Poor Outcomes of Chronic Active Epstein-Barr Virus Infection and Hemophagocytic Lymphohistiocytosis in Non-Japanese Adult Patients

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Chronic active Epstein-Barr virus infection manifests as a combination of persistent infectious mononucleosis–like symptoms and high viral load in apparently immunocompetent patients. It is closely related to Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis. These 2 abnormal Epstein-Barr virus–associated diseases are seldom reported in individuals other than Japanese children and adolescents. We report a series of 2 adult non-Japanese patients with fatal chronic active Epstein-Barr virus and 1 adult non-Japanese patient with Epstein-Barr virus hemophagocytic lymphohistiocytosis and discuss its pathogenesis and treatment options.

Epstein-Barr virus (EBV) is a highly prevalent herpes virus that can cause transient infectious mononucleosis, EBV–related malignancies, and chronic active EBV (CAEBV) infection [1]. CAEBV infection is a persistent EBV infection in combination with infectious mononucleosis–like symptoms in individuals without apparent immunodeficiency. A number of diagnostic criteria have been proposed [2–4]. High antibody titers against EBV-related proteins are not necessary for the diagnosis, because there can be a lack of serologic response in patients with CAEBV infection.

CAEBV infection is closely related to EBV–associated hemophagocytic lymphohistiocytosis (EBV–HLH); both are associated with infection of T cells or natural killer cells, whereas B cells remain negative for EBV in patients with these infections. However, EBV–HLH usually has a fulminant course over a period of weeks, although CAEBV infection may persist for months to years before complications arise. In addition, different cellular targets appear to be implicated in these 2 abnormal EBV–associated diseases [5]. In patients with either disease, life-threatening complications may occur, such as malignant lymphoma, hepatic failure, gastrointestinal perforation, disseminated intravascular coagulopathy, and HLH [6], and the mortality rate associated with these diseases is >50% [2].

The clinical characteristics of severe CAEBV infection and EBV–HLH is attributable to an increased inflammatory response caused by the hypersecretion of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-6, IL-10, and macrophage-colony-stimulating factor. Reports of CAEBV infection and EBV–HLH from places other than Japan are rare, suggesting that diagnosis of the disease may have been missed in Western countries [7–9]. We describe 3 non-Japanese adult patients, 2 with fatal CAEBV infection and 1 with fatal EBV–HLH, and discuss the pathogenesis and our experience with treatment options in these patients.

Case histories. The first case involved a 52-year-old Dutch man who was referred to treatment because of fever, night sweats, and a 6-month history of general malaise. Thirty years before, he had been successfully treated for Hodgkin lymphoma with mantle field radiation and splenectomy. Three years before presentation, he had received a diagnosis of infectious mononucleosis. Physical examination and radiographic evaluation revealed no abnormality. No evidence of immunodeficiency was detected. Serological tests and cultures for a wide range of viral, bacterial, and fungal agents did not suggest recent infections other than recurrent acute EBV infection. Also, a high EBV load of 9.0 × 106 copies/mL was measured in the peripheral blood by quantitative PCR, as described elsewhere [10]. Bone marrow biopsy analysis showed infiltration with EBV–positive polyclonal CD8+ T cells that were suppressing normal hematopoiesis. Single staining was performed to detect CD3, CD2, CD5, CD4, CD8, CD56, CD57, TIA-1, and granzyme-B molecules, and double staining was performed to detect EBER/CD3. The patient was initially treated with high-dose corticosteroids and was planned to begin aggressive immunochemotherapy. Although the patient’s EBV load decreased (figure 1), he developed liver failure, renal failure, pancytopenia, and bleeding diathesis. Four days after the start of treatment, he died because of multiorgan failure. Postmortem liver and bone marrow biopsy analyses showed large amounts of EBV–driven T cell proliferation. Monoclonality

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of this T cell population could not be proven with the use of PCR for T cell receptors β and γ.

In case 2, a 59-year-old Dutch man presented with a 1-year history of fever of unknown origin without other complaints. His medical history was unremarkable. CT of the chest and abdomen demonstrated an enlarged spleen. Bone marrow aspirate and biopsy results were normal. Serological tests and cultures for a wide range of viral, bacterial, and fungal infectious agents did not suggest an acute infection. Quantitative PCR, however, showed an EBV load of $2.7 \times 10^3$ copies/mL. Consequently, CAEBV infection was considered to be the cause of his symptoms. Using fluorescence-activated cell sorting procedures, as described elsewhere [11], we demonstrated that the EBV load was confined to the natural killer cell compartment, and the patient was treated with high-dose dexamethasone, etoposide, and cyclosporine, followed by nonmyeloablative, allogeneic hematopoietic stem cell transplantation (HSCT) after induction with fludarabine and total body irradiation [12]. After an initial favorable response, EBV load rapidly increased (figure 1), and the patient developed severe electrolyte disturbances and thrombocytopenia. There was no rash, diarrhea, or abnormal liver test results that would have suggested acute graft-versus-host disease. Thirty days after HSCT, the patient died because of acute, uncontrollable gastric bleeding that was not further diagnosed.

Case 3 involved a 30-year-old man from Burkina Faso who presented with a 2-month history of fever and respiratory distress. His medical history was unremarkable. Laboratory results showed pancytopenia, prolonged clotting times, abnormal liver biochemistry, and reduced renal function. CT of the chest and abdomen showed interstitial lung abnormalities and hepatosplenomegaly. Blood and sputum culture results remained negative. Serological test results confirmed a past EBV infection and were negative for a wide range of other acute viral infections. A high EBV load of $1.5 \times 10^6$ copies/mL was measured in the peripheral blood by quantitative PCR. Using cell sorting techniques [11], the EBV load was found to be located in the natural killer cell compartment. Bone marrow aspirate and biopsy results indicated hypercellular marrow with a reactive inflammatory response and hemophagocytosis. DNA sequencing showed no mutation in the Perforin or FAS genes. X-linked lymphoproliferative disorder was ruled out by investigating the SAP gene. Therefore, the patient received a diagnosis of EBV-HLH and was treated according to the HLH-2004 protocol with high-dose dexamethasone, etoposide, and cyclosporine A [12]. EBV load rapidly decreased to $7.2 \times 10^4$ copies/mL with an
accompanying favorable clinical response. Fifty days after the start of treatment, the patient developed respiratory insufficiency, treatment refractory hypotension, gastrointestinal hemorrhages, and renal failure. EBV load had increased to $3.5 \times 10^6$ copies/mL. Despite a repetition of treatment according to the HLH-2004 protocol, the patient died 5 days after readmission to the hospital because of multiorgan failure.

**Discussion.** CAEBV infection is rarely reported in non-Japanese adults, and the diagnosis may often be missed in Western countries. The pathogenesis of CAEBV infection remains largely unknown, but genetic or inherited immunodeficiency, coinfection with other viruses, and virus-specific properties may play a role.

Successful suppression of EBV is primarily attributable to T cell immunity [1]. Accordingly, EBV-related complications mainly occur in patients with congenital and acquired T cell immunodeficiency. Defects in genes that are essential for regulating lymphocyte activation and proliferation, such as the Perforin and FAS genes, have been found in selected patients with CAEBV infection [13]. Although these defects are not associated with the vast majority of CAEBV infection, it is possible that defects in such genes are involved in the etiology of CAEBV infection. Specific gene abnormalities were tested in 1 of our patients, and no defects in the Perforin, FAS, or SAP genes were detected. However, in the case of CAEBV infection in elderly patients, acquired rather than inherited immunodeficiency is likely to play a role in the pathogenesis of the disease. Also, because CAEBV infection is uncommon even in patients with severe T cell immunodeficiency, virus-specific mechanisms appear to be involved.

CAEBV infection may be caused by a specific virus strain [14]. Such a strain may be highly virulent or have evolved unique immune evasion strategies. However, the evidence for a unique CAEBV-infection–causing EBV strain is limited. Strains that are very different have been isolated from patients with CAEBV infection, and very similar strains have been isolated from both CAEBV-infected patients and healthy control individuals. In addition, no CAEBV infection outbreak—only a single case of familial transmission—has been reported [15]. Alternatively, coinfection with other viruses or with a second EBV strain may deceive the immune system and facilitate the development of CAEBV infection.

CAEBV infection is characterized by infectious mononucleosis–like symptoms. Our third case, however, covered a period of several weeks rather than months and may therefore be better described as a case of EBV-THL, rather than CAEBV infection. These 2 diseases possess pathologic similarities, although EBV-THL usually has a more fulminant course of disease [5]. Obviously, there is a close overlap between the 2 diseases, as illustrated by the 3 case histories presented.

CAEBV infection is a potentially fatal disease, and several treatment strategies have been proposed. Rituximab has been used to successfully treat patients with CD20+ EBV B cell infections but is ineffective for the treatment of CAEBV infection, because the infection is located in T cells and natural killer cells. In these cases, administration of immune modulating agents, such as IFN-α or IL-2, has been attempted but has not eradicated the proliferation of EBV [14]. Also, results of treatment with antiviral agents, such as aciclovir, ganciclovir, and vidarabine, have been disappointing. Several reports suggest that CAEBV-infected patients have benefited from immunotherapy that involves steroids, etoposide, and cyclosporine A, although no clinical trial has evaluated this regimen [12]. Recently, successful treatment of CAEBV infection by allogeneic HSCT was reported in Japanese children [14]. A similar approach can be considered for elderly CAEBV-infected patients, because outcomes in these patients are generally poor. Treatment may follow the HLH-2004 protocol, which uses induction immunotherapy with high-dose dexamethasone, etoposide, and cyclosporine A followed by allogeneic HSCT [12], although firm evidence for the protocol’s effectiveness is lacking. It is important to realize that the clinical condition of patients may deteriorate rapidly soon after the initiation of treatment because of a catalytic response, similar to that in the first case we reported.

CAEBV infection is a severe and often fatal disease with largely unclarified pathogenesis. It has a close overlap with EBV-THL. It is important to realize that CAEBV infection is not limited to Japanese children and adolescents but also occurs in non-Japanese adults. If CAEBV infection is suspected, evaluation of EBV-specific antibodies is not sufficient; instead, viral load should be measured with quantitative PCR. Cell sorting techniques can be used to determine if T cells or natural killer cells are involved in the infection and to confirm the diagnosis.

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