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Chromosomal Integration of the HHV-6 Genome as a Possible Cause of Persistent HHV-6 Detection in a Patient with Langerhans Cell Histiocytosis

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Dear Editor

With interest we read the article published by Csire et al. The authors present the case of a 1975 born male suffering from relapsing Langerhans cell histiocytosis (LCH, eosinophilic granuloma). Treatment consisted of irradiation, chemotherapy and repeated surgery. The human herpesvirus 6 (HHV-6) genome has been detected by PCR in several materials (blood, bone marrow, histological samples of granulomas) obtained during the clinical course of 17 years. Despite antiviral therapy the HHV-6 genome remained detectable.

The authors suggested that a persistent HHV-6 infection might be associated with development or progression of LCH [1].

In contrast it might be speculated that the chromosomal integration of the HHV-6 (CIHHV-6) genome into the genome of the patient might be the reason for the persistent detection of viral DNA.

CIHHV-6 has been described in patients with a variety of different diseases like meningitis, encephalitis, convulsions, liver dysfunction, haemolytic and aplastic anaemia, different lymphomas, and multiple sclerosis [1–12]. Furthermore, it is found in healthy individuals [4, 8, 10, 13]. It is inherited to the offspring from one or both parent(s) [3, 4, 8, 14]. Hence, the HHV-6 genome is found in every nucleated cell. The prevalence is estimated to be 0.2 to 1.3% [8, 13, 15].

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A special way of acquiring CIHHV-6 is the transplantation of stem cells with CIHHV-6 by means of bone marrow or stem cell transplantation (SCT) [16, 17].

CIHHV-6 leads to persistently high levels of HHV-6 DNA in blood and tissue, which might be interpreted as persistent active HHV-6 infection [5, 10, 12].

CIHHV-6 can be proven by fluorescent in situ hybridization (FISH) on chromosome preparations with a HHV-6 specific probe [4, 8, 10, 14]. Moreover, the suspicion of CIHHV-6 can be substantiated or ruled out by means of routine diagnostic procedures.

In individuals with CIHHV-6 the HHV-6 genome is present in any somatic cell. So detection of HHV-6 DNA in hair follicle or nails indicates CIHHV-6 [5, 10, 15].

Since there is at least one copy in every nucleic cell, a high amount of DNA copies is expected in individuals with CIHHV-6. However, the copy numbers in whole blood may be below the number of white blood cells (depending on laboratory techniques).

Since CIHHV-6 is inherited, it can be expected that (at least) one of the parents and possibly some of the siblings and the offspring have the HHV-6 genome chromosomally integrated [3, 4, 8]. If HHV-6 DNA can be detected in a first degree relative CIHHV-6 seems to be most likely. However, germ line integration with negative HHV-6 PCR in both parents might be considered.

Furthermore, the persistence of positive HHV-6 DNA detection itself indicates CIHHV-6 [8, 10, 12].

After acquisition of CIHHV-6 by SCT, HHV-6 PCR becomes positive in blood (or in tissue contaminated with blood cells) at the time of engraftment and it will stay positive thereafter [16, 17]. HHV-6 PCR results from relatives and tissue specimens (if not bloody contaminated) are expected to be negative. CIHHV-6 is present in materials from the donor (including back-up harvest).

In some individuals with CIHHV-6 HHV-6 specific mRNA was detected by reverse transcription PCR indicating the replication of (at least parts of) the HHV-6 genome [14, 18]. Furthermore, we detected viral proteins by HHV-6 antigen detection in individuals with proven CIHHV-6 (unpublished data). In contrast, viral cultures have shown negative results [8]. Thus, it has to be clarified whether replication of viral particles occurs and if there is a pathopysiological impact of CIHHV-6.

It would be of great interest to perform the above mentioned diagnostic procedures in the reported patient to confirm or rule out CIHHV-6. If the HHV-6 genome is chromosomally integrated, it can be speculated that a permanent replication of viral proteins might have an impact on the course of disease. Otherwise, CIHHV-6 might be a coincidental finding without any association with the reported disease.

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