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Letter to the Editor

Nine-year follow-up in a child with chromosomal integration of human herpesvirus 6 transmitted from an unrelated donor through the Japan Marrow Donor Program

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To the Editor

Since 1993, several investigators have reported a unique phenomenon of chromosomal integration of human herpesvirus 6 (CIHHV-6), in which HHV-6 genome is randomly integrated into a human chromosome and vertically transmitted (1, 2). In Japan, the frequency of CIHHV-6 in healthy volunteers is 0.21% (3). CIHHV-6 has also been found in patients who have received hematopoietic stem cell transplantation (SCT), including cord blood transplantation (4–6). CIHHV-6 is generally believed to be innocuous for such a recipient.

Here, we present a patient in whom CIHHV-6 was transmitted from unrelated donor marrow transplantation (UR-BMT) through the Japan Marrow Donor Program. This study was performed according to the Helsinki declaration and informed consent was obtained from the patient's guardians. A fluorescence *in situ* hybridization (FISH) study was approved by the Ethical Review Board for Human Genome Studies at Fujita Health University.

The patient was a 15-year-old girl. She presented with severe anemia with pure red cell aplasia of the bone marrow. She was diagnosed with Diamond-Blackfan anemia soon after birth. She received UR-BMT at the age of 10 years, and obtained complete donor type engraftment. At the age of 15 years, she was admitted with severe pancreatitis and hepatitis

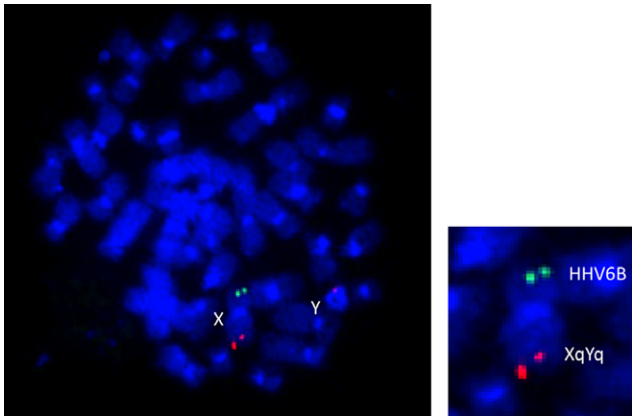

Fig. 1. Human herpevirus-6B (HHV6B) integrated into the chromosome Xp. Green signals and red signals showed HHV-6B and Xq/Yq sequence, respectively. Because the Y chromosome was also stained, this chromosome was proved to be of donor origin.

after endoscopic treatment for gallstones. She received cyclosporine for chronic graft-versus-host disease of the skin; therefore, we screened for infection with herpes simplex virus (HSV)-1, HSV-2, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, HHV-6, HHV-7, JC virus, BK virus, and parvovirus by polymerase chain reaction. Surprisingly, we found a high copy number of HHV-6 (1.1×10^7 copies/μg DNA) in the peripheral blood. We began foscarnet treatment in addition to supportive care.

Although her general status improved rapidly, the HHV-6 genome load increased to 1.3×10^7 copies/μg DNA at day 38 after admission. At this time, we suspected CIHHV-6 phenomenon and measured HHV-6 genome load of her own cryopreserved blood before UR-BMT, and the donor's cryopreserved marrow sample at transplantation. As a result, HHV-6 genome was high (1.25×10^7 copies/μg DNA) in the donor's but not in the recipient's sample. FISH confirmed integration of HHV-6B genome into the donor's chromosome Xp subtelomeric region (Fig. 1) (7).

At present, she is 19 years old and well. Normal hematopoiesis is sustained as follows: white blood cell count 6100/μL (neutrophils 61%, lymphocytes 28%, monocytes 5%, eosinophils 5%, and basophils 1%), hemoglobin 13.9 g/dL reticulocytes 19%, and platelet count 30.8×10^4/μL. Other infectious events have not been observed during this period.

Although this episode suggests that CIHHV-6 is a silent bystander, the clinical significance of CIHHV-6 is not yet determined (6, 8). Recently, HHV-6 activation from CIHHV-6 was demonstrated in a boy with severe combined immunodeficiency (9). Another important issue is the long-term data in SCT recipients, which are lacking. The follow-up duration of 9 years in this report is the longest observation time among similar cases, to our knowledge.

HHV-6 genome load in both donor and recipient should be checked before any type of transplantation, as proposed by other investigators (8, 9). A nationwide survey is needed in such recipients.

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Author contributions: H.Y. designed the research and wrote the letter; T.O. and N.S. performed FISH and viral tests, respectively; H.S. analyzed the data; H.K. and T.Y. reviewed the draft critically. S.T. supervised the study.

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