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

Michael Punzel, Gülay Korukluoğlu, Dilek Yagci Caglayik, Dilek Menemenlioglu, Sinem Civriz Bozdag, Emre Tegändigüz, Fevzi Altuntaş, Renata de Mendonca Campos, Bernd Burde, Stephan Günther, Dennis Tappe, Daniel Cadar, and Jonas Schmidt-Chanasit

Three days after donation of peripheral blood stem cells to a recipient with acute myeloblastic leukemia, dengue virus was detected in the donor, who had recently traveled to Sri Lanka. Transmission to the recipient, who died 9 days after transplant, was confirmed.

Dengue virus (DENV), an arthropod-borne RNA virus of the Flaviviridae family, has 4 serotypes that cause dengue fever or dengue hemorrhagic fever in humans. DENV has become a worldwide public health problem: current estimates indicate 390 million DENV 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, >50,000 allogeneic transplants are performed worldwide (2). 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 (3,4). Here, we report transmission of DENV 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 DENV is endemic before allowing such donations.

The Study

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 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 (G-CSF) application. According to German (http://www.zrkd.de/de/_pdf/ZRKD_Standards-V9_deutsch.pdf) and international (http://www.worldmarrow.org/fileadmin/Committees/STDC/20140101-STDC-WMDA_Standards.pdf) 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 –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 of ≤39°C, bone pain, and headache. Oral azithromycin
A serum sample test showed a weak positive result on day +1, physicians suspected a possible DENV infection. A blood sample from the recipient on day +3 was retrospectively analyzed and tested negative for DENV IgM and IgG but positive for DENV NS1 antigen and DENV RNA with a DENV RNA load of 8.6 \times 10^6 copies/mL. Sequencing of the DENV RNA load of 2.6 \times 10^6 copies/mL. Testing of the sample containing the progenitor cells showed a DENV RNA load of 4.8 \times 10^6 copies/mL.

After being informed about possible infection of the donor, the transplant physicians administered immunoglobulin to the recipient intravenously (0.5 g/kg/y for 4 days). At posttransplantation day +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 (Table). Therefore, defibrotide prophylaxis, which had been initiated on day –8, was increased to treat DENV infection confirmed by laboratory. On the same day, Staphylococcus epidermidis was detected in blood cultures and vancomycin treatment was given.

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 to 41°C, the platelet count dropped from 84,000 cells/mL on day 0 to 74,000/mL the day after. In the morning of the second day after apheresis (+2), the platelet count dropped to 47,000/mL, procalcitonine level was elevated at 1.10 µg/L, C-reactive protein level was elevated at 10.5 mg/L, and a slight skin rash developed. Because of the clinical course, on day +1, physicians suspected a possible DENV infection. A serum sample test showed a weak positive result for DENV by using IgM and IgG antibody tests (in-house indirect immunofluorescence assay), as used by Tappe et al. (5), and a strong positive result for DENV nonstructural protein-1 (NS1) antigen, demonstrating acute DENV infection. Quantitative real-time reverse transcription PCR for DENV RNA (6) was positive and showed a DENV RNA load of 2.6 \times 10^6 copies/mL. Testing of the sample containing the progenitor cells showed a DENV RNA load of 4.8 \times 10^6 copies/mL.
DENV amplicons from all samples demonstrated a DENV serotype 1 (DENV-1) genotype 1 infection of the donor and recipient. Phylogenetic analysis of the complete envelope protein coding gene of DENV 1 strains revealed that the DENV 1 genotype 1 strains detected in the donor were closely related to currently circulating DENV 1 genotype 1 strains in Sri Lanka (Figure).

**Conclusions**

This case demonstrates the transmission of DENV by allogeneic blood stem cell transplantation. However, although the transmission of DENV 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 DENV, 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 (7). DENV has an incubation period of 3–14 days, and the risk for transmission of such viruses under this exclusion is very low. Few cases of DENV transmission by blood transfusion or organ transplantation have been published or reported (8–11). 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 DENV is endemic. The physician decided to proceed with the scheduled transplantation date because of the urgent need of his patient, although he was aware of the risk for transmission of tropical diseases.

In such situations it is difficult to estimate the risk/benefit ratio, so it will require a case-by-case decision between...
Dengue Virus Transmission by Blood Stem Cell Donor

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 DENV NS1 antigen. Thus, we recommend highly sensitive and specific testing for DENV NS1 antigen if transplantation cannot be postponed because of urgent medical need.

Acknowledgments

We thank Alexandra Bialonski, Insa Bonow, Corinna Thomé, Birgit Hüsing, Ihsan Durmaz, and Sabine Köhler for technical assistance.

This dispatch is dedicated to the late Ursula Herrmann (1927–2014), for making this study possible.

Dr Punzel is a lecturer at Technical University of Dresden Medical School. His research interest is hematopoietic stem cell transplantation.

References


Address for correspondence: Jonas Schmidt-Chanasit, Bernhard Nocht Institute for Tropical Medicine, WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research, Bernhard-Nocht-Strasse 74, 20359 Hamburg, Germany; email: jonassi@gmx.de