBV frequency	Latency Program
Burkitt's lymphoma (endemic)	100%	Type 1
Burkitt's lymphoma (sporadic)	20–30%	Type 1
Classical Hodgkin's lymphoma	40%	Type 2
DLBCL associated with chronic inflammation	~70%	Type 2
EBV positive DLBCL of the elderly	100%	Type 2
Lymphomatoid granulomatosis	100%	Type 2

Table 3

EBV-associated T-cell lymphomas in immunocompetent hosts

Lymphoma	EBV frequency	Latency Program
Angioimmunoblastic T-cell lymphoma	>90%	Type 2
Extranodal NK/T-cell lymphoma, nasal type	100%	Type 2
Aggressive NK cell leukemia	>90%	Type 2

Table 4

EBV-associated lymphomas in immunodeficient hosts

Lymphoma	EBV frequency	Latency Program
Post-transplantation LPD, B-cell	>90%	Type 3
Post-transplantation LPD, NK/T-cell	>70%	Type 3
Burkitt's lymphoma (HIV)	25–35%	Type 1
Hodgkin's lymphoma (HIV)	>80%	Type 2
Primary effusion lymphoma	>80%	Type 1
Plasmablastic lymphoma	~70%	Type 1 or Type 2
Plasmablastic lymphoma, oral type (HIV)	100%	Type 1
Primary CNS lymphoma (HIV)	100%	Type 3
NHLs with primary immune disorders	>90%	Type 3
Iatrogenic immunodeficiency lymphoma	40–50%	Type 3