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Case report

Dengue virus transmission from donor to recipient during haploidentical stem cell transplantation

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ABSTRACT

Dengue fever is endemic in tropical and subtropical countries. Dengue virus transmission through hematopoietic stem cells is very rare and just two such cases have been reported previously. We report here only third case of dengue virus transmission in a 2-year-old child with thalassemia major who underwent hematopoietic stem cell transplant (HSCT) from a haploidentical related donor. One week after HSCT, the recipient developed fever, pancytopenia and signs of capillary leak. On day 10, his dengue NS1 antigen test was positive which confirmed diagnosis of dengue fever. Donor also had fever few days prior to stem cell donation which was later diagnosed to be due to dengue fever. Child had a severe clinical course of dengue leading to primary graft failure. However, he had autologous recovery of his own bone marrow and is alive and well on day+200 post HSCT. Our report highlights the transmission of dengue virus from donor to recipient through hematopoietic stem cell graft although rare but possible. We suggest that in tropical and subtropical countries where dengue is endemic, hematopoietic stem cell donors should be screened for it.

Introduction

Dengue fever is endemic in tropical and subtropical countries. Dengue virus is transmitted mostly by bite of *Aedes* mosquitoes, but transmission by blood transfusion as well as organ transplants have been well documented in literature [1]. Dengue transmission through hematopoietic stem cells is very rare and just two such cases have been reported previously [2,3]. We report here only third case of dengue virus transmission in a hematopoietic stem cell transplant (HSCT) recipient from a haploidentical related donor.

Case report

A 2-year-old boy, who was a known case of thalassemia major underwent 9/10 matched haploidentical related donor peripheral blood HSCT from his mother as donor. Conditioning regime included fludarabine 40 mg/m2/day for 4 days, busulfan 4 mg/kg/day for 4 days, thiotepa 8 mg/kg/day for 1 day, rituximab 100 mg/m2 for 1 day and rabbit anti-thymoglobulin 4.5 mg/kg/total dose. For stem cell mobilization, granulocyte colony stimulating factor (G-CSF) was administered to the donor from day-4 to day-1. One day after G-CSF injection, the donor developed fever with generalized weakness, which was managed with supportive care and was thought to be a side-effect of G-CSF. On day-1, donor's complete blood count (CBC) showed hemoglobin (Hb) 11.3gm/dL, total leucocyte count (TLC) 36600/μL, platelet count (PC) 222000/μL. The circulating peripheral blood stem cell count of the donor on day 0 was 19 CD34+ cells/μL, which was unexpectedly low for a healthy donor. The peripheral blood stem cells were collected from the donor by apheresis and final product showed 375 CD34+ stem cells/μL. Stem cell dose infused was 5.7 million CD34+ cells/kg of recipient. The recipient tolerated the stem cell infusion well with no fever or rash until day+2. Meanwhile, the donor's symptoms improved and she became afebrile two days after the apheresis procedure. For graft vs. host disease prophylaxis, cyclophosphamide was given on day+3 and day+4, tacrolimus and mycophenolate mofetil were started on day+5.

On day+7, the recipient developed high grade fever and he was managed conservatively with supportive care and antimicrobials. On day+8, he developed ascites and pleural effusion. Initially we thought it to be either because of bacterial infection or pre-engraftment syndrome but when it persisted despite appropriate antimicrobials and steroid therapy then we investigated the child for dengue fever as dengue is endemic in India. On day+10

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recipient's CBC showed that he had pancytopenia (Hb-9.1gm/dL, TLC-10/ μL, PC-2000/μL) and his dengue antigen NS1 was positive while dengue IgM was negative. So he was diagnosed to have dengue fever. At this point, the donor was clinically fine. We tested her for dengue as well. Her dengue NS1 antigen was negative but dengue IgM antibody was strongly positive which confirmed dengue fever in the donor. We suspected that probably dengue virus was transmitted to our patient from the donor through the hematopoietic stem cells infusion. Patient was managed further with crystalloids, oxygen therapy & platelet transfusions. Chest x-Ray showed bilateral pleural effusion (left > right). His ferritin was raised (9380 ng/mL), and albumin was low (2.9gm/dl). Intravenous immunoglobulin (IVIG) was given. He then developed hypertension & his thrombocytopenia persisted which raised the suspicion of transplant-associated thrombotic microangiopathy (TATMA). Antihypertensive drugs were started and tacrolimus was stopped. He required multiple packed red cell transfusion (PRBC) and platelet transfusions. Peg-GCSF was given on day+16. On day+18 child again developed fever for which blood culture was sent which was sterile. His cytomegalovirus (CMV) polymerase chain reaction test showed450 copies/mL. So IVIG was givenagain on day +21 for CMV reactivation. Repeat CMV levels were undetectable. Eltrombopag andPeg-GCSF were given for poor graft function. Gradually his condition improved and ascites and pleural effusion waned. On day+22, repeat dengue NS-1 test came negative and dengue IgM level became positive. Chimerism on day+24 showed only 20 % donor cells. Repeat chimerism on day+30, showed 2% donor cells suggestive of primary graft failure. Child was managed conservatively. However, child had autologous recovery of his own bone marrow. His ANC was >500/uL at day+38, platelet >20,000/ μL on day+50. At this writing, the child is day+200 post-transplant and is clinically well and his last CBC showed Hb-7.2gm/dL, TLC-8700/μL, PC-207000/ μL. He still requires monthly PRBC transfusions for thalassemia.

Discussion

Many studies have described emerging and re-emerging viral pathogens like dengue, rabies, HTLV, Zika and others in the transplant recipients with their severity and complications in post-transplant period [4]. Although many authors reported dengue transmission through graft in solid organ transplants like liver, kidney & heart [5]. Until now only two case reports have discussed the transmission of dengue virus through HSCT graft [2,3]. The first case was reported by Rigau-Perez et al., in which the recipient developed fever on day+4 and died on day+11. DENV-4 serotype was detected in patient's blood, ascitic fluid, and tissue samples and same serotype was isolated from the donor who also developed fever two days after bone marrow harvesting [2]. Another case was reported by Punzel M et al. in which dengue transmission through HSCT graft occurred where the unrelated donor had returned from Sri Lanka three days before donation [3]. Donor developed fever and thrombocytopenia on the day of apheresis and was diagnosed with dengue infection. On day+3, patient developed painful hepatomegaly and deranged liver functions and was diagnosed with veno-occlusive disease. Blood culture showed *Staphylococcus epidermidis* growth. Patient's condition deteriorated and he died on day+9, probably due to dengue, enterocolitis and VOD [3]. Limitation of our report is that the transmission through graft is confirmed retrospectively and the dengue viral NS1 antigen was not demonstrated in donor's stem cell sample. Many authors have described dengue illness in post HSCT patients but these patients had developed dengue illness as a result of vector transmission [6–11].

The effect of dengue infection on stem cell mobilization from the donor is not known but, in our donor, she showed poor response to G-CSF with low circulating stem cells on the day of stem cell harvest. Dengue virus is well known for suppression of bone marrow, which explains both the poor mobilization of stem cells from donor and also possibly leading to primary graft failure in our patient. Also, patients with poor bone marrow reserve (post HSCT, on immunosuppressant) are expected to have a prolonged and severe illness [12]. Our patient had severe disease. Other two cases did not describe the dengue illness course post HSCT but both of them died [2,3]. In immunocompetent individuals, dengue viremia persists for 5–7 days followed by development of antibodies. However, in post-transplant patients due to poor immune response, prolonged viremia (>15 days) has been reported in many cases [6–9]. Our case had viral clearance with appearance of IgM antibodies on day 15 of dengue illness.

Our report highlights the transmission of dengue virus from the donor to recipient through hematopoietic stem cell graft although rare but possible. We suggest that in tropical and subtropical countries where dengue is endemic, hematopoietic stem cell donors should be screened for it.

Ethical approval

Not applicable. Informed consent was obtained of the parents.

Declaration of Competing Interest

The authors report no declarations of interest.

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