LETTER TO THE EDITOR
Transmission of Chromosomally Integrated HHV-6 by Bone Marrow Transplantation

To the Editor: With interest we read the article by Lohi et al. reporting a 3.5-year-old patient under therapy for acute lymphoblastic leukemia with a very high copy number of HHV-6. The patient had been treated with antiviral drugs before chromosomal integration of the HHV-6 genome (CIHHV-6) was suspected. In the mother's blood, high copy numbers of HHV-6 were found as well, indicating inheritance of CIHHV-6. CIHHV-6 has been proven by FISH analysis [1]. We report a special way of acquiring CIHHV-6 by bone marrow transplantation (BMT).

A 10-year-old was diagnosed with acute myeloid leukemia (FAB M4) and was treated according to the AML-BFM 98 protocol. She did not obtain remission by day 67. Therefore, reinduction therapy was administered [2] and allogeneic BMT was scheduled. Pre-BMT screening for viral DNA in blood gave negative results for EBV, CMV, HHV-6, HHV-7, Adenovirus, and Parvovirus B19. After reduced intensity conditioning with fludarabine, melphalan and Campath (anti-CD52 monoclonal antibody), the patient received unmanipulated bone marrow with 4.75×10^6 CD34 positive cells/kg body weight from an unrelated 34-year-old, HLA identical, male donor. Due to CMV seropositivity of the donor, foscavir and cidofovir were started on day 1 after BMT. White blood cell engraftment (defined as 1,000 leukocytes/μl peripheral blood) was achieved on day 18. Erythrocyte and platelet transfusions were required up to day 44 and 50, respectively. From day 10 after BMT HHV-6 DNA was detected in serum with increasing copy numbers up to 2×10^5/ml serum. Despite antiviral treatment, HHV-6 copy numbers remained unchanged. To substantiate the suspicion of CIHHV-6 acquired by BMT, we performed HHV-6 PCR from donor lymphocytes which have been stored as a backup. HHV-6 DNA was detectable in donor lymphocytes as well, indicating the transmission of CIHHV-6 by BMT. FISH analysis of peripheral blood leukocytes of the patient and of donor lymphocytes demonstrated integration of HHV-6 DNA in all analyzed cells at the telomere region of the short arm of one homologue of chromosome 17 (ter 17p). The patient is in remission for 7 years. HHV-6 copy numbers remain at about 10^5/ml serum.

After acquisition of CIHHV-6 by BMT or stem cell transplantation (SCT), HHV-6 DNA is found in every cell derived from hematopoietic stem cells and HHV-6 PCR becomes positive in blood at the time of engraftment and will stay positive thereafter [3,4]. Patients with persistently high copy numbers of HHV-6 are under suspicion of having CIHHV-6 [3,4]. However, as reported by Lohi et al., it is difficult to reliably differentiate CIHHV-6 from primary infection or reactivation [1], which is common after BMT or SCT [5]. Contrary to the report by Lohi et al., it has been shown that the amount of HHV-6 copy numbers is insufficient to distinguish CIHHV-6 from primary infection [6].

While detection of high copy numbers of HHV-6 DNA in relatives indicates inherited CIHHV-6 [1][4], detection of HHV-6 DNA in donor lymphocytes obtained from the backup harvest indicates transmission of CIHHV-6 by SCT. It can be proven by FISH analysis of cells from donor and stem cell derived cells from the recipient.

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