Epstein-Barr virus-positive T/NK-cell lymphoproliferative diseases in children and adolescents

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ABSTRACT

In primary Epstein-Barr virus (EBV) infection, the virus may infect T-cells or natural killer (NK)-cells and can cause T- and NK-cell (T/NK-cell) lymphoproliferative disease, which encompasses several disease entities with a broad clinicopathological spectrum. T/NK-cell lymphoproliferative disease arising during primary EBV infection includes clonal EBV-infected T-cell proliferation in the setting of infectious mononucleosis, EBV-associated hemophagocytic lymphohistiocytosis, and systemic T-cell lymphoma of childhood. Chronic active EBV (CAEBV) infection of the T/NK-cell type is not a simple viral infection but instead is classified as a lymphoproliferative disease. The prototype of CAEBV is a systemic form that exhibits varying degrees of clinical severity depending on the host immunity and EBV factor. Hydroa vacciniforme-like lymphoproliferative disease and mosquito-bite allergy are peculiar cutaneous forms of CAEBV that involve T/ NK-cells, respectively. Abnormal activation and replication of EBV together with the proliferation and clonal expansion of infected cells, depending on the patient's immunological response, play a key role in the pathogenesis of CAEBV of the T/NK-cells type.

Keywords: Herpesvirus 4, human; Killer cells, natural; Lymphoproliferative disease; T cell

INTRODUCTION

The Epstein-Barr virus (EBV), also called human herpesvirus 4, is one of eight known human herpesvirus types in the herpes family. EBV infects 90% of humans. The primary infection is usually asymptomatic. However, in about 50% of infected young adolescents, the primary infection elicits acute infectious mononucleosis (IM), which is characterized by the polyclonal expansion of EBV-infected B-cells and a cytotoxic T-cell response [1].

Although B-cells are the major target of EBV infection, EBV can infect T-cells and natural killer (NK) cells (T/NK-cells) via acquisition of the EBV receptor, CD21, on a population of T- or NK-cells through the immunologic synapse between cytotoxic cells and EBV-infected B-cells [2,3]. This can in turn cause T/NK-cell lymphoproliferative disease (LPD) of varying severity, depending on the host's immunity and viral factors (Table 1). Acute EBV-associated hemophagocytic

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Table 1. Spectrum of EBV-associated T/NK-cell LPD in children and adolescents

Infectious mononucleosis with extensive T-cell proliferation
EBV-associated hemophagocytic lymphohistiocytosis
Systemic T-cell lymphoma of childhood
Chronic active EBV infection of the T/NK-cell type
CAEBV-T/NK, systemic
Hydroa vacciniforme-like LPD
Severe mosquito-bite allergy

EBV, Epstein-Barr virus; NK, natural killer; LPD, lymphoproliferative disease; CAEBV, chronic active EBV.

lymphohistiocytosis (EBV-HLH) and systemic T-cell lymphoma of childhood can complicate primary EBV infection, and their clinicopathological and laboratory findings exhibit profound overlap.

Chronic active EBV infection (CAEBV), systemic form, hydroa vacciniforme (HV)-like LPD (HV-LPD), and severe mosquito-bite allergy are peculiar forms of EBV-associated systemic or cutaneous T/NK-cell LPD. These diseases have various clinical findings that range from indolent to aggressive, and they induce varying degrees of cellular transformation. LPDs induced by T/NK-cell infection by EBV have been reported mainly from East Asia, including Japan, Korea, Taiwan, and China, and from Latin America, but are uncommon in Western countries. Environmental factors, which affect the age at the first EBV infection, and genetic factors, which control the immune response to EBV infection, underlie the susceptibility to the development of EBV-positive T/NK-cell LPD in young children and adolescents [4-7]. This review describes the clinical, laboratory, and pathological findings of T/NK-cell LPD associated with primary EBV infection

T-CELL PROLIFERATION IN INFECTIOUS MONONUCLEOSIS

IM is diagnosed primarily according to the symptoms and can be confirmed through a blood test for specific antibodies that indicate primary EBV infection. Clinically, IM is characterized by fatigue, fever, pharyngitis, and lymphadenopathy. Virus-associated hemophagocytic syndrome is an unusual complication that occurs in the first 2 weeks of illness. IM is characterized by the polyclonal expansion of infected B-cells and the elicited cytotoxic T-cell response [1]. Most of the symptoms of IM are caused by the proliferation of T-cells activated in response to EBV-infected B-cells. Lymphocytosis occurs during the first week, reaches a peak in the second or third week of the illness, and affects 50% to 70% of the circu-

lating white blood cells. These proliferating T-cells are usually polyclonal, although oligoclonal or monoclonal expansion of activated CD8 cells can occur during acute IM.

Because of the severe tonsillar hypertrophy with neck lymph node enlargement, the tonsils are often the first organ sampled for pathological examination to exclude malignant lymphoma. Microscopically, the architecture of the tonsils is destroyed completely with diffuse infiltration of heterogeneous small and large lymphocytes, immunoblasts, histiocytes, and variable numbers of plasma cells and eosinophils. The loss of normal architecture with massive infiltration of large B immunoblasts can be misdiagnosed as diffuse large B-cell lymphoma. Exuberant proliferation of large CD8⁺ T-cells with atypia may be misdiagnosed as peripheral T-cell lymphoma, not otherwise specified. Because infiltrating reactive T-cells can be oligoclonal or monoclonal in IM, T-cell clonality should be interpreted with caution. EBV *in situ* hybridization reveals infiltration of varying numbers of EBV-positive cells. In IM, EBV is usually positive in B-cells even in patients with exuberant T-cell proliferation that mimics T-cell lymphoma [8,9]. Determination of the cell lineage of EBV-infected cells by the double procedure of EBV-encoded RNA (EBER) *in situ* hybridization and immunostaining using cell lineage markers is helpful for the differential diagnosis. CD3 and CD79a are good markers for the double procedure, but CD20 is not recommended because the stain fades during the double procedure.

However, there are rare reports showing that EBV infects T-cells during the primary infection and can cause severe clinical symptoms and a fatal outcome [10]. Such cases have been reported using the terms fulminant EBV-positive T-cell lymphoma, fulminant IM, fatal EBV-positive hemophagocytic syndrome, or fatal HLH depending on the dominant clinical and pathological findings. According to the 2017 revised World Health Organization (WHO) classification, these cases can be diagnosed as systemic T-cell lymphoma of childhood in the presence of T-cell clonality. Although most of these cases involving EBV infection of T-cells have a dismal outcome, there is rare case report showing complete clinical recovery after prolonged symptom duration [11].

ACUTE EBV-ASSOCIATED HLH

In primary EBV infection, EBV infection of CD8⁺ T-cells may elicit a cytokine storm, which involves the release of proinflammatory and Th1-type cytokines including tumor necrosis factor α and interferon γ , and leads to secondary activation of histiocytes and macrophages. EBV-HLH is a hyperin-

flammatory syndrome that is characterized by a markedly dysregulated immune response and hypercytokinemia [12]. It accounts for about 40% of all cases of HLH and is the most common type of secondary HLH [13,14]. The diagnosis is established when EBV is documented in the blood or tissue and the HLH-2004 guideline criteria are fulfilled [15,16]. EBV-HLH can occur in association with underlying diseases such as primary HLH, T/NK-cell lymphoma/leukemia, CAEBV infection, or systemic T-cell lymphoma of childhood. However, HLH in children is usually encountered in the context of primary EBV infection without underlying disease.

Pathologically, the bone marrow, especially an aspirate smear, shows hemophagocytic histiocytes in addition to myeloid and erythroid hypoplasia. The liver biopsy shows Kupffer-cell hyperplasia, mild infiltration of small T-cells in the portal tract and sinusoids, and intrasinusoidal infiltration of hemophagocytic histiocytes. EBER *in situ* hybridization indicates EBER-positive cells in the bone marrow and hepatic sinusoids. EB viral monoclonality is detected in more than 80% of patients with acute HLH. T-cell receptor gene rearrangement is detected in 33% to 100% of patients and a cytogenetic abnormality in 30%. The presence of T-cell or EBV clonality is not considered neoplastic. Clonal cytogenetic abnormalities suggest neoplastic transformation of EBV-HLH and may lead to the diagnosis of system T-cell lymphoma of childhood. After the diagnosis of EBV-HLH, underlying diseases associated with EBV-HLH should be excluded. Primary HLH can be excluded by genetic testing and family history. T/NK-cell leukemia/lymphomas show obvious atypia of infiltrating EBV-positive cells. EBV-positive cells in CAEBV infection are deceptively benign. A long clinical history compatible with chronic EBV infection is helpful in the differential diagnosis [17,18].

EBV-HLH in children without underlying disease can be controlled effectively in more than 90% of patients. However, the remaining 10% of patients often die of fulminant disease. Patients with both hyperbilirubinemia and hyperferritinemia at the time of diagnosis have significantly poorer outcomes. The presence of clonality at the time of diagnosis is not associated with a poor outcome, but a change in clonality may be a good marker of disease activity in childhood EBV-HLH [19,20].

SYSTEMIC T-CELL LYMPHOMA OF CHILDHOOD

Systemic T-cell lymphoma of childhood was initially recog-

nized in the 2008 WHO classification under the name of systemic T-cell LPD of childhood. It was defined as a life-threatening illness of children and young adults that is characterized by the clonal proliferation of EBV-infected T-cells, but not as an obvious malignant neoplasm because cytological atypia of EBV-infected T-cells is not as atypical as that of malignant lymphoma [5]. In the revised 2017 WHO classification, this disease is defined as a malignant lymphoma and is renamed as systemic T-cell lymphoma of childhood [7]. Historically, this disease has been described under a variety of terms including fulminant EBV-positive T-cell LPD of childhood, sporadic fatal IM, fulminant hemophagocytic syndrome in children in Taiwan, fatal EBV-associated hemophagocytic syndrome in Japan, and severe CAEBV infection [21-23].

Systemic T-cell lymphoma of childhood can occur shortly after primary acute EBV infection or rarely in the setting of CAEBV. It has a rapid progression with multiple organ failure, sepsis, and death, usually within days to weeks. Viral serology is negative for EBV-determined nuclear antigen (EBNA) antibody and positive for viral capsid antigen (VCA)-immunoglobulin G (IgG) antibody, which suggests a role of primary EBV infection. VCA-IgM is positive in only one-thirds of systemic T-cell lymphoma after primary EBV infection [6].

Pathologically, hyperplasia of histiocytes and marked hemophagocytosis with increased numbers of small T lymphocytes are the most striking histological changes in the bone marrow, spleen, and liver. The infiltrating cells are predominantly CD8⁺ cytotoxic $\gamma\delta$ T-cells which are CD2⁺, CD3⁺, TIA-1⁺, granzyme B⁺, and CD56⁻. T-cell receptor gene rearrangement is clonal. EBV can be shown to be clonal by terminal repeat analysis. EBER *in situ* hybridization shows striking positivity in most small lymphoid cells, which show minimal cytological atypia as well as in the atypical cells. EBER *in situ* hybridization and immunohistochemistry confirm EBV infection in T lymphocytes [24].

EBV-HLH and systemic T-cell lymphoma of childhood have significant overlapping clinical and pathological findings, which suggest that EBV-HLH and systemic T-cell lymphoma of childhood are both part of a biological continuum rather than discrete entities [18,25,26]. Because EBV-HLH can be associated with clonal T-cell populations, the distinction between these two diseases is difficult and ambiguous. Previous studies of EBV-HLH and systemic T-cell lymphoma have shown that involvement of molecular clonality is fatal in 62% of patients, whereas involvement of karyotypic abnormalities is fatal in all patients (100%) [18]. Given that patients with karyotypic abnormalities have a dismal outcome, the most

useful marker for distinguishing EBV-HLH and systemic T-cell lymphoma is an abnormal karyotype rather than molecular clonality. During the clonal expansion of CD8⁺ T-cells, EBV-HLH seems to acquire cytogenetic alterations and to transform into a malignant neoplasm with an irreversible fatal outcome.

CAEBV INFECTION OF T/NK-CELL TYPE, SYSTEMIC

Most patients with primary EBV infection recover completely but, in some patients, symptoms associated with EBV infection persist with varying degrees of viral replication. CAEBV may involve B-cells or T/NK-cells. CAEBV of B-cell derivation is rare while CAEBV in East Asia is almost always associated with T- or NK-cell proliferation of varying degree. CAEBV was initially defined as an IM-like severe illness lasting more than 6 months that (1) begins as a primary EBV infection or is associated with markedly abnormal EBV antibody titers; (2) shows histological evidence of major organ involvement such as interstitial pneumonia, hypoplasia of the bone marrow, uveitis, lymphadenitis, persistent hepatitis, or splenomegaly; and (3) shows increased EBV RNA or proteins in affected tissues [27]. In the revised 2017 WHO classification, the diagnostic criteria for CAEBV include IM-like symptoms persisting more than 3 months, increased EBV DNA content ($>10^{2.5}$ copies/mg EBV DNA) in peripheral blood, histological evidence of organ disease, and demonstration of EBV RNA or viral protein in affected tissues in patients without a known immunodeficiency, malignancy, or autoimmune disorder [7].

Abnormal activation and replication of EBV together with the proliferation and clonal expansion of infected cells play a key role in the pathogenesis of CAEBV of the T/NK-cell type (CAEBV-T/NK). In this condition, unlike classical IM, T- or NK-cells are the main targets of EBV and proliferate to involve multiple organ systems. The proliferating cells lack histological evidence of malignancy and may be polyclonal, oligoclonal, and monoclonal according to the stage of transformation [6].

As indicated by the definition of the disease, CAEBV is defined based on the clinical and laboratory findings. Pathological changes are nonspecific except for identification of EBV-infected T- or NK-cells in the tissue taken for biopsy. Patients with T-cell CAEBV often present with high fever, lymphadenopathy, hepatosplenomegaly, and a high titer of EBV-specific antibodies, and have rapid progression of their disease. By contrast, patients with NK-cell disease often exhibit

hypersensitivity to mosquito bites, rash, and high levels of IgE, and do not necessarily have an elevated EBV-specific antibody titer [28].

Most patients with CAEBV-T/NK have no consistent immunological abnormality, although reduced NK activity and impaired EBV-specific cytotoxic T-lymphocyte activity have both been reported in some patients with this type of CAEBV [29]. The host factors that allow development of CAEBV-T/NK are not clear, but the strong racial predisposition toward CAEBV-T/NK and related diseases suggests that genetic polymorphisms in immune response-related genes are likely to be responsible for the development of this disease.

The prognosis for CAEBV-T/NK is variable. Some patients show an indolent clinical course, but many patients die of disease. The process may evolve from polyclonal to monoclonal proliferation of T- or NK-cells and eventually progress to overt lymphoid malignancy. The main causes of death are hemophagocytic syndrome, multiple organ failure, and T- or NK-cell malignancy. Patients with late onset of CAEBV-T/NK (older than 8 years), thrombocytopenia, and T-cell infection have significantly poorer outcomes [6].

HV-LPD

HV-LPD is a cutaneous manifestation of underlying CAEBV infection. HV was initially described in the Western literature as a benign self-limited photodermatosis in children that is characterized by recurrent vesiculopapular eruption that heals with vacciniforme scarring [30]. The relationship with EBV was not known at that time. Similar cutaneous lesions have been reported in Asian children and young adolescents, and are now recognized as EBV-associated cutaneous LPD with varying clinical manifestations that range from self-limited benign disease to progressive disease to cutaneous or systemic T-cell lymphoma [31-34]. In the 2008 WHO classification, this lesion was recognized as EBV-positive cutaneous T-cell lymphoma of childhood and named HV-like lymphoma [5]. In the revised 2017 WHO classification, the name was changed to HV-LPD, which better explains the diverse clinical and biological manifestations [7].

Clinically, HV-LPD was previously divided into the classic type and severe type. The classic type appears as vesiculopapules in sun-exposed skin, such as the face and arm, without systemic symptoms, whereas the severe form appears as severe disfiguring cutaneous lesions in sun-exposed and unexposed areas, with or without systemic symptoms. The severe form is compatible with HV-like lymphoma defined in

the 2008 WHO classification. Pathologically, the skin shows reticular degeneration of the epidermis and infiltration of EBV-positive small lymphocytes in the epidermis and dermis, and this infiltration often extends to deep subcutaneous tissue. The infiltrates comprise bland-looking or mildly atypical lymphocytes with an enlarged and hyperchromatic nucleus, which frequently show an angiocentric and periadnexal arrangement and septal or lobular panniculitis [35]. The immunophenotype of infiltrating cells is CD8⁺ T-cells mixed with CD4⁺ T-cells and rarely NK-cells. Flow cytometry of circulating peripheral blood reveals increased EBV-infected T-cells [36,37]. Clonality can be found in both the classic type and severe type.

HV-LPD represent cutaneous manifestations of CAEBV-T/NK with differences in clinical severity depending on the host immunity. Therefore, even patients with classic HV show a slightly elevated level of EBV DNA in peripheral blood mononuclear cells compared with normal healthy people, whereas patients with severe HV have markedly increased levels of EBV DNA associated with NK-cell lymphocytosis and other complications.

The prognosis of HV-LPD is variable. Most patients with classic HV show spontaneous remission, and some are cured after protection from sunlight, but a few patients experience recurrent eruptions despite sun protection. Classic HV rarely progresses to the severe form with age and can finally develop into cutaneous EBV-positive NK- or T-cell lymphoma. Severe HV is often accompanied by symptoms of systemic CAEBV, peripheral NK lymphocytosis, hypersensitivity to mosquito bites, and virus-associated hemophagocytic syndrome. About half of patients with severe HV develop EBV-associated NK/T-cell lymphoma in the skin or other organs 2 to 14 years after the onset of HV [6].

SEVERE MOSQUITO-BITE ALLERGY

Severe mosquito-bite allergy, also known as mosquito-bite hypersensitivity, is a cutaneous manifestation of underlying CAEBV infection. Most patients are in the first two decades of life with a median age of 6.7 years. Clinically, it is characterized by intense local skin symptoms including erythema, bullae, ulcers, and scar formation, and by systemic symptoms such as fever, lymphadenopathy, and liver dysfunction after a mosquito bite or injection. Vaccination may also bring about a similar skin reaction at the injection site in some patients. Patients have a high serum IgE level and high EBV load in the peripheral blood, and peripheral NK lymphocytosis

(80% of patients). The skin at the mosquito bite site shows epidermal necrosis and ulceration. The infiltrating lymphoid cells are CD4⁺ T-cells, CD8⁺ T-cells, and NK-cells that express cytotoxic molecules. EBV-positive cells comprise a minor population [38,39].

Activation of NK-cells latently infected by EBV and the subsequent cytotoxic T-lymphocyte response seem to play key roles in the pathogenesis of the skin lesions and systemic symptoms of mosquito-bite hypersensitivity [40-42]. The clinical course is variable. Some patients have a prolonged and indolent disease course, which may be complicated by CAEBV, systemic or HV-LPD. Half of patients die of hemophagocytic syndrome or aggressive NK-cell leukemia/lymphoma.

CONCLUSION

Primary EBV infection in childhood causes EBV-associated T/NK-cell LPD with diverse biological manifestations from reactive to neoplastic processes, including an exuberant T-cell response in IM, EBV-associated HLH, systemic T-cell lymphoma, CAEBV-T/NK, systemic form, HV-LPD, and severe mosquito-bite allergy. The overlapping clinical and morphological features of these disease entities, especially among EBV-associated HLH, systemic T-cell lymphoma, and IM, create a challenging diagnostic dilemma. The combination of clinical and laboratory findings and comprehensive diagnostic testing to assess the cell lineage and clonality of EBV-infected cells and cytogenetic changes is helpful in distinguishing each entity.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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