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CASE REPORT

Transmission of West Nile Virus Through a Hematopoietic Stem Cell Transplant

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West Nile virus (WNV) is a *Flavivirus* that can cause fatal encephalitis in susceptible hosts. It was first identified in the United States in 1999 in New York City but has since become endemic. In immunocompetent hosts, WNV infection is typically self-limited; only 1 in 150 develop meningitis/encephalitis [1]. The usual incubation period is 2 to 14 days, and polymerase chain reaction (PCR) results are negative by day 3 to 5 of illness [1, 2]. In those few with meningitis/encephalitis, their cerebrospinal fluid (CSF) tests positive for immunoglobulin M (IgM) at day 3 to 5 of illness, and their serum tests positive for IgM at day 6 to 8 [1, 3]. Once the virus has crossed into the central nervous system space, infection leads to acute neuronal necrosis with inflammation, including involvement of the spinal motor neurons. In the 1999 outbreak in New York, 32% of the patients with encephalitis had hyporeflexia and 10% had flaccid paralysis, and in 80% of those for whom electromyography was performed, the test revealed axonal polyneuropathy [3]. In another study, 93% of the patients experienced significant neurological deficits, and 25% were in a coma [4]. The incidence of WNV waxes and wanes; in Texas in 2015, 275 cases of WNV were reported, 71% of which were neuroinvasive and resulted in a total of 16 deaths [5].

In children, WNV usually causes a less-severe disease and is an uncommon cause of viral encephalitis [6]. However, immunosuppressed patients with WNV infection experience a much higher incidence of neuroinvasive disease [7]. WNV is transmitted primarily through mosquitoes, but given the high incidence of subclinical infection, it can be transmitted through other routes, including blood products and organ donation. Here, we describe the case of a child who had undergone a recent hematopoietic stem cell transplant (HSCT) and contracted WNV encephalitis, presumably through the donor bone marrow product.

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CASE REPORT

Our patient was an 8-year-old boy diagnosed with high-risk acute myeloid leukemia. He underwent a haploidentical-donor HSCT in October 2015. Before his HSCT, both the patient and the donor were long-term residents of Houston, Texas, where the transplant was conducted, and had not traveled in the year before the procedure. Our patient was hospitalized for 12 days before the HSCT and underwent conditioning therapy; the stem cell product was collected 1 day before transplantation.

Eleven days after the HSCT, the patient developed fevers without other symptoms. Results of an infectious disease workup were negative except for low-level cytomegalovirus viremia, for which foscarnet was initiated along with empiric ceftriaxone, vancomycin, and acyclovir. Because of extensive infectious disease testing that returned negative results and simultaneous evidence of donor neutrophil engraftment, his fever was presumed to be attributable to engraftment syndrome.

The patient's fevers continued, and 21 days after the transplant, he experienced an acute onset of slurred speech and progressive right-sided weakness. Magnetic resonance imaging (MRI) of his brain revealed increased T2-weighted/fluid-attenuated inversion recovery signal intensity with heterogeneous restricted diffusion and enlargement of the bilateral thalami, which are consistent with possible viral encephalitis (Figure 1). CSF analysis revealed 13 white blood cells, 0 red blood cells, a glucose level of 72 mg/dL, and a protein level of 48 mg/dL. His CSF tested negative for bacterial, viral, and fungal etiologies, including WNV antibody, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 (HHV6), HHV7, HHV8, herpes simplex virus, adenovirus, enterovirus, BK virus, JC virus, *Cryptococcus*, *Coccidioides*, *Histoplasma capsulatum*, *Toxoplasma gondii*, acid-fast bacilli, atypical mycobacteria, and *Bartonella*, and the results of viral, fungal, and bacterial cultures were negative.

On day 22, a neurological examination of the patient revealed a comatose state with hypertonicity in his upper extremities and hypotonicity in his lower extremities. An electroencephalogram revealed slow and depressed background activity with no epileptiform discharges. The results of an ophthalmological examination

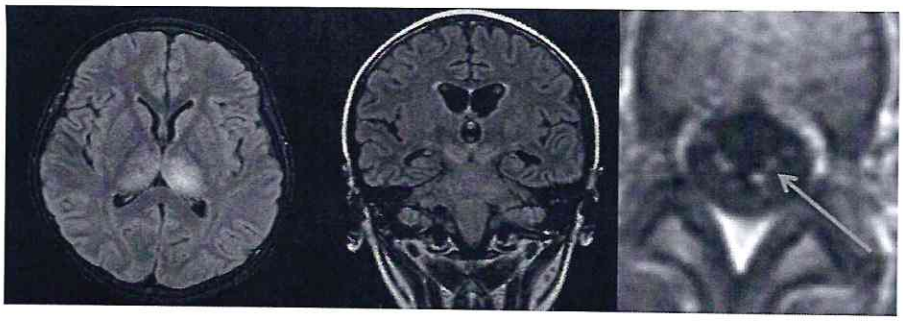

Figure 1. Magnetic resonance images. (Left) Initial sagittal T2-weighted/fluid-attenuated inversion recovery (FLAIR) sequence, which reveals increased signal in the bilateral thalami. (Center) Follow-up coronal T2-weighted/FLAIR sequence 45 days after the transplant, which shows increased T2-weighted signal in the bilateral midbrain, including the cerebral peduncles, entire midbrain dorsally, pons, and portions of the medulla, especially ventral. (Right) Abnormal nerve root enhancement.

were normal. Alternative diagnoses, including an autoimmune disease and complications related to immunoreconstitution after the transplant, were considered. On day 23, he was given high-dose methylprednisolone for 5 days for a possible autoimmune-mediated process followed by 5 days of intravenous immunoglobulin (IVIg). Repeat brain and spine MRI on day 29 revealed progression of the lesions in the thalami and new T2-weighted/fluid-attenuated inversion recovery signal enhancement, involvement of the descending corticospinal tracts, medulla, and dentate nuclei, and abnormal enhancement of the nerve roots of the cauda equine (Figure 1). The results of nerve-conduction studies and electromyography performed on day 36 were consistent with "an axonal process affecting the motor tracts without evidence of involvement of the sensory tracts," which suggested an inflammatory polyneuropathy; therefore, he underwent therapeutic plasma exchange for 5 days starting on day 37.

An ophthalmological examination on day 33 revealed linear chorioretinal lesions highly suggestive of WNV (Figure 2). Repeat CSF studies on day 30 revealed 525 white blood cells, 19 red blood cells, a glucose level of 60 mg/dL, and a protein level of 119 mg/dL, and the results of testing for infectious diseases, including WNV antibody, were negative. CSF was also sent for *Toxoplasma* and WNV PCRs (Nichols Institute, San Juan Capistrano, California). On day 42, the results of CSF PCR were positive for WNV.

Per routine policy, the donor was screened for infectious diseases 3 weeks before stem cell collection, and at that time, the results were negative for WNV IgM and IgG. Stem cell collection occurred within the standard 30-day period of testing. After the diagnosis of WNV encephalitis was made, the donor was retested, and the results were positive for IgM and IgG antibodies against WNV at high titers (IgM, 2.93 mg/dL; IgG, 3.73 mg/dL), but no evidence of viremia was found by PCR testing. These results suggest that the donor became infected either immediately before testing or between testing and stem cell collection. The timing of the patient's infection 11 days after transplant strongly suggests that it originated from the donor stem cell product, consistent with the usual 2- to 14-day incubation period of WNV. Moreover, the patient had been hospitalized for 12 days before the transplant, which made exposure to mosquitos highly unlikely during that time period.

Because the patient was severely immunosuppressed, it was presumed that he would be unable to mount an effective response against the virus. The US Food and Drug

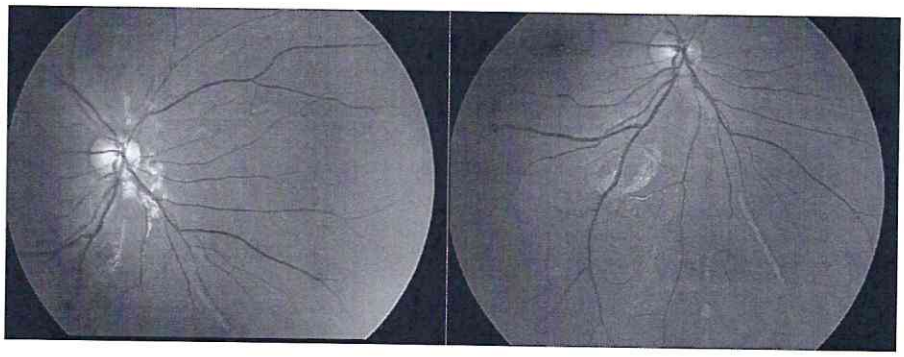

Figure 2. Retinal images, which show tan linear lesions and discrete outer-retinal and inner-punctate choroidal lesions scattered diffusely in the posterior pole and peripheral retina. Both are retinal images of the right eye. The right panel focuses on lesions around the retina and the left panel focuses on peripheral lesions.

Administration granted permission for compassionate use of convalescent donor plasma, which was collected by the Gulf Coast Blood Center from the donor and tested negative for WNV by PCR [7–9]. Despite this therapy, the patient remained critically ill and died after withdrawal of support on day 55.

DISCUSSION

We describe here a case of WNV infection transmitted via bone marrow donor product to a bone marrow transplant recipient. Although 6 case reports of WNV encephalitis in bone marrow or solid organ transplant recipients have been published [10–15], only 1 of these infections occurred immediately after transplant. In that case, the stem cells tested negative for WNV RNA, and the infection was attributed to a blood transfusion [14]. Ours seems to be the first report of WNV transmitted via the stem cell product itself. Up to 75% of immunocompromised transplant recipients who contract WNV have neuroinvasive disease, compared to only 1% of immunocompetent patents [7]. This disparity indicates that a functional immune system is critical for preventing spread of the virus across the blood–brain barrier [2, 6]. The immunocompromised state of our patient during his time of exposure to WNV likely contributed to the severity and the rapidity of the progression of his neurological involvement. The inability of his immune system to produce appropriate immunoglobulins contributed to both the difficulty with diagnosis by standard antibody testing and his inability to fight the infection.

No virus-specific therapy for treating WNV currently exists. High-titer WNV IVIg has been used in cases of WNV encephalitis in immunocompromised organ transplant recipients, some with positive results [7, 8]. The phase I/II randomized placebo-controlled trial "Assessing the Safety and Efficacy of IVIg (OMR-IGG-AM) Containing High Anti-WNV Titers in Patients With WNV Encephalitis/Myelitis" was conducted recently; the results of their therapeutic outcomes are still pending [4]. It seems that the earlier the high-titer WNV IVIg is given, the more likely the patient is to benefit [2]. In mice, if the high-titer WNV IVIg is given more than 4 days after exposure to the virus, no survival benefit is found [16]. Our patient received IVIg with unknown WNV titers 8 days after his clinical symptoms appeared.

Administering convalescent plasma is another therapeutic approach that has been tried for patients with other viral diseases with no specific therapy available. Convalescent plasma has been used in the treatment of acute infections including Ebola and H1N1 influenza [9]. Our patient received donor-derived convalescent plasma from the seroconverted stem cell donor, but it occurred late in the disease process and did not alter his clinical course.

Standard testing for WNV in immunocompromised patients should include testing serum and CSF IgM and IgG antibody levels and performing viral PCR testing [2]. Our patient was never found to be WNV antibody positive, likely because of his lack of B cells in the early posttransplant period precluding detection using standard techniques. It was a retinal examination that ultimately provided a clue to his diagnosis.

This case highlights the importance of educating transplant recipients and donors about protection from mosquitos to decrease the possibility of transmitting WNV during the immediate pretransplant period, including the use of mosquito repellant and protective clothing [17]. In addition, antibody-based diagnostic test results might be falsely negative in transplant recipients, and nucleic acid–based testing is necessary in these populations. Last, early administration of convalescent plasma and high-titer WNV plasma can be considered for immunocompromised patients with suspected WNV encephalitis. The development of point-of-care testing for WNV in donor bone marrow ultimately will be necessary to eliminate the risk of transmission during transplant.

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