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REVIEW

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Chronic active Epstein-Barr virus infection: A heterogeneous entity requiring a high index of suspicion for diagnosis

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Abstract

Chronic active Epstein-Barr virus infection of T- and NK-cell type, systemic form, is a rare entity within the spectrum of EBV-driven T- and NK-cell lymphoproliferative disorders. Established diagnostic criteria and a characteristic clinical course help to differentiate it from other closely related EBV-positive neoplasms and clinical states. We present a patient and review the natural history, pathologic features, pathogenesis, and differential diagnosis of this entity.

KEYWORDS

chronic active EBV infection, EBV, Lymphoma, lymphoproliferative disorder

1 | INTRODUCTION

Chronic active Epstein-Barr virus infection of T- and NK-cell type, systemic form (referred to hereafter as simply CAEBV) is incorporated into the revised WHO 2016 classification scheme within the section of Epstein-Barr virus (EBV)–positive T cell and NK-cell lymphoproliferative diseases of childhood.[1] Complete characterization of CAEBV has eluded physicians and researchers for decades due to its variable clinical presentations and rates of progression, pathologic overlap with other infectious and inflammatory diseases and systemic lymphomas, a propensity for EBV to infect T-, B-, and NK-cell types, and inconsistent molecular findings that included poly-, oligo-, and monoclonal lymphoproliferations. Despite this heterogeneity, it is important to recognize CAEBV as early as possible in its course, because the disease is intractable and progressive, and a few large series report an all-cause mortality of 30%-44% after 46-68 months, even with varying rates of autologous hematopoietic stem cell transplant.[2-4] We present a patient case of CAEBV, and review the history of this unusual disease, its classification and pathologic features, and current themes in pathogenesis and management.

1.1 | Case summary

A 51-year-old healthy man taking no medications presented with transient skin rash, fever, and pancytopenia which resolved after several days. He was well until one month later, when he developed fever and pancytopenia (WBC 0.6 x 10^9/L, hemoglobin (Hgb) 117 g/L; platelets (PLT) 77 × 10^9/L), with slightly elevated liver enzymes, and splenomegaly. A bone marrow biopsy was hypercellular (90%) with an interstitial T cell infiltrate (CD3+, CD2+, CD4+, CD5+, CD7-) identified by flow cytometry and immunohistochemistry. Epstein-Barr viral-encoded RNA by chromogenic in situ hybridization (EBER-CISH) was positive in the lymphocytes (Figure 1). Cytogenetic analysis revealed a normal karyotype. HTLV1/2 antibody screen was nonreactive. PCR studies for T cell receptor gene rearrangement were unsatisfactory due to poor DNA preservation. He was treated with granulocyte colony-stimulating factor (G-CSF), and his white blood cell count improved and symptoms resolved.

A bone marrow biopsy was repeated six months later showing low-level involvement by a clonal T cell population (flow cytometry: CD3+, CD4-, CD8-, CD7-, CD26-) which was difficult to appreciate on routine sections. EBER-CISH showed scattered positivity. Clinically, he was asymptomatic and feeling well with nearly normal hematologic parameters (complete blood count: WBC 4.04 × 10^9/L; Hgb 143 g/L; PLT 113 × 10^9/L) and minimally elevated aspartate transaminase (AST, 25 U/L) and alanine transaminase (ALT 23 U/L).

After 18 months of observation, his leukocyte and platelet counts gradually decreased until he became acutely ill with neutropenic fever, hepatitis, fungemia, and a tooth abscess. He was hospitalized for three weeks with abnormal laboratory parameters: WBC 0.27 × 10^9/L; Hgb 102 g/L; platelets 40 × 10^9/L, AST 58 U/L, ALT

62 U/L, and Epstein-Barr viremia (6000 copies/mL). A third bone marrow biopsy was taken with persistent involvement by an EBV-positive T cell lymphoproliferative disorder (Figure 2A). Besides antimicrobial therapy, he was given intravenous immunoglobulin and G-CSF and his symptoms and complete blood count trended toward recovery (WBC 3.1 × 10^9/L; absolute neutrophil count (ANC) 2.3 × 10^9/L, Hgb 102 g/L, PLT 159 × 10^9/L).

One month after hospitalization, he was mostly well with a normal ANC (2.3 × 10^9/L), normal PLT count, minimally elevated liver enzymes (AST 20 U/L, ALT 34 U/L), and stable quantitative EBV DNA in peripheral blood. He suffered periodic left abdominal discomfort due to splenomegaly, and two months after the hospitalization, his platelet count dropped to 81 × 10^9/L. The spleen was removed, and pathologic examination showed splenomegaly (570 g) with extramedullary hematopoiesis and the same abnormal interstitial CD3+ T cell infiltration present in previous bone marrow biopsies (positive for cytotoxic molecules TIA-1, granzymeB and perforin, and EBER-CISH). There was extensive hemophagocytosis (Figure 2B). Four weeks after splenectomy, his CBC parameters improved (WBC 5.0 × 10^9/L (ANC 1.4), hemoglobin 142 g/L, platelets 100 × 10^9/L), though liver enzymes (AST 153 U/L, ALT 158 U/L), and EBV DNA quantitative test (14 490 copies/mL) were steadily rising.

Three months after splenectomy, he was admitted to the hospital with fever and rapidly developed multisystem organ failure and disseminated intravascular coagulation. His EBV DNA quantitative test was 161,200 copies/mL, lactate dehydrogenase 19,215 U/L, and ALT and AST were 1200 U/L and 11,382 U/L, respectively. Despite steroids and transfusion support, he died two weeks after admission to the hospital with end-stage chronic active EBV infection and associated hemophagocytic lymphohistiocytosis (HLH).

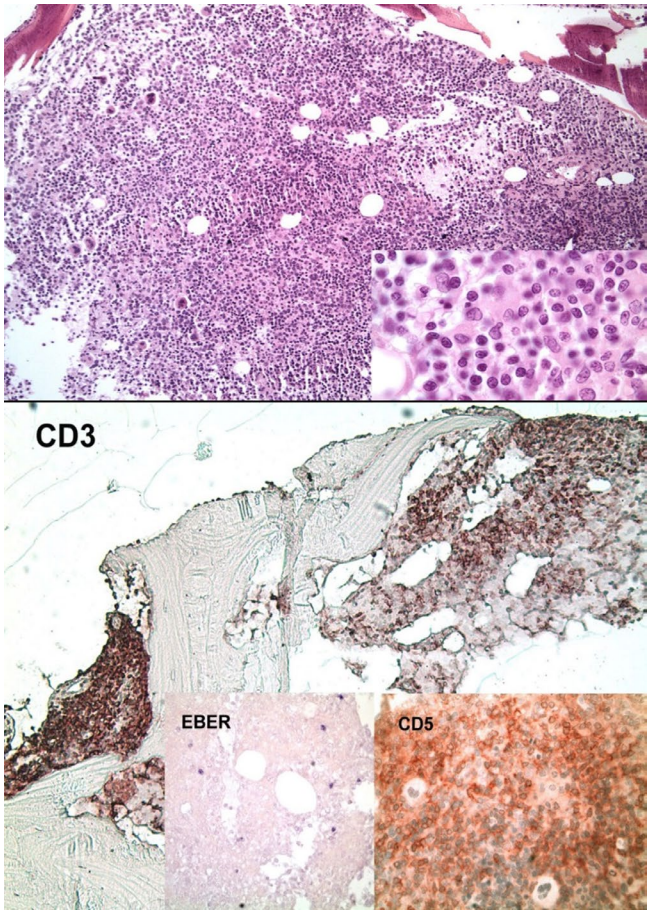

FIGURE 1 The initial bone marrow biopsy is hypercellular (upper, H&E 10x, inset: 100x) due to lymphocytic infiltration by CD3 + CD5+ T-lymphocytes (lower) with scattered EBER + cells

2 | HISTORICAL PERSPECTIVE

The evolution of the entity of CAEBV has occurred over a span of 70 years, since the first description of a series of 53 patients with a chronic infectious mononucleosis (IM) syndrome characterized by unusual fatigue, splenomegaly, and persistence of symptoms and viral lymphocytes in the peripheral blood for 3 months-4 years.[5] Subsequent reports of characteristic clinical features including fever, hepatic dysfunction, cytopenias, and patterns of positive Epstein-Barr viral serologies contributed to our understanding of the illness,[6-8] but it was not until 1988 that EBV-infected and clonally proliferating T cells were documented in a patient with CAEBV.[9] With accumulating clinical experience, diagnostic guidelines were proposed by a group of experts in 2005. These were persistent/recurrent IM-like symptoms with abnormal EBV serologies including elevated antiviral capsid antigen (VCA) and anti-early antigen (EA), and/or increased EBV genomes in peripheral blood, and exclusion of other illnesses at the time of diagnosis (EBV-associated HLH and T-/NK-cell lymphomas).[10] At the third meeting of the Asian Hematopathology Association (Nagoya, 2006), a proposed categorization to define the pathologic spectrum of CAEBV and NK/T cell lymphoproliferative disorders was adopted. This recognized the multistage progression of these diseases from that of an EBV-infected lymphocyte to a clonal T- or NK-cell lymphoma.[11] The 2008 WHO classification of tumors of hematopoietic and lymphoid tissues included CAEBV within the category of systemic EBV-T-cell-LPD of childhood, and the revised edition subsequently separated CAEBV as its own entity.[1]

3 | MAKING A DIAGNOSIS

Diagnosis of CAEBV is based on clinical and laboratory findings (Table 1—Diagnostic criteria). CAEBV is a progressive, systemic lymphoproliferative disorder that may begin as an infectious mononucleosis (IM)-like illness. It can manifest with fever, splenomegaly, hepatitis, lymphadenopathy, and occasionally other systemic findings such as cytopenias, pneumonitis, and vasculitis.[2] Serologic patterns of antibodies to EBV protein characteristic of CAEBV were described early in the development of diagnostic criteria for CAEBV. These included antiviral capsid antigen (VCA) IgG ≥ 1:5120, anti-early antigens (EA) IgG ≥ 1:640, and anti–Epstein-Barr nuclear

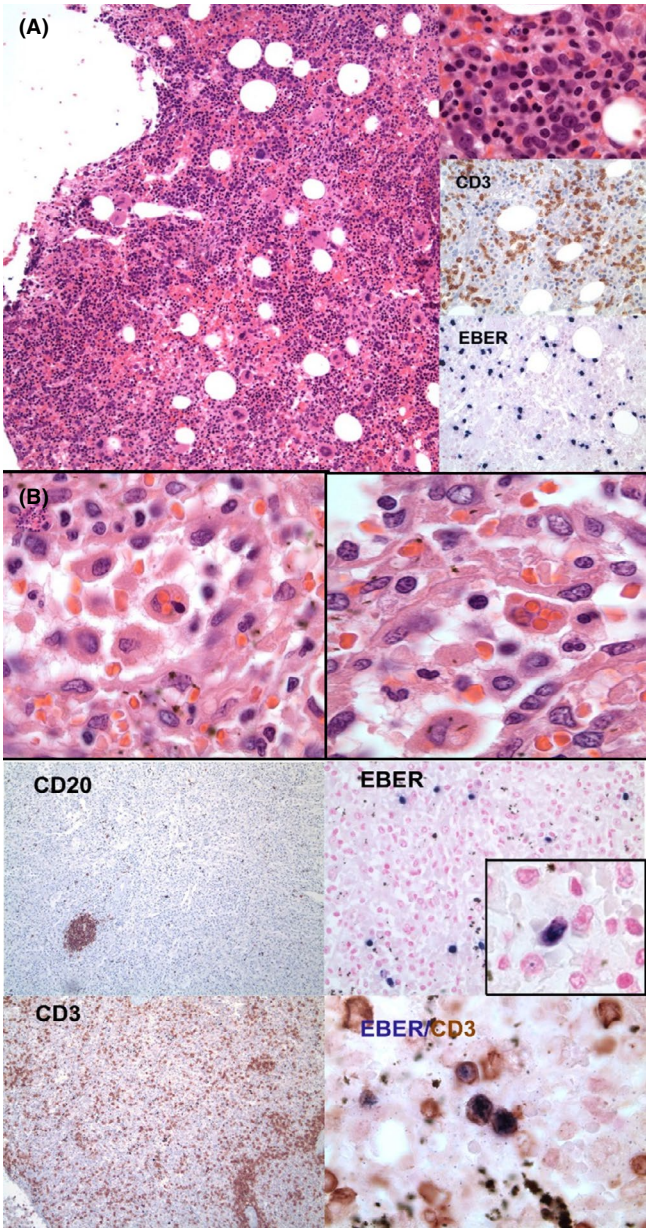

FIGURE 2 A, The third bone marrow biopsy is hypercellular, with a prominent CD3 + EBV+infiltrate (insets), B, splenectomy (right and left) showing hemophagocytosis (upper: H&E, 100×), with increased numbers of EBER-infected CD3 + T cells demonstrated with a double stain for EBER(blue nuclear stain) and CD3 immunohistochemistry (brown membrane/cytoplasmic, lower right corner panel)

antigens (EBNA) less than 1:2.[3,6] Though typical of the disease, these serologic features were not included in the most updated diagnostic guideline and DNA detection is now the preferred test. The current disease criteria have been expanded and require the illness to last at least three months, with infiltration of tissues by EBV-positive lymphocytes and specific exclusion of primary EBV infection, HIV, congenital immune deficiencies, and underlying diseases or therapies resulting in immunosuppression.[1,12]

TABLE 1 Diagnostic Criteria of Chronic Active EBV Infection of T- and NK-cell Type, Systemic Form[1,12]

Sustained or recurrent IM-like symptoms for greater than 3 mo, exclude primary EBV infection
Elevated EBV genome load in the peripheral blood (PB) (>$10^{2.5}$ copies/μg DNA)
Histologic evidence of infiltration of affected organs or PB by EBV + lymphocytes
Exclusion of other possible diagnoses including the following: Congenital immune deficiencies HIV infection Iatrogenic immunosuppressive therapies Autoimmune/collagen vascular diseases Pathologic evidence of another malignant lymphoma (classic Hodgkin lymphoma, extranodal NK/T cell lymphoma—nasal type, peripheral T cell lymphomas, aggressive NK-cell leukemia)

There is geographic predisposition to CAEBV with the vast majority of cases limited to East Asia, especially Japan and Taiwan, and China.[3,13,14] It is rare in Western populations.[15] A few reports, especially with skin-based disease, are from Latin America.[16] The reasons for this distribution are unknown, but suggest a host genetic mechanism/predisposition to EBV infection.

4 | CLINICAL FEATURES AND NATURAL HISTORY

The case presented above fits with the natural history of a typical patient with CAEBV, with a delayed time to diagnosis, chronic symptoms overlapping with other infectious and inflammatory disorders, and persistence and progression of the T cell lymphoproliferative disorder over a prolonged period ending with hemophagocytic lymphohistiocytosis and multisystem organ failure. It is reported that the time required to arrive at the diagnosis of CAEBV is approximately 20 months,[17] with an average range from 12 to 24 months.[18] The patient was of Taiwanese extraction living in the United States and is consistent with the T cell phenotype observed in a Taiwan series, although he was much older than the childhood cases described in that study.[19] In a nationwide survey in Japan, almost half of the CAEBV patients were adults,[4] and a study was recently published that focused on 54 adult patients.[18] The largest series of CAEBV studied in the United States reports an average age at diagnosis of 19 years, ranging from four to 51 years.[15]

The clinical course of CAEBV is variable. Some patients may have nonspecific symptoms and experience a delayed diagnosis; other patients may experience common symptoms and signs for years (pancytopenia, liver dysfunction, inflammation) without significant progression. Still others may show progressive deterioration, either after a period of stability that may last months or years, or quickly following an IM-like illness after presentation. A retrospective analysis of 82 patients with 8 months to 18 years of follow-up showed that 43% of patients had died after survival periods ranging from 5 months to 12 years after disease onset. Progression to and death

from systemic lymphoma occurred in 17% of patients; other causes of death included hemophagocytic syndrome (8.6%), hepatic or multisystem organ failure (14%), or transplant-related mortalities (20%).[4]

Complication rates for CAEBV are difficult to separate from other EBV-associated T/NK-cell lymphoproliferative disorders, because these cases are often reported together.[2] A 2004 cross-sectional analysis divided 43 CAEBV patients into four clinicopathologic groups (A-D), based on severity. Group D would have represented systemic EBV-positive T cell lymphoma of childhood based on the current classification. Groups A-C (39 patients) shared persistent and repeated episodes of fever of unknown origin, lymphadenopathy, organomegaly, cytopenias, and cutaneous symptoms. The groups were defined as follows: group A—nonclonal and chronic phase; group B—clonal and chronic phase; and group C—lymphoma following prodromal chronic state. The median survival was 78 months for group A, 46 months for group B, and 42 months for group C. In group C, lymphoma types were peripheral T cell lymphoma (n = 8) and NK-cell lymphoma (n = 14), developing a median of 35 months after CAEBV diagnosis (range, 3-264 months). Between groups A-C, six patients died of hemophagocytic syndrome (HPS), 12 patients died of lymphoma ± HPS, and one died of an unrelated cause.[20]

5 | PATHOLOGIC FEATURES AND LINEAGE ASSESSMENT

The pathologic features of CAEBV in histologic sections are subtle and may involve any organ that is biopsied. The pathologist's main task is to document the presence of EBV RNA or viral proteins by in situ hybridization or immunohistochemistry in affected tissues and exclude overt EBV-associated lymphomas. The lymphocytes are typically bland appearing and mimic chronic inflammatory infiltrates in extranodal sites. Histologic findings of lymph nodes include overall architectural preservation with paracortical hyperplasia with a slight increase in transformed cells in the paracortex or polymorphic infiltration. Rarely necrosis and small epithelioid granulomas have been described.[1,11] In rare instances, lymph node histopathologic features can mimic classic Hodgkin lymphoma. Chen et al recently described eight patients meeting diagnostic criteria for CAEBV with diffuse lymphadenopathy, paracortical hyperplasia, and variable numbers of Hodgkin/Reed-Sternberg–like cells with a CD3 + CD56+TIA + EBER+phenotype scattered amid an inflammatory background.[21]

The liver shows portal and sinusoidal infiltration by small lymphocytes similar to viral hepatitis. Skin lesions demonstrate lymphocyte infiltration in the mid- to upper dermis or nonsuppurative necrosis in the perivascular areas. The spleen can show red pulp congestion and atrophy of white pulp. Bone marrow may appear normal if there is minimal infiltration. If the lymphoid infiltrate is obvious, the pattern of the T- or NK-cell infiltrate in bone marrow is nonspecific, with interstitial single cells with occasional loose aggregates. EBER in situ hybridization staining is essential to making the diagnosis histologically as it confirms the presence of EBV in the proliferating lymphocytes.[1,11] However, the proportion of EBV-infected T cells does not help to separate CAEBV from other neoplastic entities in the differential diagnosis because the neoplasms that appear most similar to CAEBV also harbor EBV within the neoplastic cells.

A grading system for CAEBV was proposed by Oshima and colleagues in 2010, which is thought to reflect the multistep progression of CAEBV to lymphoma (Figure 3). Category A1 is a polymorphic lymphoproliferative disorder (LPD) with polyclonal proliferation of EBV + T/NK cells and represents a smoldering stage. Category A2 is a polymorphic LPD with oligoclonal or monoclonal proliferation of EBV + cells, and represents a chronic stage. Category A3 is a monoclonal proliferation (malignant transformation) consistent with progression to leukemia/lymphoma. Category B does not indicate cases of CAEBV, but rather is the fulminant form of a monoclonal EBV + LPD that occurs shortly after primary EBV infection and represents what is now systemic EBV-positive T cell lymphoma of childhood in the WHO classification.[1,11]

There are numerous reports that CAEBV is of T cell or NK-cell type.[2,22,23] B-cell type CAEBV was initially thought to be the predominant type occurring in Western countries, based on a report of a 28-year look back showing a higher prevalence of B-cell type in the United States. In that experience, immunophenotype was determined by double-staining for EBER and CD20 or CD3, but an unknown number of cases were inferred by the comparison of sequential sections.[15] The concept that rare cases of B-cell CAEBV are diagnosed in Japan comes from the nationwide survey which identified 3% of such cases. However, the authors acknowledged that infection of B cells was confirmed by a combination of in situ hybridization and immunohistochemistry, and that "infections of T and NK cells were not completely excluded by this method."[4] Characterization of patients with B-cell CAEBV suggests that it may be a separate disease. Patients with B-CAEBV were slightly older (mean age, 23 years) compared to T-CAEBV (mean age, 7 years). The B-CAEBV cohort had significantly greater levels of EBNA1 antibody and lower levels of early antigen and early-intermediate proteins than the T cell CAEBV comparison group,[15] which is also in contrast to the characteristic serologic pattern in the earlier descriptions of CAEBV.[3,8] Lymph node histology in patients with B-CAEBV resembled polymorphic PTLD with plasmacytoid and immunoblastic differentiation, low levels of CD19 + B cells and NK cells, and development of hypogammaglobulinemia. This suggests a possible underlying immune deficiency, either primary or secondary, related to the polymorphic B-cell lymphoproliferation.[15]

An international study recommends determination of the affected lineage (T-, B-, or NK-cell) in CAEBV. However, this can be technically difficult.[23] Determination of the infected lymphocyte subset is not routine clinical practice nor commonly reported in the published literature. A recent study examining EBV-infected blood lymphocyte cell types in 291 patients with high EBV viral loads used magnetic-activated cell sorting and confirmation by flow cytometry, followed by PCR and FISH for EBV detection. Of patients with EBV + T/NK-LPDs, 56 had CAEBV. B-cell type infection was not

observed in CAEBV but was seen in immunocompromised patients including post-transplantation states, immunosuppressive medication-related, EBV + B-LPDs, EBV + B-cell lymphomas, and infectious mononucleosis in that study. As CAEBV by definition must occur in immunocompetent individuals, the findings relating B-cell type EBV infection to immunodeficiency states and infectious mononucleosis provide additional support that this may represent a separate disease and not a phenotypic variant of CAEBV.[24]

Some authors recommend distinction between T-CAEBV and NK-CAEBV as there is an association with poorer prognosis with T-CAEBV.[3,4] However, a recent study of 54 adult patients did not detect a difference in OS between T- and NK-cell CAEBV, so data on prognosis related to cell type are conflicting.[18]

NK-cell CAEBV has shown some association with higher levels of IgE and hypersensitivity to mosquito bites and appears to demonstrate less clinical severity. The NK-cell type infections can exhibit large granular lymphocytosis.[3] In a study that directly compared T- and NK-cell types using a reliable means of lineage determination (fractionation of cells by immunobead method), patients with T-CAEBV had a poorer prognosis with a 60% death rate, more frequent fever, and anemia. In comparison, patients with NK-CAEBV had a 26% death rate, with skin manifestations, lymphocytosis, and high IgE concentrations.[22] Of note, postallogeneic hematopoietic stem cell transplantation survival rates and long-term overall survival (OS) differences were not significantly different in a large prospective analysis.[22]

6 | DIFFERENTIAL DIAGNOSIS

Clinical presentation is important in considering the differential diagnosis of CAEBV (Table 2). Fulminant EBV-positive T cell lymphomas can occur as a life-threatening illness in formerly healthy patients following acute EBV infection and rarely in patients with prior long-standing CAEBV[25]; this is incorporated into the WHO classification as systemic EBV-positive T cell lymphoma of childhood.[1] Patients present with acute onset of fever and malaise followed by organomegaly, liver failure, cytopenias, with or without lymphadenopathy. Abnormal EBV serology that includes lack of IgM antibody to EBV viral capsid antigen is reported. Development of hemophagocytic lymphohistiocytosis, organ failure, and sepsis complicates a spiraling clinical course. In these circumstances, knowledge of prior persistent/recurrent EBV-positive T cell lymphoproliferative disorder, and relapsing/remitting symptoms over three to six months would help to differentiate CAEBV from a systemic EBV-positive T cell lymphoma of childhood. The literature contributing to our current understanding of the border between CAEBV and systemic EBV-positive T cell lymphoma of childhood acknowledges some overlap, with descriptions of more severe illness associated with T cell type CAEBV in Japan[22] and Taiwan, China,[19] and incorporation of some severe cases into case series of CAEBV.[20] The WHO classification advises that the severe cases of CAEBV with EBV-positive monoclonal T cell proliferations should be considered as systemic EBV-positive T cell lymphoma rather than CAEBV.[1] The overlap raises interesting questions about how many EBV-positive T/NK-cell lymphoproliferative disorders are preceded by an unrecognized CAEBV state.

The presence of EBV + NK-cell lymphocytosis may suggest a differential diagnosis of aggressive NK-cell leukemia. Aggressive NK-cell leukemia is an EBV-positive, neoplastic proliferation of natural killer cells in peripheral blood, and bone marrow that affects young to middle age adults and can present with hepatosplenomegaly, lymphadenopathy, and systemic symptoms. It is reported mainly in Asian populations. Patients may have high fever, pancytopenia, and hepatic failure, similar to CAEBV. However, the acute onset, atypical cytologic features, and highly aggressive clinical course are not features of CAEBV. As some cases of CAEBV can evolve into aggressive NK-cell leukemia, there is overlap between these entities which may only be separated by clinical features. The natural history of aggressive NK-cell leukemia is different, with patients succumbing to a fulminant course after median survival of less than two months. While the clinical presentation may appear similar to systemic EBV + T cell lymphoproliferative disorder of childhood, the

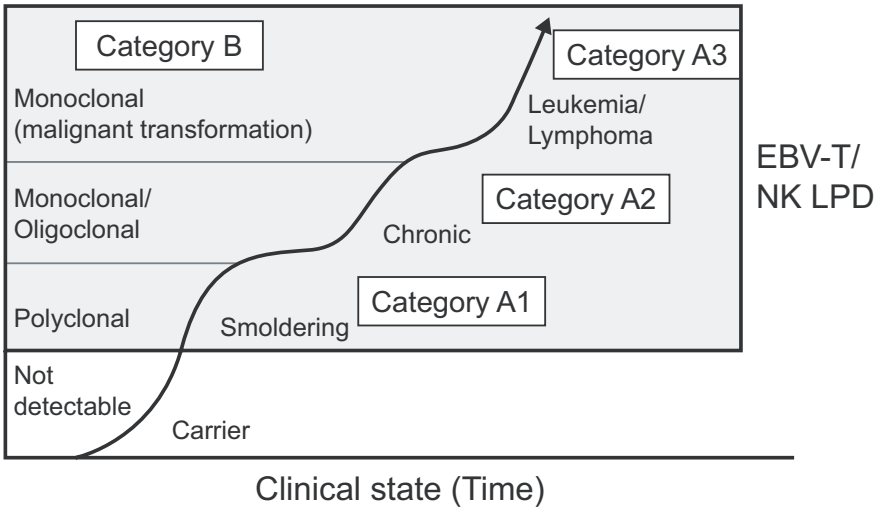

FIGURE 3 Multistage progression of pathological states of EBV + T/NK lymphoproliferative disorder. Reproduced from Ohshima K et al and The CAEBV Study Group (Ohshima et al, 2008) with permission granted from John Wiley and Sons

CD2+/CD56 + natural killer cell phenotype will assist in differentiating these entities.[26,27]

Primary EBV + nodal T cell or NK-cell lymphoma is included in the differential diagnosis of an excisional biopsy in a patient with systemic lymphadenopathy. This is a rare variant of peripheral T cell lymphoma, nos in the WHO classification with a cytotoxic T cell phenotype that characteristically affects elderly or immunocompromised patients and does not usually involve liver, spleen, and extranodal sites. Pathologic features include a relatively monomorphic proliferation of atypical lymphoma cells with centroblastic cytologic features, and monoclonal T cell receptor gene rearrangements. Patients have a poor prognosis and median survival of less than four months. Thus, on the basis of clinical and morphologic features, as well as disease distribution, rare cases of primary EBV + nodal PTCL can be distinguished from CAEBV.[26,28]

Clinical features of EBV-associated hemophagocytic lymphohistiocytosis (HLH) include sudden onset of high fever, splenomegaly, cytopenias, and liver dysfunction and may cause confusion with CAEBV, especially because CAEBV patients may develop HLH over time. Primary EBV + HLH has prominent hemophagocytosis as a histologic feature, but this is not required for diagnosis. EBV + T cells may be relatively few in number compared to CAEBV and other systemic T cell LPDs, and are usually cytotoxic CD8+ T cells in contrast to CAEBV which are more often CD4+ T cell or NK-cell proliferations. Predisposing genetic conditions including X-linked lymphoproliferative disease are associated with EBV + HLH.[26] A diagnosis of EBV + HLH requires that other EBV-associated T/NK-LPDs are excluded, and that the HLH diagnostic criteria are satisfied.[29]

Part of the spectrum of CAEBV includes an entirely cutaneous presentation, and these diseases are incorporated into the WHO as hydroa vacciniforme-like lymphoproliferative disorder and severe mosquito bite allergy.[1] The boundary between cutaneous and systemic CAEBV is blurred, because of reports of cutaneous disease evolving into a systemic lymphoproliferative disorder and

TABLE 2 Differential diagnosis of CAEBV with other T-/NK-cell EBV + neoplasms

	Clinical features	Pathology	Clonal assessment
CAEBV, systemic form	-IM-like symptoms >3 mo; protracted course of fever, cytopenias, hepatosplenomegaly, and lymphadenopathy -Variable prognosis	Subtle to variable degrees of lymphocytic infiltration in any organ Lymph nodes have paracortical hyperplasia CD4»CD8; T cell > NK cell	Monoclonal T cell receptor genes in slightly more than half of cases, depends upon the study
Systemic EBV + T cell lymphoma of childhood	-Rapidly progressive fulminant course of high fever, hepatosplenomegaly, pancytopenia, and coagulopathy occurring shortly after acute EBV infection in healthy children or in the setting of CAEBV -Death in days to weeks	Lymphocytic infiltration of liver, spleen, bone marrow, and lymph nodes with variable cytology; hemophagocytosis in bone marrow; lymph nodes have paracortical expansion and depleted B-cell areas CD2+, CD3+, CD56-, TIA1+, CD8 > CD4	Monoclonal T cell receptor genes
Aggressive NK-cell leukemia	-Fever, constitutional symptoms, leukemic blood picture, can have coagulopathy -Most cases fulminant with survival <2 mo	Tumor cells ranging from T-LGL-like cytology to blast-like cells with pale cytoplasm and granules CD2+, surface CD3-, CD3 epsilon+, CD5-, CD56+, cytotoxic+	T cell receptor genes are in germline configuration
Primary nodal EBV + T cell or NK-cell lymphoma	-Rare, presents with B symptoms and generalized lymphadenopathy with limited extranodal involvement -Poor prognosis	Similar to peripheral T cell lymphoma, NOS Predominantly CD8 + cytotoxic T cells, γδ T cells, CD56+ (small subset), CD4+ (small subset)	Monoclonal T cell receptor genes (for T cell lineage) or germline (for NK lineage)
EBV-associated hemophagocytic lymphohistiocytosis	-High fever, splenomegaly, cytopenias, liver dysfunction, other EBV-associated T/NK-LPDs excluded -Variable clinical course	Hemophagocytosis prominent in sinusoids of BM, spleen, and liver -Cytotoxic CD8 + T cells -Fewer EBV + cells in the infiltrate compared with EBV + LPDs	Can have monoclonal T cell receptor genes in up to 50% of cases
Extranodal NK/T cell lymphoma, nasal type	-Nasal obstruction or symptoms related to mass lesion in another organ site, B symptoms -Aggressive with 30%-40% survival rate	-Diffuse lymphomatous infiltrate with angiocentricity, inflammation, and necrosis - Atypical cytology -Variable cytotoxic T-/NK immunophenotype	Monoclonal T cell receptor genes in 10%-40% of cases

inclusion of cases with mosquito bite hypersensitivity in series of CAEBV.[13,23] Hydroa vacciniforme-like lymphoproliferative disorder is a disease mainly in children of recurrent vesiculopapular eruptions usually in sun-exposed skin that evolve to crusts and leave scars after healing. It occurs in children and has a broad spectrum of clinical aggressiveness, with a risk to develop systemic lymphoma in 10-15 years. Histopathologic features include intraepidermal spongiotic vesicles, and lymphocytic infiltrates in the dermis with periadnexal and perivascular accentuation.[30] Severe mosquito bite allergy is a cutaneous condition usually occurring in the first two decades of life, defined as an EBV-positive NK-cell lymphoproliferative disorder with high viral load and intense local skin symptoms. It carries a risk of development of systemic symptoms of CAEBV, or progression to aggressive T- and/or NK-cell lymphomas. The pathologic findings reflect the dermatologic presentation of ulceration, bullae, and scar formation, with occasional necrosis. The lymphoid infiltrate is polymorphous and composed of small lymphocytes, large atypical cells, and mixed inflammation including histiocytes and eosinophils.[1,26]

7 | PATHOGENESIS

The pathogenesis of CAEBV may require multiple mechanisms for initiation of infection in T cells, perpetuation of the lymphocyte clone, and evasion of the immune system. EBV normally infects B cells and epithelial cells via the CD21 receptor, which has also been detected on T cells with weak expression, possibly due to synaptic transfer. EBV infection of T- and NK- cells can also occur under high viral loads.[12] The host immune system changes in CAEBV, with cytotoxic T cells that are decreased in number and dysfunctional, and this may contribute to sustained infection.[31] Altered signaling pathways are shown to be important in the transformation of lymphocytes to malignant cells and in promoting cell survival. One study showed that EBV-induced CD40 expression of T cells with autocrine CD40/CD40L signaling resulting in activated intracellular signaling molecules (NF-κB) and suppression of apoptosis.[32] Upregulated activation-induced cytidine deaminase (AID) expression has been detected in the peripheral blood mononuclear cells of EBV + T-/NK-cell lymphoproliferative diseases, which may contribute to genomic instability.[33]

8 | PROGNOSTIC FACTORS

Timely diagnosis of CAEBV is important to avoid development of life-threatening complications such as aggressive EBV + systemic lymphomas, hemophagocytic lymphohistiocytosis, sepsis, or organ failure. At diagnosis, it is difficult to predict prognosis and the course that the disease will follow as it evolves. Despite this, the clinician must determine how to proceed with a balance of immunosuppressive medication, chemotherapy, and escalated intensive therapies including allogeneic hematopoietic stem cell transplantation.[34] A nationwide study of prognostic factors for CAEBV in Japan identified thrombocytopenia and age at disease onset (≥8 years) as factors correlated with mortality. Given that definitions of adult age are not uniform, they performed a multivariate logistic regression analysis and identified increasing age as a significant factor related to CAEBV-associated mortality.[4] A prospective analysis several years later confirmed that age at onset of disease is a risk factor for mortality, and this was significant along with liver dysfunction on multivariate analysis, while thrombocytopenia was associated with increased mortality on univariate analysis.[2] A recent study of adult-onset patients in Japan (>15 years of age) found that thrombocytopenia, high EBV antibody titer, the presence of HLH, and not receiving hematopoietic stem cell transplantation (HSCT) were independent poor prognostic factors.[18] The aggressiveness of adult-onset CAEBV demonstrated by these studies highlights the importance of recognizing that CAEBV is not only a pediatric disorder, and brings into question whether we should continue to affix the "of childhood" modifier to the end of "EBV + T- and NK-cell lymphoproliferative diseases" in the WHO classification scheme.

Currently, allogeneic HSCT is the only intervention with a measurable impact on survival rates. A prospective study of mostly CAEBV that included some cutaneous CAEBV cases and EBV + HLH found that HSCT resulted in a 15-year survival rate of 60.6% with transplant compared to 25.7% without transplant, with a trend toward a better outcome if transplantation occurred before age 15.[2]

9 | CONCLUSION

In summary, CAEBV is a rare disease that may wax and wane with heterogeneous symptoms and inflammation for months to years. It requires a high index of suspicion for diagnosis and is important to recognize in the early stages before it progresses into a systemic lymphoma, HLH, and/or life-threatening infection. Tissue biopsies are not always performed because a mass may not be present. When a biopsy is performed (such as from bone marrow, spleen, or liver), testing for EBV by in situ hybridization on tissues and suggesting EBV DNA testing in blood in patients with suspicious clinical features may reveal the etiology and prompt appropriate therapy. This stresses the important role the pathologist may play in assisting the clinical team in recognizing CAEBV in their patients.

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