EPSTEIN-BARR INFECTION AFTER BONE MARROW TRANSPLANTATION

To the Editor:

Epstein-Barr virus (EBV) lymphoproliferation is now a significant cause of morbidity and mortality after mismatched family or matched unrelated donor bone marrow transplantation (BMT). Antiviral agents including Acyclovir have been ineffective for this complication because they affect only the replicative phase of EBV infection and cannot modify the growth of transformed B cells. Oettle et al recently reported a patient who developed evidence of EBV infection after a BMT from a mismatched sibling. Resolution was...
ascribed to administration of Ganciclovir and intravenous Ig. However, this conclusion assumes that active EBV infection would otherwise fail to resolve in these immunosuppressed patients. We suggest an alternative explanation, ie, that resolution may be the result of an effective immune response generated by the patient and describe a BMT recipient in whom EBV infection resolved spontaneously, coincident with the development of an effective cytotoxic response.

UPN 213, a 12-year-old white female with chronic myelogenous leukemia in accelerated phase received a BMT from a matched unrelated donor who was a 6 of 6 serologic match and DRB1 identical. T-cell depletion of the donor marrow with antibodies to CD6 and CD8 and posttransplant Cyclosporin were used for graft-versus-host disease (GVHD) prophylaxis. She engrafted with an absolute neutrophil count of 500 on day 28 and experienced only transient grade I skin GVHD. Cytogenetic studies at day 21 and day 100 showed all metaphases to be of donor (male) origin. At day 140, she presented with fever and night sweats and was found to have a pleural effusion. Pleural fluid was obtained and found to contain 4,600 white blood cells/μL, with 62% lymphocytes, which were predominantly CD3+. Microbiologic studies were all negative, but immunofluorescence studies showed the presence of EBNA 2 and LMP-positive lymphocytes. Semiquantitative polymerase chain reaction studies of circulating mononuclear cells were highly suggestive of an acute infection with EBV. Peripheral blood mononuclear cells, which had shown only low amounts of signal pretransplant and in the early posttransplant period, showed a dramatic increase in the levels of EBV DNA (Fig 1) coincident with the onset of her febrile illness. Cytotoxicity assays using peripheral blood mononuclear cells as effector cells showed high-level killing of autologous (donor) lymphoblastic cell line (LCL; Fig 2), mismatched LCL, and an activated killer target. Because of this high level of cytotoxic activity, the patient did not receive any antiviral therapy. Her disease subsequently resolved clinically and follow-up studies showed levels of EBV DNA in peripheral blood had declined sharply (Fig 1). Similarly, levels of anti-EBV infection cytotoxic activity that were high during the acute illness declined as EBV DNA levels decreased (Fig 2). There has been no development of EBV lymphoproliferative disorder.

We suggest that EBV infection posttransplant may present as a spectrum of disease. In some patients, immune system recovery is sufficient to mount an effective immune response and EBV infection will present as a severe but self-limiting acute illness. In contrast, patients in whom immune recovery is delayed and who cannot mount an effective immune response may develop EBV lymphoproliferative disorder. Thus, although Ganciclovir may be a useful agent to treat EBV infection in BMT recipients, apparent resolution of the disease in response to therapeutic intervention may relate instead to the generation of cytotoxic responses rather than to the antiviral effect of Ganciclovir.

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