

REVIEW ARTICLE

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Advances in Understanding the Pathogenesis of Epstein-Barr Virus-Associated Lymphoproliferative Disorders

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ABSTRACT

Epstein-Barr virus (EBV) was discovered 50 years ago from an African Burkitt lymphoma cell line. EBV-associated lymphoproliferative disorders (LPDs) are life-threatening diseases, especially in children.

In this article, we review EBV-associated LPDs, especially in the area of primary immunodeficiency disease (PID). We searched PubMed for publications with key words including EBV infection, lymphoma, LPDs and PID, and selected the manuscripts written in English that we judged to be relevant to the topic of this review.

On the basis of the data in the literature, we grouped the EBV-associated LPDs into four categories: nonmalignant disease, malignant disease, acquired immunodeficiency disease and PID. Each category has its own risk factor for LPD development. EBV-associated LPD is a complex disease, creating new challenges for diagnosis and treatment.

Keywords: Epstein-Barr virus; Lymphoproliferative disorder; Primary immunodeficiency disease

INTRODUCTION

The Epstein-Barr virus (EBV), which belongs to the human herpesvirus family, was discovered 50 years ago from an African Burkitt lymphoma cell line. More than 90% of the human population is infected with EBV.¹ Primary EBV infection is usually asymptomatic

in childhood, but it is often associated with a self-limiting infectious mononucleosis (IM) in approximately one-third of cases during adolescence or adulthood.² A vigorous immune response consisting of natural killer (NK) cells and EBV-specific cytotoxic CD8⁺ T lymphocytes controls the primary infection and the periodic reactivation that occurs in all EBV-positive individuals.³ While EBV is often found in a latent mode of infection in B cells, lifelong persistence of EBV in infected individuals involves occasional reactivation to the lytic state, and a partial lytic infection appears to be important in EBV-induced B-

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cell and epithelial tumors.⁴ EBV can infect resting B cells and transform them into lymphoblastoid cell lines.⁵ This property makes it a causative agent for many human cancers, especially for some lymphoproliferative disorders (LPDs) that result from the dysregulated production of lymphocytes. It is clear that impaired immune function, particularly T-cell dysfunction, is more important for the development of mature B-cell lymphoma.⁶ There is a delicate balance between the host immune system and the virus, subjecting the virus to the anti-viral immunity of the host and limiting the production of virus particles.⁷ Disruption of this balance may lead to the development of EBV-associated LPDs, which can be divided into four categories: nonmalignant disease, malignant disease, acquired immunodeficiency disease and primary immunodeficiency diseases (PIDs) (Table 1).⁸ In this article, we describe some new findings regarding the predisposition of LPDs to uncontrolled EBV infection, and we focus on the EBV-LPDs in PIDs.

EBV-Associated Nonmalignant Disease

EBV was first associated with IM in 1968, and further epidemiological studies confirmed that EBV was a causative agent of IM.¹ IM typically occurs in primary EBV-infected adolescents and young adults, who present with fever, pharyngitis, cervical lymphadenopathy, hepatitis and other inflammatory symptoms. However, primary EBV infection mainly occurs during early childhood and IM is common among children in Japan.⁹ IM usually follows an uneventful course with full recovery. Complications of IM include autoimmune hemolytic anemia, hemophagocytic syndrome, thrombocytopenia, splenic rupture and neurologic manifestations.¹⁰ Some patients with IM were reported to have atypical manifestations and mimic EBV-associated T-cell LPDs.^{11,12} These findings confuse the proper diagnosis of IM and T-cell lymphoma.

EBV-Associated Malignant Disease

Burkitt lymphoma (BL) was first described in equatorial African children in 1958. It is a highly proliferative B-cell tumor with three subtypes, which have been described as endemic, sporadic and immunodeficiency-associated BL.¹³ EBV is the most important trigger and has been detected in virtually all cases of endemic BL. However, EBV is considered less important in both sporadic and

Table 1. Epstein-Barr virus-associated diseases

Nonmalignant diseases

Infectious mononucleosis
Oral hairy leukoplakia

Malignant diseases

Burkitt lymphoma
Hodgkin lymphoma
Diffuse large B-cell lymphoma
Extranodal NK/T-cell lymphoma
Opportunistic lymphoma
Pyothorax-associated lymphoma
Virus-associated hemophagocytic syndrome
Leiomyosarcoma
Follicular dendritic cell sarcoma
Lymphoepithelioma-like carcinoma
Breast carcinoma
Hepatocellular carcinoma
Nonglandular nasopharyngeal carcinoma
Gastric cancer
Salivary gland carcinoma
Angioimmunoblastic T-cell lymphoma
Senile EBV-associated B-cell lymphoproliferative disorders
Chronic active EBV infection

Acquired immunodeficiency diseases

HIV-associated lymphomas
Post-transplantation lymphoproliferative disorder
Lymphomatoid granulomatosis
Methotrexate-associated lymphoma

Primary immunodeficiency diseases

Severe combined immunodeficiency
Wiskott-Aldrich syndrome
X-linked lymphoproliferative syndrome
ITK deficiency
CD27 deficiency
MAGT1 deficiency
STK4 deficiency
Coronin-1A deficiency
XMEN disease

immunodeficiency-associated BL because it is detected in up to 20% and 30-40% of cases, respectively.¹³

EBV is found to be necessary but not sufficient to cause endemic BL, and the coincidence of malarial infection preceding endemic BL supports a temporal interaction with EBV.¹⁴ Hodgkin lymphoma (HL) is a distinct disorder in which the characteristic neoplastic

cells, known as Hodgkin's Reed-Sternberg cells, are interspersed in an inflammatory milieu and only constitute approximately 2% of the total tumor mass.² Not all subtypes of HL harbor EBV to the same degree, and there are data suggesting that the incidence of EBV-positive HL is age-related.¹⁵ EBV is more commonly associated with classic HL, especially the mixed-cellularity subtype.¹⁶ The nonclassic nodular lymphocyte-predominant HL cases are very rarely associated with EBV.¹⁶

Diffuse large B-cell lymphoma (DLBCL) is a morphologically heterogeneous group of non-Hodgkin lymphomas (NHLs) characterized by diffuse proliferation of large neoplastic lymphoid cells with a B-cell phenotype.¹⁷ DLBCL is the most common lymphoma, and comprises 30-40% of adult NHLs. EBV-positive DLBCL was reported to have an incidence of 9-15% among Asians or Latin Americans, and the incidence was found to be <5% in Western populations.¹⁷ EBV-positive DLBCL of the elderly is also known as age-related EBV-positive B-cell LPDs without a predisposing immunodeficiency. These patients tend to be older than 60 years of age, although younger patients have also been reported.¹⁸ EBV-positive DLBCL of the elderly shows a type II or III pattern of EBV latency. Its prognosis is inferior to that of age-matched DLBCL without EBV infection.¹⁹

Chronic active EBV infection (CAEBV) is characterized by persistent or recurrent IM-like symptoms for more than three months, increased EBV genome levels, and no underlying identifiable immunological abnormalities.²⁰ EBV-infected cells often induce oligoclonal lymphoproliferation of T- and NK-cells, but rarely of B-cells, eventually leading to the selective growth of T- or NK-cell lymphoma during the clinical course of CAEBV.²¹ Extranodal NK/T-cell lymphoma of nasal type and aggressive NK-cell leukemia/lymphoma patients 50 years old or younger showed clinicopathologic features similar to those of monoclonal CAEBV-associated NK-cell LPD patients.²² Moreover, a severe form of CAEBV, characterized by the clonal expansion of EBV-infected T or NK cells, was found to be prevalent in East Asian countries.²³

The EBV genomes are found with variable frequencies among EBV-associated malignant diseases, and cross-talk between EBV-positive malignant cells and their reactive neighboring cells would provide proliferative and anti-apoptotic signals, leading to

tumor cell survival and expansion.

EBV-Associated Acquired Immunodeficiency Disease

Human immunodeficiency virus (HIV)-associated lymphomas occur in patients with HIV infection. These lymphomas have a much higher probability (60- to 165-fold greater) of developing diffuse aggressive NHL and HL than that in the general population, and the affected patients frequently present with DLBCL.²⁴ EBV is present in approximately 30% of HIV-positive DLBCLs. One or more latent EBV proteins are expressed in these lymphomas, contributing to variable mechanisms of transformation and molecular heterogeneity.²⁵ EBV was associated with HIV-associated lymphomas not only in DLBCL, but also in primary central nervous system (CNS) lymphoma, plasmablastic lymphoma and other types of lymphoma. The prevalence (21.7%) of CNS involvement in patients with HIV-associated lymphomas is considerably higher than that of non-HIV lymphoma patients (2-7%), and EBV is found in almost all CNS lymphomas.²⁶ It should be noted that in the absence of a clinical suspicion of toxoplasmosis, the detection of EBV DNA in the cerebrospinal fluid (CSF) is a well-established diagnostic tool for identifying primary CNS lymphoma in HIV-infected individuals.²⁷ Plasmablastic lymphoma was originally described as a CD20⁻ CD138⁺ tumor arising almost exclusively in the setting of HIV. This lymphoma lacks CD20 expression and cannot be classified as a large B-cell lymphoma.²⁸ HIV itself is not known to be oncogenic, but components of its genome have been found to be incorporated into chromosome 15 in some cases of T-cell lymphomas.²⁹

Post-transplantation lymphoproliferative disorder (PTLD) is a group of lymphoid hyperplasias and neoplasias that occur in the context of post-hematopoietic stem cell and post-solid tumor transplantation and immunosuppression. In addition to EBV seropositivity, immunosuppression is a well-known risk factor for the development of LPD. The best characterized immunosuppression-related LPDs are those seen in PTLD. PTLD can be generally divided into two groups: a B-cell type and an NK/T-cell type. It has been reported that 80% of B cell PTLD cases arise in the immediate post-transplantation period from EBV-infected lymphocytes and may have a good prognosis following cessation of immune suppression, whereas only 10 to 15% of NK/T-cell PTLDs are

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associated with EBV infection.³⁰ The pathogenesis of PTLTD is a result of EBV-induced transformation of B cells in the setting of impaired anti-EBV cellular immunity from iatrogenic immunosuppression. Patients aged <10 (and >60) years had a higher risk of PTLTD, and this may be related to the decreased immune surveillance of EBV-infected cells.³¹ The risk of PTLTD is increased when an EBV-negative recipient receives a transplant from an EBV-positive donor.^{32,33}

Lymphomatoid granulomatosis is a very rare EBV-associated B cell LPD. The most common site of involvement is the lung, with less frequent involvement of other extranodal sites including the skin, kidney, liver, and CNS.³⁴ Most cases involving the lung represent a proliferation of EBV-infected B cells with a prominent T-cell reaction and vasculitis. Lymphomatoid granulomatosis is present in a considerable number of immunosuppressed patients and the presumed latency III pattern of EBV expression leads us to hypothesize that the role of EBV in the pathogenesis of lymphomatoid granulomatosis is similar to that seen in PTLTD, where EBV is believed to play a role in the transformation of EBV-infected B-cells in the absence of adequate T-cell surveillance.³⁵

Methotrexate-associated lymphoma occurs in immunosuppressive states due to the use of methotrexate. EBV reactivation is observed in half of such cases, suggesting that EBV contributes to the pathogenesis. The risk of NHL was not significantly increased in patients treated with methotrexate, but their incidence of HL appeared to be higher.³⁶ Approximately 60% of reported cases have shown at least partial regression in response to methotrexate withdrawal.³⁷

Immunosuppressive therapy (IST), such as antithymocyte globulin, is widely used for the treatment of aplastic anemia. However, the occurrence of EBV-LPD without stem cell transplantation has been documented in patients with IST for aplastic anemia.³⁸ As described above, EBV-LPD in acquired immunodeficiency diseases varied. Thus, treatment strategies ranged from restoration of normal cellular immunity to anti-B cell monoclonal antibodies, conventional chemotherapy and radiation.

EBV-Associated Primary Immunodeficiency Disease

The incidence of LPD in PID has been found to range from 0.7 to 15%, depending on the type of

disease.³⁹ Accurate quantification of the risk may be difficult because PID is rare, and the incidence of lymphoma is low, leading to a reliance on small case series for estimates. Some types of PID are well known for developing EBV-associated LPDs as their main feature. These PIDs mainly consist of defects related to lymphocyte cytotoxic pathways or T-cell dysfunctions.⁴⁰ The clinical features of these diseases vary, but they do share some common features, including a predisposition to EBV-positive lymphoma.

Severe combined immunodeficiency (SCID) is caused by different genetic defects that produce variable NK-, T- and B-cell abnormalities. The incidence of developing cancer is 1.5% before the age of one year, and mainly NHL, HL and leukemia occur.⁴¹ SCID patients can develop delayed but lethal B-cell LPD after EBV infection, and the LPD appears to resemble those arising in immunosuppressed patients, such as solid organ transplant recipients.^{42, 43} In contrast, Touzot et al.⁴⁴ reported a SCID patient with massive expansion of maternal T cells in response to EBV infection. LPDs in SCID are almost exclusively limited to childhood, and half of the lymphomas appear in children younger than 10 years of age.⁴⁵

Wiskott–Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by thrombocytopenia with small platelets, eczema, recurrent infections, autoimmune disorders, IgA nephropathy and an increased incidence of hematopoietic malignancies.⁴⁶ WAS patients have an approximately 100-fold greater risk for developing lymphomas.⁴⁷ NHL constitutes more than 60% of tumors, and leukemia, HL and BL are also observed in individuals affected with WAS.⁴⁸ EBV infection is not rare in WAS patients, and EBV infection of B cells in patients often leads to B-cell lymphoma, suggesting a direct relationship with a defective immune system.⁴⁹ B-cell lymphoma responds dramatically to treatment with specific anti-CD20 immunotherapies, such as rituximab, and can remain in remission for a long time.⁴⁹

X-linked lymphoproliferative disease (XLP) is an X-linked immunodeficiency syndrome resulting from loss-of-function mutations in *SH2D1A* (XLP-1) and *XIAP/BIRC4* (XLP-2). *SH2D1A* encodes the SLAM-associated protein (SAP) expressed in T and NK cells, but not in B cells, and SAP is defective or absent in patients with XLP-1.⁵⁰ *XIAP/BIRC4* mutation influences XIAP protein, a well-characterized member of the IAP family, and leads to XLP-2.⁵⁰ The

predominant EBV target cells in XLP-related EBV-HLH are CD19⁺ B cells, whereas EBV-infected cells are CD8⁺ T cells in sporadic EBV-HLH.⁵¹ Following infection with EBV, patients with XLP mount a vigorous, uncontrolled polyclonal expansion of T and B cells. However, LPDs have been described only in XLP-1. Some studies have demonstrated that XIAP protein is a potent target for the treatment of cancer on the basis of the anti-apoptotic function of XIAP.⁵² Therefore, it seems that the absence of XIAP protects patients from cancer, explaining why XLP-2 patients do not develop LPDs. LPDs in XLP-1 patients are mainly NHLs of B-cell origin, especially BL, although cases of T-cell NHL and HL have been described.⁵² Twenty-two percent of all lymphomas in XLP-1 patients occurred without evidence of prior EBV exposure, which demonstrates that LPDs can develop in XLP-1 patients even without previous EBV infection.⁵⁴

IL-2-inducible T-cell kinase (ITK) deficiency is associated with fatal EBV-associated LPD in girls as well as in boys, with a clinical picture similar to that seen in XLP. ITK is a member of the Tec kinase family. These proteins are important mediators of antigen receptor signaling in lymphocytes, and ITK is believed to be the predominant Tec kinase in T cells and one of the key molecules involved in invariant NKT (iNKT) cell maturation and survival.⁵⁵ Therefore, ITK deficiency is characterized by deficient iNKT cells as well as XLP-1. EBV-associated HL and BL have been frequently associated with ITK deficiency.^{55,56} Pulmonary involvement with large interstitial nodules was observed in the majority of patients. An ITK-deficient patient with polyclonal proliferation of small B cells in the lungs was not suggestive of any malignant lymphoma.⁵⁷ Treatment with rituximab resulted in complete clinical remission with resolution of the pulmonary lesions and a negative EBV titer in serum, indicating the efficacy of rituximab as a treatment for ITK deficiency. All ITK-deficient patients are EBV-seropositive.

CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia.^{58,59} CD27 plays a role in anti-viral responses, anti-tumor immunity and alloreactivity.⁶⁰ T-cell-dependent B-cell responses were abnormal while anti-polysaccharide antibodies were detectable.⁵⁹ Moreover, CD27^{-/-} mice show impaired primary and memory CD4⁺ and CD8⁺ T-cell responses.⁶¹ Although EBV-

specific immunity involves virus-specific humoral components, CD8⁺ effector T cells are considered essential for long-term virus control. EBV infection is supposed to be the trigger of this disease, and an EBV-seronegative, CD27-deficient individual has not yet been identified. EBV-LPDs were found in two patients with CD27 deficiency. Both patients responded immediately to rituximab treatment, but EBV viremia recurred soon after.⁵⁸

STK4 deficiency causes a primary immunodeficiency syndrome affecting T cells, B cells and possibly neutrophils.⁶² STK4 (also named MST1) was originally identified as a ubiquitously expressed kinase with structural homology to yeast Ste20.⁶³ In humans, STK4 expression was highest in naive T cells, suggesting that it plays a role in a T-cell subset.⁶⁴ STK4-deficient patients had CD4⁺ T lymphopenia and markedly reduced naive T-cell counts. In contrast to normal T cells, STK4-deficient T cells showed a persistently high rate of apoptosis not only in CD4⁺ but also in CD8⁺ T-cells.⁶⁴ These findings suggest that STK4 is essential for T-cell survival and could play a role in cell cycle progression and T-cell proliferation.⁶⁴ Despite the peripheral B-cell lymphopenia, all patients had hypergammaglobulinemia, and had measurable levels of autoantibodies, possibly because of unrestricted plasma cell expansion.⁶² Persistent EBV viremia and EBV-associated B-cell LPD were noted in 50% of reported cases.^{62,64} It remains unclear whether unrestricted B-cell expansion by EBV infection is the result of defective T-cell responses or intrinsic mechanisms in STK4-deficient B-cells.

Coronin-1A deficiency associated with a hypomorphic *Coronin-1A* mutation is a primary immunodeficiency with increased susceptibility to EBV-induced lymphoproliferation in patients.⁶⁵ *Coronin-1A* is essential for the development of a normal peripheral T-cell compartment and plays a key role in T-cell receptor-signaling and T-cell homeostasis.⁶⁶ Immunological assessment revealed reduced numbers of naïve CD4⁺ and CD8⁺ T cells as well as iNKT cells. EBV infection was common in this disease, and three in four reported patients showed evidence of EBV infection.^{65,67} All three EBV-seropositive patients showed an early onset of EBV-associated B-cell LPD. The relationship between EBV and LPD in Coronin-1A deficiency requires further investigation.

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Table 2. Epstein-Barr virus incidence in different primary immunodeficiency diseases-associated lymphoproliferative disorders

Disease	Associated features	Causative gene	Immune defects	Relationship with LPD
SCID	Severe, recurrent infections, chronic diarrhea, ear infections, recurrent fungal infection	Some T-cell-associated genes	Modestly decreased T cells; modestly or normal B cells and decreased serum immunoglobulin	Lethal B-cell LPD with EBV infection ⁴²
WAS	Thrombocytopenia with small platelets, eczema	WAS	Progressively decreased T-cells; abnormal lymphocyte responses to anti-CD3; decreased IgM and often increased IgA and IgE	Mostly NHL; leukemia, HL and BL are also observed. EBV-associated LPD was only seen in B-cell lymphoma ⁴⁶⁻⁴⁸
XLP-1	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis and aplastic anemia	SH2D1A	Normal or decreased B cells	Fulminant IM, B-cell NHL, especially BL. 22% lymphoma in XLP that can be without EBV infection ^{53, 54}
ITK deficiency	EBV-associated lymphoproliferation	ITK	Modestly decreased iNKT cells; normal B cells; normal or decreased serum immunoglobulin	EBV-associated LPDs, mostly HL and BL ⁵⁵⁻⁵⁷
CD27 deficiency	Combined immunodeficiency and persistent symptomatic EBV viremia	CD27	Undetectable CD27 ⁺ lymphocytes and decreased iNKT cells	EBV-associated LPDs ^{58, 59}
STK4 deficiency	Recurrent bacterial infections, viral infections, mucocutaneous candidiasis, cutaneous warts, and skin abscesses	STK4	T- and B-cell lymphopenia; markedly reduced naive T-cell counts and T cells showed a persistently high rate of apoptosis; hypergammaglobulinemia	50% of patients present with EBV-associated B-cell LPDs ^{62, 64}
Coronin-1A deficiency	Recurrent respiratory infection, EBV infection	Coronin-1A	markedly decreased naive CD4 ⁺ T cells, CD8 ⁺ T cells and iNKT cells	EBV-associated B-cell LPDs ⁶⁵
XMEN disease	Recurrent viral infection	MAGT1	Low CD4 ⁺ T-cell counts and inverted CD4/CD8 ratio	EBV-associated B-cell LPDs ^{68, 69}

SCID: severe combined immunodeficiency, LPD: lymphoproliferative disorder, EBV: Epstein-Barr virus, WAS: Wiskott-Aldrich syndrome, NHL: non-Hodgkin lymphoma, HL: Hodgkin lymphoma, BL: Burkitt lymphoma, XLP: X-linked lymphoproliferative syndrome, IM: infectious mononucleosis, iNKT: invariant natural killer T

XMEN disease, an X-linked immunodeficiency with a magnesium defect, EBV infection and neoplasia, is characterized by loss-of-function mutations in the gene encoding magnesium transporter 1 (*MAGT1*), persistently high levels of EBV with increased EBV-infected B cells and heightened susceptibility to EBV-

associated lymphomas.⁶⁸ *MAGT1* plays an essential role in the free intracellular magnesium influx involved in the control of EBV by T and NK cells.⁶⁹ Patients with XMEN disease exhibited low CD4⁺ T-cell counts, leading to an inverted CD4/CD8 ratio. T cells from XMEN patients exhibited defective induction of several

activation markers, such as CD69, CD25, Fas (CD95) and CTLA-4, in response to TCR stimulation.⁶⁹ Remarkably, many of the patients did not seek medical attention until they developed EBV-associated malignancies, sometimes as old as the age of 45 years.⁶⁸ EBV-associated LPD in PID are listed in Table 2. EBV is a unique herpesvirus that infects only humans and primates. There is no mouse model of EBV-LPDs. Therefore, we are required to study human immunology, hematology and oncology in patients with EBV-associated LPDs.

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