Early-Onset Guillain-Barré Syndrome Associated with Reactivation of Epstein-Barr Virus Infection after Nonmyeloablative Stem Cell Transplantation

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We report a case of early-onset acute Guillain-Barré syndrome associated with reactivation of Epstein-Barr virus (EBV) infection after nonmyeloablative stem cell transplantation (NST). Reactivation of EBV infection preceded disease onset, and the virus load increased concomitantly with disease progression (doubling time, 2.7 days). This case raises concern about the expanding scope of manifestations associated with reactivation of EBV infection after NST.

Reactivation of Epstein-Barr virus (EBV) infection (hereafter “EBV reactivation”) frequently occurs after allogeneic hematopoietic stem cell transplantation (HSCT), but symptoms attributable to this event are considered rare and have remained poorly characterized [1]. The primary concern with EBV infection in this situation is the development of EBV-driven post-transplant lymphoproliferative disorder (PTLD), which is associated with uncontrolled proliferation of B cells [2]. Patients with PTLD may present with unexplained fever, with or without lymphadenopathy. However, it is increasingly recognized that the spectrum of clinical manifestations associated with EBV reactivation and PTLD is much wider than previously thought and may involve virtually any organ system [3]. Thus far, studies of EBV reactivation have been limited to persons undergoing HSCT who are receiving myeloablative conditioning. Recently, molecular monitoring of EBV load in peripheral blood or plasma samples has been employed for the early diagnosis and prediction of EBV-associated PTLD [4]. Here, we report a case of early-onset acute sensorimotor neuropathy that was associated with EBV reactivation after nonmyeloablative stem cell transplantation (NST).

**Case report.** A 49-year-old man with myelodysplastic syndrome, which had been diagnosed 6 months previously (trisomy 8, with <10% blasts in bone marrow), received an HLA-matched hematopoietic stem cell transplant from his sister. Both patient and donor were seropositive for EBV, cytomegalovirus, herpes simplex virus, varicella zoster virus, and toxoplasma. There was no clinical or serological evidence of recent pretransplant primary EBV infection in the recipient or donor. The nonmyeloablative conditioning regimen consisted of intravenous samarium (6.6 millicuries/kg for 1 day), followed by fludarabine (30 mg/m² q.d. for 6 days), busulfan (3.2 mg/kg q.d. for 2 days), and antithymocytic globulin (2.5 mg/kg q.d. for 4 days). Graft-versus-host disease prophylaxis consisted of low-dose short-term cyclosporine. The patient received unmanipulated granulocyte colony-stimulating factor mobilized peripheral blood stem cells (18.9 × 10⁶ cells/kg; 4.44 × 10⁹ CD3+ cells/kg). He received antiviral prophylaxis with oral acyclovir (800 mg q.i.d.) and was monitored for cytomegalovirus infection weekly using pp65 antigenemia and PCR assays.

His initial transplantation course was unremarkable, and bone marrow engraftment was documented on day 11 after transplantation. On day 20 after transplantation, the patient started to experience tingling and numbness in both hands. Over the next several days, he developed descending muscle weakness involving the upper and lower extremities. Physical examination revealed areflexic motor paralysis, with mild to moderate sensory disturbance. The WBC count was 8.6 × 10⁹ cells/L, and the lymphocyte count was 1.38 × 10⁹ lymphocytes/L. The findings of nerve conduction studies were consistent with severe sensorimotor neuropathy. Brain CT findings were normal, and examination of a CSF specimen revealed acellularity, with a high protein level (1197 mg/L; upper limit of normal level, 650 mg/L) and a normal glucose level. CSF immunoglobulin electrophoresis revealed IgG κ monoclonal band. Serum immunoglobulin electrophoresis revealed no paraprotein. A diagnosis of acute symmetrical sensorimotor peripheral neuropathy (Guillain-Barré syndrome) was made.

The results of CSF cultures were negative. Serological tests for cytomegalovirus, herpes simplex virus, varicella zoster virus,
and toxoplasma showed no evidence of reactivation. Findings of serological tests for EBV were compatible with past infection, without evidence of reactivation (viral capsid antigen IgM level, 2 AU/mL; viral capsid antigen IgG level, 133 AU/mL; and EBV nuclear antigen IgG level, 61 AU/mL [levels of ≥20 AU/mL are considered positive for each value]). The results of PCR tests of peripheral blood samples for cytomegalovirus and human herpes virus 6 were negative, as were the results of PCR of CSF samples for cytomegalovirus, human herpes virus 6, and EBV.

The patient was treated with intravenous immunoglobulin (2 g/kg q.d.) for 5 days. However, his condition deteriorated, with development of respiratory muscle involvement and respiratory insufficiency that required mechanical ventilation. The patient developed a sepsis-like syndrome with multiple-organ failure. The results of PCR of a plasma sample were positive for EBV DNA, and blood culture results remained negative. He was treated with broad-spectrum antibiotics and intravenous acyclovir, but he died shortly thereafter, on day 34 after transplantation. Consecutive plasma specimens were retrospectively analyzed for EBV load.

Methods. Consecutive plasma samples were prospectively collected at weekly intervals starting from the time of transplantation and were stored at −70°C until assayed. Quantification of EBV DNA in plasma samples (in genome copies/mL) was performed by real-time PCR assay. Primers and probe were derived from the EBV alkaline DNase gene, and the results were related to a quantitated plasmid standard containing the same amplified region cloned into a TA vector (Invitrogen). The assay accurately detects viral DNA in plasma over a linear range of 50 to 10^7 genome copies/mL. Reactivation was defined as a plasma EBV DNA level of >50 copies/mL [4].

The kinetics of virus growth was determined by plotting virus load versus time. The doubling time of EBV load was calculated on the basis of the best-fit curve (Excel 2000; Microsoft), using the equation \( \ln(2)/a \), where “a” is the growth constant [5].

Results and discussion. Acute sensorimotor neuropathy is rare in hematopoietic stem cell transplant recipients [6]. Reported cases have been attributed to toxic effects of the conditioning regimen or to preceding viral infection (mainly cytomegalovirus infection), which are frequently evidenced indirectly by serological assays [6]. In nonimmunocompromised individuals, cases of Guillain-Barré syndrome have been associated with primary EBV infection, and it has been demonstrated that neurological complications can dominate the clinical presentation. EBV has also been reported to be the cause of transverse myelitis after HSCT [7].

The patient described here had direct molecular evidence of EBV reactivation, which occurred as early as 5 days after undergoing transplantation and 15 days prior to the onset of neuropathy (figure 1). EBV load kinetics followed a logarithmic curve with a high growth rate and a short doubling time of 2.7 days, so that, by the onset of disease, the EBV load was >10^7 copies/mL (figure 1). The virus load continued to increase while clinical disease took on a fulminant course. Of interest, doubling times of a similar range have been shown for cytomegalovirus in previously cytomegalovirus-seropositive immunocompromised individuals who developed active cytomegalovirus infection and disease [8]. The unusual early occurrence and the strong temporal correlation with the ascending virus load support the role of EBV reactivation in the development of neuropathy and in the fulminant course of disease with multiple-organ failure in the absence of any other identifiable cause. Early-onset fulminant PTLD has been described in transplant recipients with primary EBV infection shortly before they underwent transplantation [9]; however, there was no evidence of recent onset primary infection in the patient or donor in our report.

The pathogenesis of neuropathy remains unclear. The results of CSF PCR were negative for EBV DNA, excluding direct infection of the CNS. The disease could be immune mediated, associated with imbalanced proliferation of EBV-activated B cells in the CNS, or associated with direct infection of peripheral nerves. The specific finding of IgG k in the CSF could reflect EBV-induced monoclonal B cell proliferation in the CNS.

Of note, some of the medications used in the patient’s conditioning regimen are potentially neurotoxic: fludarabine can cause mild peripheral neuropathy, encephalopathy, seizures, visual deficits, and coma; busulfan may cause seizures; and cyclosporine is associated with confusion, aphasia, dystonia, seizures, and coma with white matter lesions. However, neither the clinical manifestations of the patient nor the laboratory and radiological findings were compatible with drug-induced neurotoxicity.
The increase in the virus load and the development of disease occurred while the patient was receiving treatment with acyclovir, which is known to inhibit lytic EBV infection. Although high-dose oral acyclovir was not effective, intravenous acyclovir appeared to abrogate viral DNA replication (figure 1), although this occurred too late in the course of this patient’s condition. Increase in the virus load despite receipt of antiviral treatment has been reported in patients who develop PTLD [1], and the efficacy of antiviral treatment for the prevention of EBV-related disorders has not been established for persons undergoing HSCT. However, there is evidence that prophylactic antiviral therapy is associated with a reduction in the risk for PTLD among solid organ transplant recipients [10]. It has been recently shown that preemptive rituximab therapy can prevent the development of PTLD in high-risk hematopoietic stem cell transplant recipients [4].

Major risk factors for EBV reactivation and EBV-associated PTLD in patients receiving myeloablative conditioning include receipt of a transplant from an unrelated donor, receipt of a T cell–depleted allograft, use of antithymocytic globulin, and treatment of graft-versus-host disease [3]. To our knowledge, this is the first report of severe fulminant EBV-associated neurological disease in a patient undergoing NST without graft manipulation. The patient’s immune reconstitution, as reflected by the total WBC and lymphocyte counts, was achieved as early as 3 weeks after transplantation, which is compatible with what has already been published by our group and others, regarding immune reconstitution after NST [11]. The only known risk factor in the patient’s clinical course was the administration of antithymocytic globulin. Because antithymocytic globulin is commonly administered as part of nonmyeloablative conditioning, which is increasingly employed in many transplantation centers [12], the rate of EBV reactivation after HSCT is expected to increase. The possible beneficial effect of antithymocytic globulin in NST conditioning remains to be investigated. On one hand, it may secure engraftment and minimize the severity and incidence of graft-versus-host disease; on the other hand, it might increase the incidence of infection. Thus, the overall role of antithymocytic globulin therapy can be assessed only in a prospective randomized study, one of which is currently underway.

This case underscores the need to suspect EBV infection during unexplained clinical deterioration in at-risk persons who are undergoing HSCT. Virus load monitoring could enhance our understanding of the expanding scope of clinical manifestations associated with EBV reactivation after HSCT and could lead to the establishment of preemptive and therapeutic approaches. Studies by our group are under way to determine the rate and clinical relevance of EBV reactivation following NST.

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**References**