Dengue Virus Transmission by Blood Stem Cell Donor after Travel to Sri Lanka; Germany, 2013

[Announcer] This program is presented by the Centers for Disease Control and Prevention

Dengue virus, an arthropod-borne RNA virus of the *Flaviviridae* family, has 4 serotypes that cause dengue fever or dengue hemorrhagic fever in humans. Dengue virus has become a worldwide public health problem; current estimates indicate 390 million dengue virus infections and 96 million clinically apparent cases in 2010. The virus is found in tropical and subtropical regions around the world and is hyperendemic to areas in Asia and Latin America.

Hematopoietic stem cell transplantation has become a major treatment option for patients with hematopoietic malignancies and immune deficiencies. Each year, more than 50,000 allogeneic transplants are performed worldwide. Despite mandatory testing of donors and strict exclusion criteria to prevent transmission, risk remains for transmission of communicable diseases, including tropical diseases for which screening is not usually performed. To the best of our knowledge, only the transmission of malarial parasites has been reported during stem cell transplantation. Here, we report transmission of dengue virus to a peripheral blood stem cell recipient by a donor who had recently traveled to an area to which the virus is endemic. We recommend testing of recent travelers returning from areas to which dengue virus is endemic before allowing such donations.

Acute myeloblastic leukemia was diagnosed in a 51-year-old man in Germany in September 2012. According to international standards, cytogenetic and molecular examination determined that this form of leukemia was "poor risk" at the time of diagnosis. Because of the patient's risk status, the physicians intended to perform allogeneic stem cell transplantation after induction and consolidation chemotherapy, which was scheduled to end in January 2013, and a conditioning chemotherapy regimen, which was planned to be given in March. Because of a lack of a related HLA-matched donor, an international donor search was performed; 1 fully matched unrelated female donor was identified in the German National Registry. The 24-year-old woman, who was registered as a volunteer donor in the German Bone Marrow Donor Registry, was selected.

The donor had scheduled a trip to Sri Lanka, and was to return 3 days before the scheduled start of granulocyte-colony-stimulating factor, or G-CSF, application. According to German and international guidelines, such travel should have led to the postponement of donation because many infectious diseases are endemic to Sri Lanka. However, the donor was unable to postpone her trip, and the recipient was in urgent need of the transplant. The transplant physicians agreed to keep the dates as scheduled and confirmed the exception as Declaration of Urgent Medical Need of the transplant.

Five days before the scheduled transplant day, or day minus 5, the recipient tested positive for *Klebsiella pneumoniae* infection of the central venous catheter. The catheter was removed and piperacillin/tazobactam treatment was initiated.

The donor had returned from her trip 3 days before the start of G-CSF-injections without any signs of infection. On the day of apheresis (day 0), the donor showed signs of a respiratory

infection with axillary temperature, bone pain, and headache. Oral azithromycin and ibuprofen were given. The stem cell mobilization result was poor. Before apheresis, the donor's blood count showed mild thrombocytopenia after G-CSF mobilization. Standard leukopheresis processing of blood from the donor was performed without problems.

A second apheresis or a bone marrow collection was considered, but neither was performed because the clinical condition of the donor worsened. Her temperature increased, the platelet count dropped on day 0 to the day after. In the morning of the second day after apheresis, the platelet count dropped, procalcitonine level was elevated, C-reactive protein level was elevated, and a slight skin rash developed. Because of the clinical course, on day plus 1, physicians suspected a possible dengue virus infection. A serum sample test showed a weak positive result for dengue virus by using IgM and IgG antibody tests, and a strong positive result for dengue virus nonstructural protein-1, or NS1, antigen, demonstrating acute dengue virus infection. Quantitative real-time reverse transcription PCR for dengue virus RNA was positive.

After being informed about possible infection of the donor, the transplant physicians administered immunoglobulin to the recipient intravenously. At post transplantation day plus 3, antibiotic drug therapy was switched from piperacillin/tazobactam to meropenem. On the same day, physical examination revealed painful hepatomegaly and increased total bilirubin, diagnosed as hepatic veno-occlusive disease. Therefore, defibrotide prophylaxis, which had been initiated on day minus 8, was increased to treatment dose. On day plus 7, empiric antifungal therapy was added. On the same day, *Staphylococcus epidermidis* was detected in blood cultures and vancomycin was given. On day plus 8, the recipient experienced severe abdominal pain accompanied by hematochezia, hypoxia, and metabolic acidosis. Bacteriologic culture of a tracheal aspirate grew *Acinetobacter baumannii*, which was only susceptible to colomycin and tigecyclin. The recipient was transferred to the intensive care unit and died from cardiopulmonary arrest 9 days post-transplant. A blood sample from the recipient on day plus 3 was retrospectively analyzed and tested negative for dengue virus IgM and IgG but positive for dengue virus NS1 antigen and dengue virus RNA. Sequencing of the dengue virus amplicons from all samples demonstrated a dengue virus serotype 1 genotype 1 infection of the donor and the recipient. Phylogenetic analysis of the complete envelope protein coding gene of dengue virus 1 strains revealed that the dengue virus 1 genotype 1 strains detected in the donor were closely related to currently circulating dengue virus 1 genotype 1 strains in Sri Lanka.

This case demonstrates the transmission of dengue virus by allogeneic blood stem cell transplantation. However, although the transmission of dengue virus was demonstrated, the patient's death was probably caused by hepatic veno-occlusive disease and toxic enterocolitis related to the conditioning regimen.

To avoid transmission of tropical viruses such as dengue virus, under German Federal Ministry of Health rules, blood and stem cell donors are excluded from donation 4 weeks after returning from areas to which such disease agents are endemic. Dengue virus has an incubation period of 3 to 14 days, and the risk for transmission of such viruses under this exclusion is very low. Few cases of dengue virus transmission by blood transfusion or organ transplantations have been published or reported. This case represents a difficult situation: a patient in urgent need of a lifesaving transplant that must be performed without delay and the only matched donor scheduled for travel to a region to which dengue virus is endemic. The physician decided to

proceed with the scheduled transplantation date because of the urgent need of this patient, although he *was* aware of the risk for transmission of tropical diseases.

In such situations it's difficult to estimate the risk/benefit ratio, so it will require a case-by-case decision between donor interests and recipient needs. All diagnostic tools should be used to minimize the risk for viral transmission *before* transplantation. This could have been easily accomplished in this case, because preprocedure samples from the donor tested positive for dengue virus NS1 antigen. Thus, we recommend highly sensitive and specific testing for dengue virus NS1 antigen of every donor returning from regions to which dengue virus is endemic for dengue virus NS1 antigen, if transplantation cannot be postponed because of urgent medical need.

I'm Dr. Mike Miller, for *Emerging Infectious Diseases*, and I've been reading an abridged version of the article *Dengue Virus Transmission by Blood Stem Cell Donor after Travel to Sri Lanka; Germany, 2013*. You can read the entire August 2014 article online now at cdc.gov/eid.

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