West Nile Encephalitis in 2 Hematopoietic Stem Cell Transplant Recipients: Case Series and Literature Review

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Most human cases of West Nile virus infection are acquired via bites from an infected mosquito. In some cases, infection may also be transmitted by infected blood products or transplanted organs. There have been recent publications suggesting that chemotherapy and immunosuppression may increase a person’s risks of developing central nervous system disease if the person is infected with the West Nile virus. Because patients undergoing hematopoietic stem cell transplantation not only are immunocompromised, but also receive multiple blood products, they are at a particularly high risk for acquiring symptomatic disease if exposed to the West Nile Virus. We describe here 2 patients who underwent hematopoietic transplantation at our institution and subsequently developed fatal West Nile virus infections.

West Nile virus (WNV) is a single-stranded RNA virus of the genus Flavivirus and is transmitted by mosquitoes. The infection primarily involves birds; humans are incidental hosts. WNV was first recognized in the United States in 1999, when it caused an epidemic of meningoencephalitis on the east coast [1]. Since then, cases of both human and animal infection have spread rapidly westward. The number of human cases of WNV infection in the United States reported to the Centers for Disease Control and Prevention (CDC) as of 12 March 2003 was 4156, with 284 deaths [2]. To date, of 33 cases of possible blood transfusion–related WNV infection that are under investigation by the CDC, evidence that the WNV infection was transmitted through blood transfusion has been found in 9 cases, including in 1 of the cases reported in this series [3].

The number of hematopoietic stem cell transplant recipients who receive a diagnosis of WNV infection is not known. There are no data concerning the clinical course and outcome in such patients. We report here 2 cases of WNV encephalitis in patients who received hematopoietic stem cell transplants and review the literature concerning WNV in immunocompromised patients.

CASE 1

A 58-year-old man from Illinois with a history of relapsed acute myeloid leukemia (AML) was admitted on 3 September 2002 to the bone marrow transplant unit of The University of Texas M. D. Anderson Cancer Center (Houston) to undergo reduced-intensity conditioning with fludarabine, busulfan, and antithymocyte globulin (ATG) followed by a matched unrelated-donor (MUD) bone marrow (BM) transplant.

During the course of his therapy for AML, the patient had received numerous blood transfusions in Illinois and at M. D. Anderson Cancer Center. In addition, during the 2 weeks the patient was in Houston prior...
to his admission for BM transplantation, he had also received donor platelets 1 day and 3 days before admission. The patient had no other significant past medical or travel history.

The patient was admitted to the hospital 6 days before the planned BM infusion. At admission, prophylactic levofloxacin, vancomycin, and fluconazole therapy was started. The patient received ATG (10 mg/kg per day for 4 days), fludarabine (30 mg/m² per day for 4 days), and busulfan (3.2 g/kg per day for 3 days and 1.6 g/kg per day for 1 day) as the preparative regimen for the transplantation.

On the hospital day 2 (five days before transplantation), the patient developed a fever of 39.4°C without any apparent source of infection. Therapy with broad-spectrum antibiotics was started, and the patient defervesced on day 4. One day after the onset of fever, right shoulder weakness developed, without any sensory changes, pain, headache, or visual changes. Physical examination showed weakness of the deltoid and triceps muscles with decreased triceps reflexes bilaterally. Findings of an initial MRI of the brain and right brachial plexus were normal. On hospital day 7, the patient received the BM infusion without event. However, 1 day after transplantation, he again developed a fever of 38.6°C. At this time, the weakness in the patient’s right arm became more pronounced and subsequently progressed to involve his left upper extremity and lower extremities.

A lumbar puncture performed on hospital day 8 revealed an opening pressure of 25 mm Hg and clear CSF, and laboratory analysis of a CSF specimen revealed a glucose concentration of 103 mg/dL (normal range, 40–70 mg/dL), an elevated protein level of 66 mg/dL (normal range, 15–55 mg/dL), but no WBCs or RBCs. Results of microbiological studies of a CSF specimen were all negative, including bacterial stains and cultures; cryptococcal antigen testing; PCR for human herpes virus-6, herpes simplex viruses 1 and 2, and varicella zoster virus; and acid-fast bacilli staining and culture. No leukemic cells were noted.

On hospital day 9, the patient became confused and developed generalized weakness. On day 10, the patient became unresponsive, with flaccid extremities. He was then transferred to the intensive care unit and intubated for airway protection. He was subsequently transferred to our institution, and his corticosteroid dose was tapered. However, he experienced progression of his GVHD and began to receive high-dose intravenous corticosteroids, as prescribed by his oncologist. Two days later (i.e., 4 days before his transfer to our institution), the patient became progressively weaker and was febrile (temperature, ≤38.3°C). He was admitted to his local hospital and began to receive a regimen of broad-spectrum antibiotics. He was not neutropenic at the time, and cultures of blood, urine, and nasal swab specimens were all sterile. Two days before transfer to our institution, the patient’s fever rose to 40°C, and he had several seizure-like episodes for which phenytoin therapy was administered. The findings of an initial CT scan and EEG showed no abnormalities. A serum sample was also obtained for anti-WNV antibody testing.

The patient had been receiving regular blood-product transfusions for anemia and thrombocytopenia in Oklahoma. The patient had no recent travel history, but had an extensive medical history, including diabetes mellitus type 2 and atrial fibrillation.

On initial assessment at our institution, the patient was found to be afebrile and severely obtunded. Findings of a neurological examination showed resting nystagmoid movements with roving eye movements and reactive pupils. The patient also exhibited a positive corneal reflex, gag reflex, and oculocephalic (doll’s eyes) reflex. Motor examination showed no spontaneous movement. Deep tendon reflexes were depressed throughout, and ankle jerks were absent bilaterally. Babinski’s examination revealed bilateral down-going toes.

Findings of an EEG showed severe, diffuse, generalized slowing that was nonreactive to exogenous stimulation and was consistent with severe encephalopathy. MRI showed a bright signal in the region of the red nucleus within the midbrain that was seen on both T2 and fluid-attenuated inversion recovery images. The results of a laboratory analysis of CSF samples obtained on hospital day 2 showed a WBC count of 5 cells/
Figure 1. Case 1: MRI of a 58-year-old man from Illinois who had acute myeloid leukemia, received a matched unrelated-donor blood and marrow transplant, and was confirmed to have West Nile virus encephalitis. A, Axial MRI fluid-attenuated inversion recovery study at the level of the midbrain reveals a bilobed hyperintense signal in the region of the red nucleus that is slightly affecting the surrounding tissues (arrows). B, Coronal MRI T1 postcontrast study through the midbrain reveals enhancement in the red nucleus (arrows).

µL, an RBC count of 30 cells/µL, a glucose concentration of 129 mg/dL, and an elevated protein concentration of 147 mg/dL. The results of Gram’s staining for bacteria, India ink testing for cryptococci, and viral and bacterial cultures were negative. Serum samples obtained that same day yielded weakly positive results when tested for anti-WNV IgM antibody (Enzyme ImmunoAssay (EIA) index 2.01, cutoff <2.0; Houston City Health Laboratory). Serum samples obtained a few days earlier at the patient’s local hospital also yielded positive results when tested for anti-WNV IgM antibodies (EIA index 2.55, cutoff < 2.00; Focus Technologies, Cypress CA). Tests performed on both of these samples were negative for anti-WNV IgG antibodies.

The patient remained obtunded, and, given his poor neurological state, the family decided to withdraw life support 1 week after his transfer to our institution. After the patient’s death, an autopsy was performed, and the brain tissue samples were found to be positive for WNV by PCR at the CDC (Fort Collins, CO). Histopathologic examination of the brain tissue showed changes that were consistent with viral encephalitis (figure 2).

DISCUSSION

The CDC has confirmed the transmission of WNV from a single organ-donor to 4 organ-recipient in Georgia and Florida [4]. The organ donor had received multiple transfusions of blood products prior to death, raising the question of whether these blood-product transfusions could have transmitted WNV to the recipients. In Michigan, 2 recipients of blood products, 1 of whom also received a liver transplant, had test results that were positive for WNV infection after receiving blood products derived from a single blood donation. Several other cases, including 1 of the cases discussed above, have since been confirmed to have been transmitted through blood transfusions. These investigations provide evidence that WNV can be transmitted through blood transfusions [5].

To the best of our knowledge, these are the first reported cases of WNV infection in recipients of hematopoietic stem cell transplants. Both patients described here came from areas where cases of human WNV infection have occurred. The first patient resided in Illinois, the state where the most cases were reported in 2002 (884 cases). The second patient came from Oklahoma, which has had only 21 cases of human WNV infection to date. However, both patients had spent some time in Texas before receiving a diagnosis of WNV infection. In 2002, Texas has had a total of 202 cases of known WNV human infection, with 13 deaths [2]. Therefore, both patients had opportunity to be infected via mosquito bites rather than via the blood transfusions. However, CDC investigation revealed that, at least in case 1, the patient contracted the infection through a blood transfusion that he received in Illinois. Two other individuals who received blood components from the same blood donation were also infected.

The clinical features of WNV are varied, and a diagnosis cannot be made on clinical grounds alone. Most infections are clinically asymptomatic [6, 7]. The 1999 New York City epidemic survey showed that fever developed in ~20% of persons infected with WNV, and that only one-half of these febrile
patients had seen their physician [1]. Uncomplicated WNV infection usually presents with the sudden onset of fever, headache, and myalgia. A generalized roseolar or maculopapular rash and generalized lymphadenopathy have also been noted in up to 50% of symptomatic patients [8]. The acute phase lasts for <1 week, but prolonged fatigue can result.

Severe neurological disease due to WNV remains uncommon. Two serosurveys conducted in New York City during 1999 and 2000 showed that ~1 in 150 infections resulted in meningitis or encephalitis [9]. Those with neurological disease may present with symptoms ranging from headache to coma. Flaccid paralysis occurs in 10% of patients [1]. Data from the outbreak of WNV infection in Israel showed headache in 90% of patients with meningoencephalitis, confusion in 48%, neck stiffness in 13%, cervical pain in 14%, seizure in 9%, photophobia in 9%, and limb weakness in 4% [10]. The New York data further suggest that the serum samples obtained from patients with encephalitis accompanied by muscle weakness are more likely to be positive for WNV antibodies (27%) than are the serum samples obtained from patients with encephalitis alone (14%) or those with aseptic meningitis (6%) [1].

CT findings are generally normal in patients with suspected WNV infection involving the CNS; MRI findings appear to be a more accurate means of detecting abnormalities. In the New York city outbreak, 31% of the patients who underwent MRI showed evidence of enhancement of the leptomeninges, the periventricular area, or both [1]. EEG findings were abnormal, with no clear localization and only focal or generalized slowing, in most of a series of patients from Israel studied during the outbreak in 2000 [10].

The CSF findings are nonspecific, characterized by pleocytosis, elevated protein levels, and normal glucose levels [11]. Our patients showed elevated protein levels but very little pleocytosis, which was likely because of their severe immunosuppression.

The risk factor most clearly associated with encephalitis and death is age [1, 12, 13]. It is unclear whether immunocompromised patients are at an increased risk for WNV infection and whether the disease is more severe in these patients. In the New York City outbreak, 14% of the patients with encephalitis had a known history of immunosuppression. However, none of these patients were hematopoietic stem cell or organ transplanted.

Figure 2. Case 2: Microglial nodules (A and B) were present throughout the brain stem and were particularly prominent in the medulla, as seen here. Perivascular lymphocytic infiltrates (C) were also present throughout the brainstem. Neuropil edema with associated reactive gliosis (D) was marked in areas of the brainstem corresponding to the MRI of the midbrain, seen on T2 weighted and fluid-attenuated inversion recovery images. (All panels, hematoxylin-eosin stain; original magnification, ×100).
plant recipients. Nonetheless, patients with diabetes mellitus, who made up a portion of the 14% of immunocompromised patients, did show an increased risk for death, even after adjustment for age (age-adjusted relative risk, 5.1) [1]. It is interesting that 5 of the 6 patients who contracted WNV through blood transfusions had clear underlying immunocompromised states. Two patients were organ transplant recipients, and 3 patients had a diagnosis of malignancy [3]. Other recent publications have also suggested that exposure to WNV infection in patients receiving chemotherapy and immunosuppression may increase their risk of developing severe nervous system disease [14–16]. The fact that, in all 4 recipients of an organ transplant from the donor infected with WNV, symptomatic WNV infections developed, resulting in the death of 1 of these patients, suggests that organ transplant patients are at increased risk. Similarly, patients who have received a hematopoietic stem cell transplant, even several months after transplantation, are at high risk for opportunistic infections, including viral infections. It follows that these patients are likely at increased risk for WNV infection, either transmitted by arboviral vectors or by blood transfusion. Moreover, many of these patients, even after initial recovery from their myeloablative therapy, receive immunosuppressants, such as tacrolimus or corticosteroids to control GVHD, that may place them at further risk.

Therapy for WNV infection is essentially supportive. Anti-viral agents such as ribavirin and IFN-α are effective in decreasing viral replication in vitro, but data regarding their clinical efficacy are lacking [17–19]. In the study from Israel, 37 patients with meningoencephalitis were treated empirically with ribavirin, but the results of multivariate analysis showed no effect of treatment on mortality rates [20]. One of our 2 patients was treated with IFN-α without effect. The possible benefit of intravenous immunoglobulin for treatment of high titers of anti-WNV antibodies has been described in a lung transplant recipient with WNV encephalitis [21].

CDC investigations have shown that WNV can be transmitted through blood and organ donations. A mathematical modeling study designed by Biggerstaff and Petersen [22] to estimate the risk of transmission via blood transfusion found the risk to be 2 cases of infection per 10,000 transfusions during the New York City outbreak. However, this was estimated at the peak of the epidemic; the rates are probably lower in fall and winter months. This situation poses a problem in screening donors for blood banks. The US Food and Drug Administration (FDA) currently recommends excluding all donors who have even minor symptoms, from mild fever to headache, from donating blood products. Unfortunately, there is currently no accurate or rapid screening tool that can exclude patients with asymptomatic WNV infections from donating blood. On 12 December 2002, the American Association of Blood Banks, the American Red Cross, and the American Blood Centers, with the concurrence of the FDA, recommended that all blood components collected between 26 June and 1 December 2002 be removed from available inventory because of the possibility of contamination with WNV. Physicians who care for recipients of blood transfusions and tissue or organ transplants need to educate themselves and their patients to recognize the early signs of WNV infection. Aggressive donor education and selection may be necessary. It has even been suggested that donors from particular geographic areas may need to be excluded from blood donation during certain seasons. This may be very difficult, however, given the already severe shortages in the blood supply.

Screening the blood supply for the WNV virus, as is routinely done for HIV and hepatitis C, may be necessary, because, at most, only 20% of infected patients become symptomatic. The CDC, several state public health laboratories, and others have developed tests that can detect very small amounts of WNV in biological specimens [23]. However, the cost of screening the entire blood supply may be prohibitive. Moreover, the serum samples obtained from donors who have been exposed to WNV infection may test positive for IgM antibodies up to 12 months after exposure, making this an unreliable indicator of recent infection [24]. An alternative option may be to screen only the blood that is being given to severely immunosuppressed patients.

Although the numbers of patients reported with WNV infection start to decrease at the beginning of fall and the end of mosquito season, it is clear that preventive measures, including effective screening methods, should be developed. In warmer states, the potential for year-round transmission exists.

References


