To the editor:

Monitoring of EBV reactivation is justified in patients with aplastic anemia treated with rabbit ATG as a second course of immunosuppression

Recently Scheinberg et al[1] reported their findings on cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation following antibody-based immunosuppressive regimens in patients with severe aplastic anemia. Although in the majority of patients EBV reactivation was observed, no EBV-related disease was observed; therefore the authors conclude that there is no need to routinely monitor viral reactivation in these patients. We generally agree with that; however, in some patients monitoring reactivation of EBV might be necessary, which is supported by the following case report describing a patient with severe aplastic anemia (SAA) being treated with rabbit antithymocyte globulin (ATG) and cyclosporin, developing life-threatening EBV-related lymphoma.

A 42-year-old EBV seropositive woman with SAA who did not respond to previous treatment with horse antithymocyte globulin (40 mg/kg for 4 days) and cyclosporine, was treated with rabbit antithymocyte globulin (12.5 mg/kg for 4 days) and cyclosporine 10 months after the horse-ATG. Two weeks later she was admitted with fever, a painful throat, minor enlarged submandibular, axillary, and inguinal lymph nodes, and hepatosplenomegaly. Laboratory investigations showed hemoglobin (Hb) 7.0 g/dL (4.4 mM), thrombocytes 6×10^9/L, leucocytes 2.2×10^9/L, of which 76% were lymphocytes, no fragmentocytes, creatinine 226 μM, and LDH at 811 U/L. She rapidly deteriorated and needed dialysis and mechanical ventilation. Biopsy of an inguinal lymph node showed an EBV-associated diffuse large B-cell lymphoma expressing LMP-1 (latent membrane protein), EBER, and EBNA-2 (EBV nuclear antigen). Polymerase chain reaction (PCR) of peripheral blood showed 4×10^6 EBV-DNA copies/mL. To restore T-cell function, cyclosporine was discontinued, but because urgent treatment of her lymphoma was required, rituximab (375 mg/m^2) was administered at the intensive care unit. Because of persisting hepatosplenomegaly and stagnant EBV copies after 2 treatments with rituximab, cyclophosphamide was added (750 mg/m^2), leading to clinical improvement and disappearance of circulating EBV copies. At this moment, 2 years later, her blood counts are improved, without the need for immunosupressive therapy. No EBV reactivation or recurrent lymphoma occurred.

In contrast to the series by Scheinberg, in our patient, reactivation of EBV did lead to severe clinical disease. This might be partly related to the higher dose of rabbit ATG we administered, but it can be well explained by the observation of Scheinberg that all patients receiving rabbit ATG showed reactivation of EBV, with median peaks of viral loads being 60-fold higher and the median duration of PCR positivity almost 2-fold longer compared with horse ATG. The authors suggest that rabbit ATG is more immunosuppressive, supported by the longer duration of lymphopenia they observed. However, a relation with its administration as a second course of ATG could not be excluded.

Therefore, we suggest monitoring EBV reactivation in patients being treated with rabbit ATG as a second course of immunosuppression. These patients probably benefit from early detection of reactivation, considering that a continuous rise in EBV DNA load was indicative of imminent disease in T-cell–depleted allogeneic transplantations, which was not observed after non–T-cell–depleted allogeneic transplantations.[2] This confirms the hypothesis of Schein-berg that progression of disease correlates with the inability to generate an effective immune response. Whether in the non–transplantation setting EBV-reactivation justifies preemptive treatment with rituximab[3] or should lead to watchful waiting, as the data of Scheinberg suggest, needs to be determined.[1,4]

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Response

EBV reactivation in the immunosuppressed: to treat or not to treat?

Wondergem et al raise the issue that in certain patients with aplastic anemia treated with immunosuppressive therapy, Epstein-Barr virus (EBV) reactivation may sometimes transcend a subclinical stage and progress to an EBV-lymphoproliferative process. In our paper, the intention was to suggest that monitoring EBV and cytomegalovirus (CMV) viral load is not necessary for patients treated with standard immunosuppressive protocols, but with novel immunosuppressive schedules, more potent immunosuppressive agents or repeated treatments, an increased awareness of EBV (and CMV) disease is warranted.