Correspondence

Human Herpesvirus 6 Genome Integration: A Possible Cause of Misdiagnosis of Active Viral Infection?

To the Editor—The recent article by Clark et al. [1] describing the genetic transmission of integrated human herpesvirus (HHV)–6 through stem cell transplantation was of considerable interest. Using fluorescent in situ hybridization and polymerase chain reaction analyses, the authors demonstrated that chromosomally integrated HHV-6 genome was transmitted from the donor to the recipient. Consequently, according to the authors, the rapid increase in HHV-6 load in the peripheral blood of the recipient during the posttransplantation period, which paralleled the increase in white blood cell (WBC) count, was more likely associated with hematopoietic reconstitution rather than with an active viral infection. In the light of this observation and of some other reports, the authors postulated that very high HHV-6 loads (>1 × 10^7 copies/mL) in the peripheral blood of transplant recipients might be misinterpreted as active HHV-6 infection, even though nonreplicative integrated viral genome may be the true cause. In the Discussion, the authors noted that the posttransplantation profile of HHV-6 load for their patient was nearly identical to the one we previously reported for a stem cell transplant recipient (patient 1) [2], suggesting that this patient might also have integrated HHV-6 genome in his peripheral leukocytes. This patient was a 45-year-old man undergoing allogeneic stem cell transplantation because of chronic myeloid leukemia. We do agree that the hypothesis of HHV-6 DNA integration should be considered for this patient, in view of the increase in HHV-6 load paralleling the increase in WBC count (fig. 1). Unfortunately, no information regarding the stem cell donor is currently available, but the patient is still alive and a blood specimen could be obtained. If his HHV-6 load is still high, further investigations might be undertaken to evidence a possible integration of HHV-6 genome in the recipient’s hematopoietic cells. Nevertheless, we think that the link between HHV-6 infection and the clinical and biological features observed during the first month after transplantation (i.e., fever, cutaneous rash, transient leukopenia, and thrombocytopenia) also remains a relevant hypothesis, because no other etiology was established. Indeed, replication of HHV-6 during the posttransplantation period cannot be totally ruled out. In this situation, markers of active viral infection,

Figure 1. Time course of human herpesvirus (HHV)-6 load and white blood cell (WBC) count in patient 1, a stem cell transplant recipient whose profile has been reported in a previous study [2]. BG, before graft; PBMCs, peripheral-blood mononuclear cells.
such as viral transcripts [3], might be useful to distinguish multiplication of hematopoietic cells carrying integrated viral DNA from active viral replication.

It is important to note that a very high HHV-6 load throughout the posttransplantation period is rare and was unique among the 78 patients in our study [2]. Similarly, one single subject among 200 healthy blood donors was found to have a high HHV-6 load (3.3 × 10^6 copies/1 × 10^6 peripheral-blood mononuclear cells [PBMCs]), according to a preliminary study conducted in our hospital (authors’ unpublished data). HHV-6 DNA integration itself appears to be infrequent, and its mechanism is poorly understood. Luppi et al. [4] and Torelli et al. [5] first reported the existence of integrated HHV-6 genome located on chromosome 17 in 2 healthy individuals. Since then, few other investigators have described a similar phenomenon, suggesting the possible vertical transmission of chromosomally integrated HHV-6 [6,7]. Several different chromosomes have been implicated [8]. Further studies are needed to advance our knowledge of this particular form of viral persistence.

In contrast, clear HHV-6 reactivation was observed in 40% of the patients we studied, mainly during the first month after transplantation, as was evidenced by an initial increase followed by a decrease in HHV-6 load, with a peak at ∼1 × 10^6–1 × 10^7 copies/1 × 10^6 PBMCs [2]. This profil of HHV-6 infection remains an unambiguous target for antiviral therapy if association with the development of severe clinical symptoms is clearly demonstrated. This opinion does not entirely fit with another conclusion drawn by Clark et al. The authors postulated that knowledge of HHV-6 integration should prevent the unnecessary administration of potentially toxic antivirals despite the measurement of a high HHV-6 load, and they proposed systematic pretransplantation screening of donors regarding HHV-6 infection to prevent the misdiagnosis of active HHV-6 infection during the posttransplantation period. This strategy appears to us to be expensive and time-consuming in hospital settings. Antivirals such as ganciclovir and foscarnet have provided great clinical benefits despite adverse side effects, in the case of HHV-6–associated encephalitis in stem cell transplant recipients [9]. Of note, in the study by Clark et al., the patient received ganciclovir for treatment of human cytomegalovirus infection, but changes in HHV-6 load during the treatment period are not shown. In our opinion, antiviral drugs should still be considered the first therapeutic approach in the case of clinical symptoms concomitant with a high HHV-6 load occurring in a transplant recipient.

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Potential conflicts of interest: none reported.

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The Journal of Infectious Diseases 2006;194:1019–20 © 2006 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2006/19407-0020$15.00

Human Herpesvirus 6 Latency Characterized by High Viral Load: Chromosomal Integration in Many, but Not All, Cells

To the Editor—We read with great interest the study by Clark et al. that reported the transmission of human herpesvirus (HHV)-6 genome, integrated on chromosome band 17p13.3, through stem cell transplantation [1]. This finding indicates that a high HHV-6 load in the peripheral blood/serum is not necessarily indicative of an active infection, which would require clinical intervention, but, rather, may be indicative of a type of latent infection characterized by the integration state of HHV-6. The biological meaning of such a phenomenon is presently unknown, but the detection of ≥1 HHV-6 copy/hair follicle cell in this adult stem cell donor led the authors to suggest that the virus is inherited in the germ line and is found in all cells in the body [2], which is consistent with Japanese reports of vertical transmission of chromosomally integrated HHV-6 from parent to child [3–5].

We would like to expand on these findings by pointing out that we have described 7 instances (2 in patients with non-Hodgkin lymphoma, 3 in patients with Hodgkin disease, 1 in a patient with mul-