Clinical and Virological Characteristics of Patients with Chronic Active Epstein-Barr Virus Infection Treated with Hematopoietic Stem Cell Transplantation: Insights and Questions

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(See the article by Gotoh et al. on pages 1525–34)

In this issue of *Clinical Infectious Diseases,* Gotoh et al. [1] report on the largest cohort of patients in a single center who had severe chronic active (CA) Epstein-Barr virus (EBV) infection and underwent hematopoietic stem cell transplantation (HSCT). EBV is a latent γ-herpesvirus, and >90% of the world's population is EBV positive. During primary infection, EBV establishes lifelong latency in the memory B cell compartment, and the number of latently infected B cells within an individual remains stable for years [2]. Healthy persons mount a vigorous humoral and cellular immune response to primary infection. Although EBV-specific antibodies neutralize virus infectivity, the cellular immune response, consisting of $CD4^+$ and $CD8^+$ T cells, is essential for controlling primary and latent EBV infection [3]. Most persons recover from the acute phase of primary EBV infection with no long-term sequelae.

Latent EBV infection is associated with a heterogeneous group of diseases, including CAEBV infections and malignancies [4, 5]. Interestingly, several of these diseases have unique geographic distributions, arguing that genetic and environmental factors play an important role in addition to EBV in their pathogenesis [5]. Severe CAEBV infection is a good example of a disease with a strong geographic bias. It is most commonly seen in Japan, and in the majority of cases, EBV resides in T cells or natural killer (NK) cells. Patients with severe T cell and NK cell CAEBV infection do not have an underlying immunodeficiency, and the etiology to date remains poorly understood [6–9].

Patients with severe CAEBV infection may present with a variety of clinical signs and symptoms, including fever, hepatosplenomegaly, lymphadenopathy, and skin lesions, including hypersensitivity to mosquito bites and hydroa vacciniforme [7]. Laboratory findings include unspecific abnormalities, such as liver dysfunction, thrombocytopenia, and anemia, and EBV-related abnormalities, including elevated antibody titers against viral capsid antigen and/or early antigen and an elevated EBV DNA load. Although these abnormalities are seen in patients with other EBV-associated disease, the diagnosis of severe T cell or NK cell CAEBV infection is established by confirming the presence of EBV in T or NK cell subsets. Most patients also have evidence of clonal expansion in their respective T or NK cell population [7, 8]. Patients with severe CAEBV infection are at great risk of developing lymphomas, leukemias, or hemophagocytic syndrome, and preemptive HSCT has been advocated to prevent these complications [10, 11]. Gotoh et al. [1] report on their experience using HSCT to treat patients with severe CAEBV infection. The series included 15 patients and is the largest series published to date. Of these 15 patients, 14 were evaluable, and the authors report a long-term survival rate of 50%. This is similar to survival rates reported by Kawa et al. [11] for a smaller cohort of patients with severe CAEBV infection (5 of 8 patients survived) and to rates reported for patients with familial hemophagocytic syndromes [12]. Three of the 7 deaths in the study by Gotoh et al. [1] were attributable to disease recurrence, and 4 patients died of treatment-related complications. The authors performed an extensive analysis of factors that might

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predict outcome and found that young age and early diagnosis correlated with favorable outcome. Conversely, multiorgan involvement, as measured by elevated plasma EBV DNA levels at diagnosis and the number of "life-threatening complications" related to severe CAEBV infection, was associated with poor outcome. Interestingly, cytokine levels and EBV strain differences, determined by *LMP1* gene sequencing, were not associated with prognosis.

In summary, the results reported by Gotoh et al. [1] highlight that early diagnosis improves outcome for patients with severe CAEBV infection after HSCT; in addition, performing HSCT before a patient develops "life-threatening complications" results in better outcome. This study is also a reminder of how little we know about the etiology of severe T cell and NK cell CAEBV infection. Kasahara et al. [9] reported that the pattern of lymphocyte infection differs between patients with severe CAEBV infection and those with hemophagocytic lymphohistiocytosis in Japan. However, it remains unclear how the virus infects T and NK cells. Zhang et al. [13] recently identified several genes that are differentially expressed in NK and T cell lines derived from patients with severe CAEBV infection, but additional studies are needed to confirm the biological relevance of these findings.

Although HSCT remains the only curative option for severe CAEBV infection, EBV-targeted therapies may become an alternative in the future. Because antiviral agents, such as acyclovir, only prevent productive viral replication and do not affect EBV latency, these agents are of limited therapeutic value for the treatment of severe CAEBV infection. However, the efficacy of antiviral agents for the treatment of EBV-associated malignancies can be greatly enhanced by inducing the expression of the virus-associated thymidine kinase in latently EBV-infected cells [14]. This strategy has shown promising results in several preclinical EBV-positive tumor models, and the results of phase 1 clinical studies are encouraging [15, 16]. EBV-targeted immunotherapy is another approach to eradicate EBV-infected T and NK cells in patients with severe CAEBV infection. Although polyclonal T cells specific for EBV antigens or enriched for the EBV-encoded LMP2 antigen have been used successfully to treat EBV-associated diseases, including malignancies, the experience in patients with severe CAEBV infection is thus far limited and warrants further investigation [17–20].

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