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CASE REPORT

Nosocomial Dengue Infection in a Haematopoietic Stem Cell Transplantation Unit

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Abstract

As haematopoietic stem cell transplantation (HSCT) continues to expand, infectious complications due to endemic viral and parasitic agents will became relevant. Dengue virus (DENV) infection is endemic in tropical and subtropical countries, and it is transmitted from person to person through mosquitoes. Transmission through transfusion and haematopoietic stem cells has also been described. We report a nosocomial outbreak of DENV affecting 4 transplant recipients. Patients presented fever, skin rash, hepatitis and haemorrhage. Since all patients acquired DENV during the immediate post-transplant period, the disease transmission, although not proved, could be through blood components.

Introduction

In the haematopoietic stem cell transplant (HSCT) setting the immunosuppression imposed by the disease and pretransplant conditioning chemotherapy followed by immunosuppressive drugs makes patients extremely vulnerable to infections from bacterial, fungal, parasitic and viral agents. DENV is caused by four related RNA flavivirus: DENV-1, DENV-2, DENV-3 and DENV-4. The virus is transmitted primarily among humans by mosquitoes, in most cases *Aedes aegypti*. Nosocomial transmission has been reported including transfusion transmitted (TT), HSCT graft transmitted and by contaminated needle or by mucocutaneous route [1-6]. DENV is an acute febrile illness. In immunocompetent individuals is usually asymptomatic in up to 75% of cases. The WHO 2009 classification divides DENV cases into two forms: Non-severe and severe. The non-severe form is denominated dengue fever and is like an uncharacteristic viral illness with most patients recovering without major complications. The severe form can be accompanied by complications like plasma leakage, hemorrhage, and impaired consciousness, myocardial, hepatic and pulmonary dysfunction. During the febrile phase of the early illness, diagnostic can be done detecting viral nucleic acid (NATT) by RT-PCR or by detection of the virus-expressed soluble non-structural protein 1 (NS1). After the acute phase of the infection, serology assays detecting specific anti-viral IgM and IgG has a place [7,8].

In Argentina DENV is endemic in the northern country region but in recent years, during the warm months, episodic outbreaks occurred in the central region where the reported subjects were treated.

We report an outbreak of DENV in a bone marrow transplant unit involving 4 HSCT patients developing DENV during the early post-transplant period.

A case was defined as any patient with DENV associated symptoms and positive dengue diagnostic test including nucleic acid amplification test (NATT) like RT-PCR to detect virus RNA in blood, serum or plasma

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or NS1 antigen test detecting dengue virus antigen. The serotype involved was DENV-2 in all cases. The pts were admitted in the hospital for the HSCT procedure at least 15 days before DENV diagnosis. Cases were diagnosed over a 2-day interval. The subjects received many blood component transfusions from diverse donors. Although not proven, a transfusion transmitted disease is our main hypothesis.

Case 1: A 29-year-old male pt. with Hodgkin Lymphoma in 2nd complete remission underwent an autologous HSCT. Pre-transplant conditioning regimen was bendamustine, cyclophosphamide and VP-16. On day +10 because of neutropenic fever per protocol antibiotics were administered. On day +13, granulocytic recovery occurred although fever persisted and appeared a maculopapular pruritic rash affecting face, trunk and upper limbs. Engraftment syndrome was suspected and a 3-day course of meprednisone was given with resolution of fever and rash. On day + 19 the pt. developed fever again. A diagnosis of DENV was made by NS1 (NS1 Rapid Test Cassette Jus Chek©) assay. RT-PCR (Taqman®) was positive for DEN-2. Parvovirus B19 and HSV-6 virus RT PCR assays were negative. No effects on granulocytic or platelet recovery were observed and no other complications occurred. Fever resolved and patient was discharged on day +23.

Case 2: A 66-year-old male with high-risk myelodysplastic syndrome underwent an HLA haploidentical HSCT. Pre transplant conditioning was with busulfan and fludarabine. Graft versus host disease prophylaxis was post-transplant cyclophosphamide, tacrolimus and mofetil mycophenolate. On day +3 the pt. developed neutropenic fever with coagulase-negative staphylococci bacteriaemia. Per protocol antibiotics were started. On day +10, severe enteritis was diagnosed with *Enterococcus faecium* bacteriaemia. On day +18 because a septic shock the pt. was transferred to the ICU where mechanical ventilation was required for 8 days. New blood cultures found *Klebsiella pneumoniae, Enterococcus faecium* and *Candida guilliermondii*. On day +28 primary graft failures was diagnosed and a second haploidentical transplant with the same donor was performed. On day +3 of the second transplant, fever persisted and upper and low gastrointestinal bleeding manifested. On day +5 maculopapular pruritic rashes appeared in upper limbs and trunk with persistent fever. Dengue NS1 assay was positive. Dengue IgM and IgG test were negative. RT-PCR was positive for DEN-2. Other striking laboratory findings were elevated aspartate aminotransferase and alanine aminotransferase: > 4000 U/L and 1522 U/L, respectively (NR: 10-35 U/L)) and altered coagulation test: Prothrombin time 21% (NR: 70-100%) and aPTT 85s (NR: 25-40s). Gastrointestinal bleeding persisted with no response to transfusion support. The patient died on day +7 due to refractory hypovolemic shock secondary to gastrointestinal hemorrhage.

Case 3: A 62-year-old woman with refractory aggressive lymphoma in first complete remission had undergone an autologous HSCT after a conditioning regimen with carmustine, cyclophosphamide and etoposide. On day +1 neutropenic fever developed with abdominal symptoms and diarrhea. Per protocol antibiotics were administered. On day +6 under persistence of fever a non-pruritic generalized maculopapular skin rash that involved the face and ears pavilions associated with facial edema appeared. A skin biopsy revealed perivascular lymphocyte dermatitis. RT-PCR for parvovirus B19 and HSV-6 were negative. Meprednisone was started with slow improvement of skin rash and facial edema. On day +16 the pt was discharged with WBC 11.2 × 10E9/l and platelet 22 × 10E9/l. Two days later was admitted because of fever with severe thrombocytopenia (11 × 10E9/l). Dengue NS1 test was positive and DENV was diagnosed on day +18. RT-PCR was positive DEN-2. Platelets transfusion support was required. No bleeding episodes occurred. Fever resolved and the pt was discharged on day +26.

Case 4: A 14-months-old boy with malignant infantile osteopetrosis underwent an allogeneic HSCT. Conditioning regimen was with busulfan and fludarabine. Graft versus host disease (GVHD) prophylaxis included rabbit thymoglobulin, tacrolimus and methotrexate. On day +13 antibiotics were administered because of neutropenic fever. The pt developed respiratory failure requiring mechanical ventilation. Granulocyte engraftment was on day +16. No platelet engraftment was achieved. Repeated episodes of fever occurred responding to antibiotic treatment. On day +56, grade IV acute GVHD was diagnosed with grade 4 skin involvement confirmed by biopsy with generalized erythroderma and peeling. GVHD was refractory to steroids with transient improvement after subsequent lines of therapy with mycophenolate mofetil and infliximab. On day +120 skin lesions worsened, characterized by generalized erythroderma with purpuric lesions and severe peeling. Based on skin rash and persistence of fever, DENV fever was suspected and diagnosed by NS1. RT-PCR was positive for DEN-2. Respiratory failure worsened which required mechanical ventilation. Bleeding through upper airway and veno puncture sites was noted. Remarkable laboratory finding was mild elevation of aminotransferases (AST 330 U/L and ALT 260 U/L). The patient died on day +121 due to respiratory failure.

Discussion

Infectious complications are one of the main causes of morbidity and mortality following HSCT. Individual factors like mucosal damage, myelosuppression and a central venous access increase the infections risk. The impact of published nosocomial infections outbreak is scarce, maybe for reluctance of the transplant physicians to report this sort of complications or misdiagnosis of them and can imply bacterial, fungal and viral agents

[9-11]. DENV fever is endemic in the northern region of Argentina and episodic outbreaks occur in the central region during warm months. From august 2023 to April 2024, 333.000 cases of DENV were reported in Argentina. This indicates an increase of over 300% compared to the previous year. The incidence of severe dengue fever was 0.2%, with a mortality of 0.071%. The most common serotype is DEN-2, followed by DEN-1. We estimate that over one million people presented viremia during this period. Mandatory testing of blood components for transfusion does not include dengue [12]. This epidemiological situation renders dengue fever as a potential infectious complication among blood and derived product recipients.

We report a nosocomial DENV outbreak affecting 4 HSCT patients in the early post-transplant period. The episode we report occurred in the summer (year 2024) during an epidemic outbreak. The reported outbreak occurred on the HSCT unit at Sanatorio Anchorena, a general hospital in Buenos Aires, Argentina on March 2024. The unit carried out approximately 70 HSCT yearly mostly in adults with blood malignancies. All patients were diagnosed with DENV-2 by RT-PCR. Main symptoms were fever in all cases and skin rash in 3 patients. Two pts manifested a marked elevation of liver enzymes simultaneously with DENV diagnosis. One patient died due to severe hemorrhage. In other patient we consider DENV as a contributing cause of death.

The patients received multiple different blood products not tested for DENV. DENV was diagnosed at 15, 56, 35 and 116 days from admission (case 1 to 4, respectively), which makes a vector transmitted disease very unlikely.

In this cluster, all patients were diagnosed with DEN-2, the most common circulating virus subtype.

Clinical findings were like other reports. De Sousa, et al. reported five HSCT DENV patients with fever, myalgia, thrombocytopenia, and skin rash. Severe dengue fever occurred in one patient. In this study it was seen a prolonged viraemia lasting for more than 15 days [13]. A recent review from the Worldwide Network for Blood and Marrow Transplantation (WBMT) of dengue infection in patients receiving allogeneic HSCT, the most common presentation form was fever and only three patients presented with severe dengue fever, of which one survived [14].

Transfusion transmitted (TT) DENV has been reported in the literature.

After the 2012 DENV epidemic, a study from Brazil found that 0.5% of blood donations were tested positive for dengue virus. In the same study only 6 patients out of 16 who received blood with RNA-positive were considered to be TT DENV, with no recipient developing a highly symptomatic infection [15]. In another a study from Brazil, de Oliveira, et al. evaluated the risk TT dengue in recipients of HSCT. Five out of 93 patients were considered DENV positive by seroconversion, but in the investigation of blood components, none showed a positive RT-PCR. These and others case reports show that symptomatic infection in blood recipients does occur, albeit rarely [16]. The lower infection rate observed after exposure to a human-derived parenteral inoculum compared to a mosquito-derived cutaneous inoculum can be explained by differences in glycosylation patterns of the virus replicating in mosquitoes or humans, and/or the injection of mosquito saliva, which triggers local inflammation that can increase local virus replication and systemic infection [17,18].

Transmission through haematopoietic stem cell graft has also been described. The first case was reported in Puerto Rico during the 1994 dengue epidemic. DEN-4 was detected in blood, ascitic fluid and tissue samples of the recipient and in the donor, who developed fever 2 days after marrow harvest [19]. In another report, a patient received an HLA haploidentical graft from his mother. The donor developed fever before donation. The patient developed fever and capillary leak and DENV was diagnosed on the patient and the donor [4]. Another case occurred in an unrelated HLA matched HSCT in which the donor had returned from Sri Lanka 3 days before donation [20].

There is no antiviral treatment for DENV infection. Supportive care includes fever control, and management of intravascular volume, bleeding and plasma leakage [21,22]. Blood transfusion and other blood products, including platelet concentrate, fresh frozen plasma, and cryoprecipitate, should be used in patients with severe bleeding and impaired coagulation status [23,24].

DENV is endemic in many countries, with severe disease forms showing the highest incidence in some areas of Southeast Asia, Western Pacific, Central and South America regions, with nearly 100 million new cases each year. Fever, leucopenia, thrombocytopenia, and cutaneous rash are common symptoms, which are also often seen because other causes in HSCT recipients. Consequently, diagnosis of dengue may not be suspected, even in endemic regions. A high suspicion index should be kept in all HSCT recipients and cancer patients living in endemic areas or during episodic outbreaks [25]. Prevention and testing are the gold standard to avoid transfusion or transplant transmitted infectious diseases [26-28]. Blood and HSCT donors should be asked to report any febrile illness in the day's previous and following donation and should be recommended to avoid travel to endemic areas in the 4 weeks before donation. Our findings highlight the need of screening blood components in endemic areas and during episodic outbreaks preferably by RT-PCR. The same applies to HSCT donors. Screening should be done as close as possible to haematopoietic cell donation, since DENV could be acquired between the tests was

performed and the graft obtained. Furthermore, it is important that the results are available before the pre-transplant conditioning regimen begins. Testing and immediately cryopreservation of the graft could be an option. Like with other endemic virus and parasitic diseases, DENV reports in the HSCT setting are scarce and a nosocomial outbreak called our attention. Publication of this outbreak could increase the awareness in HSCT units improving the diagnosis and transmission prevention.

Ethical Approval

Not applicable. Informed consent was obtained from the patients.

Conflict of Interest Statement

The authors have no competing interests.

Acknowledgment

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