To the editor:

**Engraftment of donor cells with germ-line integration of HHV6 mimics HHV6 reactivation following cord blood/haplo transplantation**

Human herpes virus 6 (HHV-6) infection occurs in >95% of the population before the age of 2 years and remains latent in adults. Although HHV-6 reactivation commonly occurs following cord-blood transplantation, the majority of cases are self-limiting. A minority who reactivate HHV-6 develop disease, particularly encephalitis, which can lead to cognitive impairment and death. Some centers use empiric foscarnet therapy in patients who reactivate HHV-6 with high copy numbers, because the risk for encephalitis is increased in this setting. Recently, it was discovered that 1% to 2% of individuals have germ-line integration of HHV-6, leading to vertical transmission of the virus. Such individuals have HHV-6 DNA integrated into every somatic cell, and high copy numbers of the virus are persistently detected by polymerase chain reaction (PCR) in the absence of viral reactivation and/or replication.

Here, we present a case where a recipient of a combined cord/haploidentical transplant had exceedingly high copy numbers of HHV-6 detected during neutrophil recovery as a consequence of engraftment with cells from the haploidentical donor, who had genomic integration of HHV-6, rather than from viral reactivation. A 26-year-old man with treatment-refractory severe aplastic anemia underwent conditioning with cyclophosphamide/fludarabine and equine-ATG followed by transplantation of a 4/6 HLA-matched cord unit combined with granulocyte colony-stimulating factor (G-CSF)–mobilized CD34-selected hematopoietic progenitor cells from his haploidentical brother. Neutrophil recovery occurred on day 11 (absolute neutrophil count >500 cells/μL), with chimerism studies showing engrafting myeloid cells to be haplo-donor in origin and T cells to be cord, haplo-donor, and recipient in origin. Routine PCR on whole blood for HHV-6 before engraftment was negative but became highly positive (995000 copies/mL) by day +14. The detection of high viral copy numbers of HHV-6 concomitant with neutrophil recovery and absence of symptoms led to the suspicion of germ-line integration of the virus in the haploidentical donor. Subsequent studies showed HHV-6 levels were high in whole-blood specimens (38950 copies/mL) but virtually undetectable in the plasma (<250 copies/mL). A droplet digital PCR assay on mononuclear cells collected from the haplo-donor revealed a HHV-6 virus/cell ratio of 1.03 consistent with viral integration. Lineage-specific chimerism studies showed that early myeloid engraftment was 95% haplo-donor in origin when HHV-6 copy numbers were at their highest. Remarkably, HHV-6 copy numbers declined precipitously and proportionally to an observed switch from haplo to cord myeloid chimerism, as engrafting cord T cells eradicated hematopoiesis from the haplo-donor (Figure 1). Droplet digital PCR performed on mononuclear cells collected on day +42 revealed the HHV-6/cell ratio had declined precipitously to 0.02, consistent with the switch from haplo to cord myeloid chimerism.

In most cases, the detection of HHV-6 in blood following stem-cell transplantation represents reactivation of latent virus in the recipient. As highlighted by this case, one should consider the

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**Figure 1.** Correlation between HHV6 copy numbers, neutrophil recovery, and myeloid chimerism from the haploidentical donor. ANC, absolute neutrophil count; ALC, absolute lymphocyte count; %CD3, % T-cell chimerism; %M, % myeloid chimerism.

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possibility that genomic integration of HHV-6 in the stem-cell donor may account for HHV-6 detection, particularly when high copy numbers are detected early posttransplant, concomitant with neutrophil recovery. This phenomenon is dependent on the kinetics of donor engraftment; therefore, the time integrated HHV-6 becomes detectable posttransplant would likely be later and the slope in the rise of viral copy numbers lower following a typical single or double cord transplant compared with the case presented here where early robust engraftment of the haplo-donor occurred. In this case, HHV-6 copy numbers served as a marker for engraftment of the haploidentical donor rather than HHV-6 reactivation, highlighting a scenario where potentially toxic empiric antiviral therapy is unnecessary and should be avoided.

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References


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