Features of Chronic Active Epstein-Barr virus Infection and Related Human Diseases

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Abstract: A chronic undefined illness characterized by infectious mononucleosis (IM)-like symptoms and signs, possibly associated with Epstein-Barr virus (EBV) infection, designated as so-called chronic active EBV infection (CAEBV), is focused and discussed in this mini-review. Patients with CAEBV often develop T cell lymphoproliferative disorder (LPD)/lymphoma or NK cell LPD/lymphoma. Unique manifestations with generally poor prognosis of the disease prompt us to understand in particular the entity, diagnosis and treatment.

Keywords: CAEBV, diagnosis, treatment.

INTRODUCTION

Cases with prolonged or recurrent infectious mononucleosis (IM)-like symptoms and signs, characterized mostly by fever, lymph node swelling, hepatosplenomegaly and fatigability, were already reported in the literature in the late 1940s [1]. In the middle 1970s, Horwitz *et al.* demonstrated that such patients had high prevalence of antibodies against Epstein-Barr virus (EBV) early antigen-restricted (EA-R), suggesting the presence of reactivation of EBV infection [2]. Afterwards, until 1980s, there were many reports of similar cases associated with EBV reactivation [3-5]. One of the features of disease had the tendency of high occurrence rates generally observed among adult females. In 1984, Dubois *et al.* proposed the diagnosing criteria for the disease mainly consisting of 1) the presence of EBV reactivation tested by the antibody responses against EBV and 2) no definite underlying disease particularly such as malignancy, neither rheumatic diseases nor infectious diseases associated in patients with immunodeficiency [6]. Simultaneously, chronic fatigue syndrome (CFS) was also suggestive to be derived from the similar condition, but today CFS is concluded to be the different disease entity [7].

In contrast, a severe type of chronic EBV infection (CEBV) is usually observed in childhood. In 1978, Virelizier *et al.* described a 5-year-old girl who had an intermittent fever, generalized lymphadenopathy, interstitial pneumonia, thrombocytopenia and polyclonal hypergammaglobulinemia [8]. Additionally, she had EBV-determined nuclear antigen (EBNA)-positive lymphocytes in her lymph nodes and peripheral blood, and had extremely high IgG antibody titers against viral capsid antigen (VCA) and EA, as well. The patient was reported to be expired owing to the development of lymphoblastic leukemia without EBNA-positive malignant cells during her course of illness. Following this, Joncas *et al.* described a similar patient in 1984 [9]. Furthermore, we described six Japanese patients with possibly severe type of CEBV in 1987, who had almost same symptoms and signs when compared to those reported earlier, and had similar laboratory findings including the tendency of pancytopenia, polyclonal gammopathy and/or liver dysfunction [10]. The majority of the patients had poor prognosis. In 1988, suggested criteria were first proposed for this unique type of serious illness as termed severe CEBV [11]. However, there had been tremendous confusion about the naming and/or terminology of the disease. Therefore, we proposed the novel criteria for the disease mainly by the clinical, virological, immunological and pathological findings in 1991 [12]. CEBV is for the disorder known to be caused by EBV with characteristic manifestations seen in patients with IM, without extraordinarily high antibody titers to EBV-replicating antigens such as VCA and EA, and severe chronic active EBV infection (CAEBV) syndrome (SCAEBV) for a disorder associated with more severe clinical and hematological findings, and with extremely high antibody titers to EBV-related antigens.

PATHOGENETIC MECHANISM(S) AND DIAGNOSIS OF SCAEBV AND CAEBV

An extremely high antibody titers and the presence of EBV genome in the affected tissues were all strongly suggestive as a causative role of EBV infection for SCAEBV. To date, studies had been carried out including whether the presence of viral mutation, co-infection of other lymphotropic viruses such as adenovirus, a particular immunodeficiency, and/or underlying some genetic factors responsible for the development of disease. However, presently there is no confirmative evidence for an each etiological possibility. Nevertheless, the facts described in 1988, as the development of the EBV genome-positive T cell lymphoma in patients and EBV infection at T lymphocytes in the circulation in a patient with SCAEBV highly indicated the causative role of EBV for the disease [13, 14].

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Almost patients with SCAEBV developed mostly T cell lymphoma during the course of disease [15]. T lymphocytes are considered to be one of the main immune mediators, producing many cytokines to regulate and control the significant infection and proliferation, and therefore the EBV-infected T cells appear to be one of the keys for recognizing the pathogenetic role and the various clinical phenotypes of SCAEBV. Interestingly, EBV-positive T cell lines were established only from the patients with SCAEBV [16].

Collectively, followings are considered to be the possible pathogenetic mechanisms for the development of SCAEBV; 1) infection of EBV to human T lymphocytes initially, 2) extraordinary replication of EBV or proliferation of EBV-infected cells in affected tissues, and finally toward 3) malignant transformation of EBV-infected cells.

Recently, certain patients with active EBV infection mimicking SCAEBV had been described, consisting of an increased copy numbers of EBV DNA in peripheral blood without extremely high antibody titers against EBV replicative antigens [17]. Therefore, we proposed the diagnosing guidelines for so-called CAEBV including such cases [18]. In patients with CAEBV, T cell lymphoproliferative disorder (LPD)/lymphoma or NK cell LPD/lymphoma, hemophagocytic lymphohistiocytosis and/or hypersensitivity to mosquito bites often develop during the course of illness. Furthermore, Mexican and US researchers proposed a concept of the disease named as fulminant EBV-positive T cell LPD characterized by; 1) disease to be totally fatal, 2) generally associated with the primary infection of EBV, but it occasionally occurred in patients with SCAEBV, 3) the lack of hereditary or acquired EBV-specific immune defenses, 4) possibly underlying the ethnic differences predominantly Asian ancestry, and 5) occasionally no antibody response to EBV in spite of the presence of active infection with the clonal T cell proliferation [19]. This entity is highly attractive and should be considered or differentiated from SCAEBV and/or CAEBV.

Tissue specimens of SCAEBV or CAEBV generally show the type II latency of EBV expressing EBNA1, latent membrane proteins and EBV-encoded RNAs [20]. When the pathological finding being clarified for the disease, it should be used as the final diagnosis to avoid the unnecessary confusion. Additionally, although Cohen *et al*. recently proposed to facilitate further clinical and biological studies of EBV-driven LPD [21], in the future precisely providing the classification of LPD will be beneficial for more understanding and diagnosing these anecdotal diseases.

Major historical landmarks of CEBV, SCAEBV and CAEBV are shown in Table **1**.

TREATMENT FOR PATIENTS WITH SCAEBV AND CAEBV

Many therapeutic approaches had been attempted, such as using immunoenhancers, immunosuppressants, antiviral and antitumor treatments, but to date there is no confirmative evidence for the effectiveness [20, 22-25], More recently, a hematopoietic stem cell transplantation (HSCT) was performed with some success in cases with T cell LPD/lymphoma or NK cell LPD/lymphoma associated with CAEBV [18, 26]. Further studies are required for more certain treatment by the fundamental recognition of the disease including mainly virological, immunological and pathological studies [20].

Notable therapeutic approaches are shown in Table **2**.

CONCLUDING REMARKS

EBV is ubiquitous among vast majority of human individuals, and its infection generally results in subclinical. However, in certain circumstances it causes benign diseases such as IM, and highly associates with human malignancies including lymphoma and nasopharyngeal carcinoma. SCAEBV, CAEBV and their related diseases, described herein, having no underlying diseases, are serious because of their poor prognosis. Clarifying the pathogenetic mecha-

Table 1. Historical Landmarks of CEBV, SCAEBV and CAEBV

Subject	Reported yr.	Author(s)	Reference no.*
CEBV described	1948	Isaacs	[1]
CEBV and positive antibodies to EA-R	1975	Horwitz *et al.*	[2]
SCAEBV described	1978	Virelizier *et al.*	[8]
Serology of CEBV	1982	Tobi *et al.*	[3]
Criteria for CEBV	1984	Dubois *et al.*	[6]
Large numbers of patients with CEBV	1985	Jones *et al*.	[4]
		Straus *et al.*	[5]
Criteria for severe type of CEBV	1988	Straus	[11]
EBV in T cell lymphoma with SCAEBV		Jones *et al.*	[13]
EBV at circulating T lymphocytes with SCAEBV		Kikuta *et al.*	[14]
Case definition for SCAEBV	1991	Okano *et al.*	[12]
Precise characters of SCAEBV and CAEBV	2001	Kimura *et al.*	[17]
Guidelines for so-called CAEBV	2005	Okano *et al.*	[18]

*: Refer to the numbered reference in the text.

Table 2. Notable Therapeutic Approaches for SCAEBV and CAEBV

Subject	Reported yr.	Authors	Reference no.*
Interleukin-2	1987	Kawa-Ha *et al.*	[22]
Ganciclovir	1993	Ishida *et al.*	[23]
Interferon-gamma		Fujisaki *et al.*	[24]
EBV-specific cytotoxic T lymphocytes	1996	Kuzushima *et al.*	[25]
HSCT	2000	Okamura *et al.*	[26]

*: Refer to the numbered reference in the text.

nism(s) of them will provide us with more recognizing the broad spectrum of diseases, which are etiologically linked to the EBV infection, without the definite diagnosis and treatment.

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