Active EB virus infection in adults: a case series of 8 patients in a single institution and a review of related literature

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ABSTRACT

Adult patients with chronic active EB virus infection (CAEBV) are few; however the disease runs an aggressive course. The goal of this study was to investigate the clinical characteristics, treatment as well as prognosis of CAEBV in adults. The clinical data of eight adult patients with CAEBV were analyzed retrospectively. There were five male and three female patients with a median age of 47(25–67) years old. The main clinical manifestations were fever, lymphadenopathy, splenomegaly, liver damage, abnormal coagulation and cytopenia. Peripheral blood EB virus DNA titers were significantly higher in all patients (4.14×10^4 – 4.60×10^5 copy/mL). Most patients received treatment with glucocorticoids, cyclosporine and chemotherapy containing etoposide (as recommended in the HLH–2004 program or the scheme of ECOP). One patient progressed to aggressive natural killer (NK) cell leukemia in 5 months after diagnosis. Another patient without fever or cytopenia is still living now, after receiving hormone therapy. The remaining 6 cases died with a median survival of 15 months. In conclusion, CAEBV in adults is a rare but serious disease, often with multiple system damage, from which the prognosis is very poor. Further research is necessary to improve the understanding of this disease.

Keywords: adult, Epstein–Barr virus infections, lymphoproliferative disease

INTRODUCTION

Epstein–Barr virus (EBV) is a ubiquitous herpes virus which affects more than 95% of humans. Most infections occurred in children without obvious symptoms, while infections in adolescents or young adults often result in infectious mononucleosis. Rare persons with the EBV infection develop a life-threatening disease called chronic active EB virus infection (CAEBV). As mentioned in the 2008 NIH International Classification Meeting on EBV-associated lymphoproliferative diseases, the clinical term of CAEBV consists of a broad spectrum of diseases which includes chronically active EBV infection, hydroa vacciniforme, hydroa vacciniforme-like lymphoma, severe mosquito bite allergy and systemic EBV⁺ T-cell lymphoproliferative

disorders (LPD) in children^[1].

CAEBV is characterized by fever, lymphadenopathy, splenomegaly, liver impairment and cytopenia. Some patients also present interstitial pneumonia, uveitis and hemophagocytic syndrome. CAEBV can involve the B cell or natural killer (NK) /T cell with histological findings ranging from reactive polyclonal hyperplasias to monoclonal malignant proliferation. As it mainly affects children and teenagers, the diagnosis of adult CAEBV should be very cautious. High levels of EBV DNA in the blood, elevated levels of EBV RNA or viral proteins in affected tissues and histological evidence of organ disease are often observed in affected patients. In order to better understand this disease, we have reviewed the clinical data of 8 CAEBV patients diagnosed in our hospital and studied the available data.

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These findings could have various implications.

MATERIALS AND METHODS

Patients

We reviewed 8 patients diagnosed with CAEBV in our hospital between September 2012 and September 2016. All patients fulfilled the criteria as follows: (1) age ≥ 18 years; (2) persistent symptoms, including fever, liver impairment, enlargement lymphoma, hepatosplenomegaly and cytopenia; (3) EBV-DNA load of peripheral blood increased ($\geq 1 \times 10^3$ copies/mL); (4) histological evidence of major organ involvement and increased EBV⁺ T cells in related tissue; (5) excluding aggressive NK cell leukemia, extranodal NK/T cell lymphoma and peripheral T-cell lymphoma; (6) no history of immunodeficiency or immunosuppressive agent. This study was approved

by the Ethics Committee of Hangzhou First People's Hospital.

Imaging and laboratory examinations

Imaging examinations included systemic lymph node B-ultrasound, chest and abdomen CT. Blood tests included blood routine, blood chemical, coagulation function, EBV-related antibodies, blood EBV-DNA. Bone marrow cell morphology, bone marrow biopsy histopathology, and flow cytometry immunophenotyping were also performed. The immunohistochemical tests included CD2, CD3, CD5, CD7, CD19, CD20, CD56, TIA and granzyme B. The lymph node biopsy was performed when necessary and EBV infection in tissue was confirmed by using *in situ* hybridization for EBV-encoded mRNA (EBER)(Fig. 1). Some patients underwent positron emission tomography-computed tomography (PET-CT).

Fig. 1 Histopathology of the nasopharynx in patient of case 4. (A) Infiltrating lymphocytes are small in size. (B) Lymphoid cells are positive for CD3. (C) *In situ* hybridization for EBV-encoded small RNA(EBER) shows numerous positive lymphocytes.

RESULTS

Clinical features

Of all the 8 patients, there were 5 males and 3 females with a median age of 57 years (range: 25–67 years). Their clinical characteristics were shown in **Table 1**. The most common clinical manifestations were fever (7 cases), elevated liver enzymes (8 cases), splenomegaly (8 cases), systemic lymphadenopathy (5 cases) and coagulation dysfunction (4 cases). Cytopenia was observed in 5 cases, 1 of them presented thrombocytopenia and only one case presented with anemia. Five patients received a whole-body PET-CT examination. Two patients were found concurrent with hemophagocytic syndrome (HLH), the PET-CT revealed systemic bone metabolism with splenomegaly, and a slightly high fluorodeoxyglucose (FDG) metabolism. The remaining three cases showed multiple enlargement lymphadenopathy and splenomegaly without a significantly increased FDG metabolism. T-cell infection was observed in all patients. The summary of infection status and host cell is listed in **Table 2**.

Treatment and outcome

Most patients received treatment with glucocorticoids, cyclosporine, and chemotherapy containing etoposide as mentioned in the HLH-2004 program^[2]. Three patients (case 1, 3 and 6) with concurrent HLH were initially given a HLH-2004 regimen which was immediately effective for a short period, however, after that the disease progressed rapidly and the patients eventually died of multiple organ failure. Case 2 received glucocorticoids, thalidomide, cyclosporine and etoposide, but died of respiratory and circulatory failure after receiving ECOP (etoposide, cyclophosphamide, vincristine, and prednisone) chemotherapy. Case 4 had a good initial response to hormone therapy, with her temperature controlled by adding cyclosporine and etoposide. However, recurrent fever persisted after initial treatment. Five months later, the disease quickly transferred to aggressive NK cell leukemia. Chemotherapy consisting of EPOCH (doxorubicin, etoposide, cyclophosphamide, vincristine, prednisone), GELOX (gemcitabine, oxaliplatin, L-asparaginase) combined with etoposide was not effective and the patient soon

Table 1 Clinical characteristics, treatment and prognosis of 8 cases

Case No.	Age/y, Gender	Clinical characteristics	Treatment	Time from onset to diagnosis/m	Survival time and status
1	57, M	Recurrent fever, liver damage, thrombocytopenia, systemic lymphadenopathy and splenomegaly	HLH-2004	9.5	2.5 months
2	39, M	Recurrent fever, liver damage, cytopenia, abnormal coagulation, rash, uveitis, interstitial pneumonia, pericardial effusion, systemic lymphadenopathy and splenomegaly	Hormone, thalidomide, cyclosporine, VP16, ECOP	3.5	Died of HLH
3	55, F	Recurrent fever, liver damage, cytopenia, abnormal coagulation and splenomegaly	HLH-2004, Flu, plasmapheresis	12	17 months
4	37, F	Recurrent fever, anemia, liver damage, abnormal coagulation and splenomegaly	Hormone, cyclosporine, VP16, EPOCH, GELOX+VP16	11	Died of respiratory and circulatory failure
5	57, M	Recurrent fever, liver damage, systemic lymphadenopathy and splenomegaly	Hormone, ECOP	12	3 months
6	38, F	Recurrent fever, liver damage, cytopenia, abnormal coagulation and splenomegaly	HLH-2004	3	Died of HLH
7	25, M	Rash, systemic edema, bilirubin elevation, systemic lymphadenopathy and splenomegaly	Hormone	2	6.5 months
8	67, M	Recurrent fever, liver damage, rash, systemic lymphadenopathy and hepatosplenomegaly	Antiviral treatment	2	Died of ANKL

HLH: hemophagocytic lymphohistiocytosis; ANKL: aggressive natural killer-cell leukemia; VP16: etoposide; Flu: fludarabine; ECOP: etoposide+cytoxan+ vincristine+ prednisone; EPOCH: etoposide+ epirubicin +cytoxan+ vincristine+ prednisone; GELOX: gemcitabine+ oxaliplatin+ lasparaginase.

Table 2 Infectious state of EBV and host cell

Case No.	VCA-IgG	VCA-IgM	EA	EBNA	EBV-DNA($\times 10^5$ copies/mL)	Tissue EBER	Immunophenotype
1	+	-	-	+	3.16	Lymph node (+)	T
2	+	-	+	+	7.41	Lymph node (+)	T
3	+	-	+	+	3.05	Bone marrow (+)	T
4	+	-	+	+	3.41	Lymph node and nasopharyngeal region (+)	T
5	+	-	+	+	3.05	Lymph node (+)	T
6	+	-	+	-	2.05	Bone marrow (+)	T
7	+	-	+	-	4.60	Lymph node (+)	T
8	+	-	-	+	4.14	Lymph node and marrow (+)	T

VCA: viral capsid antigen; EA: early antigen; EBNA: EB virus nuclear antigen; EBER: EB virus encoded small RNA.

died of liver and heart failure. Case 7 presented without fever or cytopenia and is still survived until now after hormone therapy. Case 8 was given anti-virus and liver-protecting therapy and was closely followed up. Six out of eight patients died during follow-up with a median survival time of 15 months.

DISCUSSION

CAEBV is a special clinical syndrome present with recurrent fever, lymphadenopathy, splenomegaly, liver impairment and cytopenia that lasts more than three months. It predominantly infects healthy children and teenagers. In a study by Kimura *et al.*^[3] showed that the median age for CAEBV was 11.3 years (range: 9 months – 53 years) and they concluded that adult-onset CAEBV is rare. In the current study, all the patients were adults with a median age of 57 years.

Primary EBV infection and infectious mononucleosis are often caused by infected B-cells, while the host

cell of CAEBV is mostly the T/NK-cell. A consensus reached in the 2008 NIH International Classification Meeting on EBV-associated lymphoproliferative disease suggested that CAEBV could be divided into two subtypes according to the different host cell. Kasahara *et al.*^[4] reported that CAEBV and EBV associated HLH were mainly caused by CD4⁺ T or NK cells and CD8⁺ T cells respectively. While Kimura *et al.*^[5] demonstrated that CAEBV can be also caused by CD8⁺ T and $\gamma \delta$ T cells. Thus the identification of infected cell is critical to establish the diagnosis. *In situ* hybridization (ISH) with EBER is widely used to detect EBV-infected cells in tissue specimens^[6,7]. Owing to difficulties in tissue acquisition in some patients, to identify the host cell according to peripheral blood tests would allow diagnosis more convenient and less invasive. Recently scholars have applied a novel flow cytometric ISH assay to analyse the phenotype of EBV-infected cells by using a peptide nucleic acid probe specific for EBER^[8]. They found that the result can be used not only to diagnose

EBV infection but also to clarify the pathogenesis and prognosis. Unlike those reported in Asian, where EBV is always detected in T or NK cells in tissues, CAEBV in the USA is usually detected in B cells in tissues^[9]. This indicates that the type of host cell in EBV may be race specific.

The pathogenesis of CAEBV is not well understood. The defective of cytotoxic T-cell (CTLs) may relate to the pathogenesis of CAEBV. Previous studies revealed that CAEBV patients showed an insufficient EBV immune response, especially in the T cell response to latent membrane protein 2 (LMP2) expressed by EBV^[10,11]. This may cause the T or NK cell clonal proliferation activated by latent EBV infected cells. No related genetic mutation of XLP and familial HLH has been detected in CAEBV patients until now. Kimura *et al.*^[3] analyzed 82 patients with CAEBV, of which 76% were monoclonal and 13% were oligoclonal, and concluded that the identification of clonality of EBV infected cells is also important support tool to establish diagnosis.

The clinical presentation of CAEBV can be varied. According to a study by Cohen^[9], the most common signs and symptoms were lymphadenopathy(79%), splenomegaly(68%), fever(47%), hepatitis(47%), hypogammaglobulinemia(44%), pancytopenia(42%), hemophagocytosis(32%), hepatomegaly(32%), interstitial pneumonitis(26%), central nervous system disease(21%), and peripheral neuropathy(21%). Arai *et al.*^[12] analyzed the clinical features of 23 adult-onset patients. The clinical findings at onset were described as including fever(74%), liver lesion(dysfunction or hepatomegaly)(43%), lymphadenopathy(22%), neurological symptoms(17%), and cardiopulmonary symptoms(13%). Hypersensitivity to mosquito bites(HMB) was detected in one patient. Other symptoms such as interstitial pneumonia, uveitis and hemophagocytic syndrome were uncommon. In this study, case 2 constantly presented with uveitis, interstitial pneumonia and hydropericardium. CAEBV often runs concurrently with life-threatening syndromes including EBV-HLH, interstitial pneumonia, disseminate intravascular coagulation (DIC), hepatic failure, coronary aneurysm and central nervous system (CNS) involvement^[3,13-15].

The diagnosis of CAEBV requires clinical evidence, the presence of EBV antibodies and/or EBV DNA load or the histologic finding of tissue damage caused by EBV. Okano *et al.*^[16] revised the criteria for the diagnosis of CAEBV in 2005, so now the diagnosis of CAEBV must fulfill: (1) EBV-related symptoms, including persistent fever, hepatitis, extensive lymphadenopathy, hepatosplenomegaly, etc; (2) increased antibody titers of VCA-IgG and EA-IgG, and/or increased EBV⁺

cell detected in tissue; (3) no evidence of any prior immunologic abnormalities or other recent infection that might explain the condition. Current criteria don't emphasize the clinical course of CAEBV these days, but the detection of EBV-DNA and EBV-RNA of tissue or peripheral blood (PB) is critical. In this study, all the evidences of EBV infected tissues were confirmed by EBER ISH. For patients without extensive lymphadenopathy, the detection of EBER in bone marrow specimens presented at a high positive rate^[17].

EBV infection can cause multiple systematic organ damage. With acataleptia multiple systematic organ damage, chronic myocarditis and hepatitis occurs without clear reason, skin lesions concurrent with mosquito bites and large granular lymphocytes detected in PB, a highly suspicious of CAEBV should be considered by clinical doctors. Liver damage is the most common presentation of CAEBV as same as the results in this study which happened in all patients. Case 3 went to the hospital for his abnormal liver function test and wasn't correctly diagnosed at first. HLH is also a complication of CAEBV with a high transfer risk to lymphoma. Thus, lymphoma must be excluded when diagnosis is established. Whole body PET-CT may be a good method to make a differential diagnosis which is required for CAEBV. The bone marrow aspiration and lymph node biopsy when necessary are valuable during follow-up. Kimura *et al.*^[5] reported 6 cases of CAEBV (NK cell 4 cases, T cell 2 cases) which progressed to NK cell lymphoma, and 4 of them became NK cell leukemia. In the current study, 3 cases presented secondary HLH, and case 4 transferred to NK cell leukemia after 5 months.

No consensus for the therapy of CAEBV has been reached. Antiviral therapy such as acyclovir and ganciclovir isn't completely effective. Immunomodulator IL-2 and TNF- α or immunosuppressor corticosteroid and cyclosporin have not generally been successful and relapses are common^[9]. Although previous studies have reported effective rates of using corticosteroid and cyclosporine as 32% and 24% respectively^[3,9], others (especially patients with advanced disease) may be unresponsive. Rituximab was partly effective in X-link LPD and B-cell CAEBV, but combined chemotherapy of R-EPOCH and bortezomib was unresponsive^[9]. In this study, case 1 and 3 were initially responded to combined therapy of corticosteroid, cyclosporin and etoposide, but relapsed and progressed very soon and became unresponsive to previous therapy. This suggested that a novel effective therapy was desired. JAK inhibitors may have a therapeutic effect on CAEBV^[18].

Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for CAEBV with a prolonged

remission rate of 57% ~ 63% at present^[5,19-23]. Recently, Kawa *et al.*^[24] reported HSCT following non-destructive pretreatment (reduced intensity hematopoietic stem cell transplantation, RIST) will receive a better outcome. For 18 pediatric CAEBV patients treated with RIST, 3-year overall survival rate was $(95.0 \pm 4.9)\%$, and the 3-year event-free survival was $(85.0 \pm 8.0)\%$. While patients with CAEBV without any other progressed symptoms will keep stable for years even with no treatment^[3]. HSCT is still accompanied by a high risk for transplantation-related complications. Therefore, HSCT can be performed after a comprehensive evaluation.

Various adverse prognosis factors have been recognized including age ≥ 8 years, thrombocytopenia (less than $104 \times 10^9/L$ at diagnosis) and T-cell EBV infection^[3]. Other studies reported that older age and liver damage were the independent prognosis factors of death^[3,5]. The presence of different infected cells was also related to prognosis. The previous study found that $CD4^+$ T cells infection had a shorter survival time than NK cells infection which may also attribute to the older median age (14.5 years)^[12].

In conclusion, CAEBV in adult-onset presents more aggressive than child-onset, and most patients with recurrent symptoms and progressive disease are susceptible to concurrent life-threatening syndromes including HLH, interstitial pneumonia and lymphoma. In our study, three patients with HLH were responsive to HLH-2004 therapy but relapsed and died of multiple organ failure very soon. This indicated that active treatment for HLH was required and a novel agent such as antithymocyte globulin (ATG)^[25], alemtuzumab^[26] or DEP^[27] regimen may be a better choice. Patients with active disease had a poor prognosis, as reported in previous studies^[24,28]. Allogeneic HSCT should be performed as early as possible.

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