Powassan virus infection likely acquired through blood transfusion presenting as encephalitis in a kidney transplant recipient

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Abstract

A kidney transplant patient without known tick exposure developed encephalitis three weeks after transplantation. During the transplant hospitalization, the patient had received a blood transfusion from an asymptomatic donor later discovered to have been infected with Powassan virus. This report describes a probable instance of transfusion-transmitted Powassan virus infection.

Introduction

Powassan virus, a tick-borne flavivirus, is a rare cause of febrile illness, meningitis, and encephalitis in North America.[1] Most human infections occur in the upper Midwest and the Northeast, where *Ixodes scapularis* is the primary vector.

In July 2018, a kidney transplant recipient from Indiana developed fever and encephalitis. Antibodies to Powassan virus were detected in serum and cerebrospinal fluid (CSF) samples. Because Powassan virus is not known to circulate in ticks in Indiana, a novel mode of transmission was suspected. We describe the clinical features and epidemiologic investigation of this case, which demonstrate probable transfusion-transmitted Powassan virus infection.

Methods

Diagnosis of Powassan virus infection in the kidney recipient

Serum collected pre- and post-transplant and serum and CSF collected after symptom onset were tested for evidence of Powassan virus infection using immunoglobulin (Ig) M antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA), plaque reduction neutralization test (PRNT), and reverse transcription-polymerase chain reaction (RT-PCR) to detect Powassan virus RNA. Powassan virus MAC-ELISA and RT-PCR testing was performed at the Centers for Disease Control and Prevention (CDC) Arboviral Diseases Branch (Fort Collins, Colorado).

Investigation of the organ donor and second organ recipient

The Organ Procurement and Transplantation Network (OPTN) Patient Safety System was promptly notified of a possible donor-transmitted infection. The organ donor had died following a hemorrhagic stroke. Serum obtained from the donor prior to organ recovery was tested for evidence of Powassan virus infection using IgM MAC-ELISA, PRNT, and RT-PCR. The only other organs utilized from this donor were both lungs, which were allocated to a single recipient. Post-transplant serum from this lung recipient was tested by Powassan virus IgM MAC-ELISA and PRNT. The

tissue agency also recovered bone, soft tissue, and a saphenous vein from the organ donor, all of which were quarantined and eventually discarded.

Blood donor investigation

Three blood donors were interviewed about potential tick exposure prior to donation. A non-transfused plasma co-component from one donation was tested for Powassan virus by RT-PCR, MAC-ELISA, and PRNT. Co-components were not available for the other two donations. All three donors provided additonal serum samples for Powassan virus testing 4–6 months after initial donation.

Environmental investigation

Ticks were collected by drag sampling near the patient's home and in additional sites in the county of residence. Captured *I. scapularis* ticks were screened for Powassan virus RNA by RT-PCR.

Results

Kidney Recipient

A woman in her thirties developed severe frontal headache, fever, weakness, myalgias, and diarrhea 24 days after undergoing kidney transplantation at a Wisconsin hospital. During her transplant hospitalization, she had received red blood cell transfusions from three blood donors on post-operative days one, two, and five. She presented to a hospital in Indiana, where she received broad-spectrum antibiotics without improvement. Thirty-three days after transplantation, she was admitted to her transplant center in Wisconsin with fever, headache, chills, confusion, photophobia, nausea, and diarrhea. No neurological deficits were noted on initial examination. CSF analysis revealed 5 nucleated cells/mm^3, 80 red blood cells/mm^3, a protein level of 55 mg/dL, and normal glucose concentrations (supplemental Table 1). Anti-infective therapy was initiated for meningitis. Magnetic

resonance imaging (MRI) of the brain demonstrated nonspecific, abnormal T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) signal in the cerebellum and pachymeningeal thickening and enhancement (Supplemental Figure 1A and 1E), the latter attributed to recent lumbar puncture.

Between the third and fourth hospital day, she developed tremors, ataxia, dysarthria, sensorineural hearing loss, and bilateral blurred vision. Brain MRI on the third hospital day demonstrated new loss of CSF suppression on T2-FLAIR images and diffuse pial enhancement in the cerebellum (Supplemental Figure 1B and 1F). Extensive testing revealed no evidence of a specific pathogen, malignancy, or auto-immune disorder (Supplemental Table 1). Empiric anti-infective therapy was discontinued and treatment with intravenous corticosteroids was initiated. On the seventh hospital day, the symptoms of ataxia, confusion, and blurred vision began to improve, although hearing loss persisted. Brain MRI on hospital day nine showed decreased cerebellar enhancement (Supplemental Figure 1C and 1G).

Due to the clinical features of fever, quickly evolving cranial nerve deficits and cerebellar dysfunction, yet relatively mild CSF lymphocytic pleocytosis, suspicion centered around viral pathogens associated with encephalitis. After testing for herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, herpes zoster virus, and human herpes virus 6) was negative, testing for arboviruses was requested through the Wisconsin State Laboratory of Hygiene and the CDC. Thirteen days after symptom onset, Powassan virus-specific IgM antibodies were detected in serum and CSF. Neutralizing antibodies to Powassan virus were detected in the serum at a titer of 1:10, rising to 1:320 on another serum sample collected 5 days later (Table 1). Archived pre-transplant serum had no detectable Powassan virus RNA, IgM, or neutralizing antibodies (Table 1).

A follow-up brain MRI two months later showed near complete resolution of cerebellar enhancement (Supplemental Figure 1D and 1H). Five months after hospital

discharge, the patient had returned to work full time. She reported full recovery of hearing, but noted anxiety and difficulty managing multiple tasks.

Organ donor and second organ recipient

Banked plasma and serum samples collected from the donor before organ procurement had no detectable Powassan virus RNA, IgM, or neutralizing antibodies. The lung recipient reported no symptoms of illness and had no serologic evidence of Powassan virus infection (Table 1).

Blood donors

Donor 2, who was from Wisconsin, reported working in the woods in Northern Wisconsin and removed an embedded tick one month prior to blood donation. This donor provided a single unit of packed red blood cells to the kidney recipient on post-operative day two, 22 days before symptom onset (Supplemental figure 2). RT-PCR testing performed at the CDC on the plasma co-component from this blood donation revealed a low level of POWV RNA (cycle threshold value, 36.5), with one of three primer sets positive in duplicate (Table 1). Powassan virus IgM and neutralizing antibodies were not detected in this sample, however, repeat teating on serum collected from the blood donor 6 months later was positive for Powassan virus IgM and neutralizing antibodies (Table 1).

Environmental investigation

Drag sampling at the patient's home and a nearby park yielded no ticks. Twenty-four *I. scapularis* ticks were collected from two other sites in the same county, but none had detectable Powassan virus RNA.

Discussion

This investigation demonstrates the first documented probable transmission of Powassan virus through blood transfusion from an asymptomatic donor. The clinical spectrum of Powassan virus disease ranges from clinically inapparent infection to fatal necrotizing encephalitis.[1, 2] There is often a prodrome of fever, myalgias, and headache, followed by focal or diffuse neurologic signs, including paralysis, seizures, encephalitis, and coma. Lymphocytic pleocytosis and elevated protein

concentrations in the CSF are characteristic.[3] Brain MRI may show T2-weighted enhancement and/or edema of the cerebellum, cerebral cortex, leptomeninges, thalamus, basal ganglia, or midbrain.[2, 3] Mortality during the acute phase of illness is 10-15%. The majority of survivors have long-term neurologic sequelae.[3, 4]

We are aware of one prior report of Powassan virus encephalitis in an organ transplant recipient.[5] In Europe, where a highly related tick-borne encephalitis virus circulates, three transplant recipients developed fatal encephalitis from an infected organ donor.[6] Reported outcomes of Powassan virus encephalitis cases in immune-compromised patients have been severe or fatal [2, 3, 7]. Thus, early warning of the organ procurement organization of a potential donor-derived infection is critical. In this case, investigation found no evidence of transmission via organ transplantation.

It is possible that our patient experienced a milder course of illness because transmission did not occur through a tick vector. Tick saliva has been shown to enhance Powassan viremia and disease severity in experimental infection models.[8] Alternatively, the mild clinical manifestations described here may have been a result of waning viremia in the blood donor. It is also possible that corticosteroid treatment was beneficial.

The optimal management of Powassan virus encephalitis is undefined. In a recent series of 14 patients with Powassan virus encephalitis, all five patients who received intravenous corticosteroids survived, while 5 of the 9 patients who did not receive steroids died.[4] Intravenous immunoglobulin has been used in Powassan virus encephalitis and West Nile virus infection with mixed results.[3, 9]

This report adds to the growing literature of flavivirus transmission through transfusion of blood products.[10, 11] The U.S. blood supply is currently screened for two flaviviruses, West Nile virus and Zika virus, through nucleic acid tests. Between 2009 and 2018, 12,835 cases of West Nile virus neuroinvasive disease were reported. In contrast, over the same period, only 133 cases of Powassan virus disease were reported.[12] Given the extremely low incidence of Powassan virus disease even

in endemic regions, the cost-benefit ratio of screening would likely be high. Moreover, there is currently no FDA-licensed test to screen the blood supply for Powassan virus.

Clinicians should consider the diagnosis of Powassan virus infection in patients who present with febrile illness, aseptic meningitis, or encephalitis. Transmission of Powassan virus infection through blood transfusion may result in disease appearing in non-endemic regions, as demonstrated here. Immunocompromised patients are at risk of severe disease or less grave, but persistent neurologic symptoms.

Notes.

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1 **Table 1:** Summary of Powassan virus testing of renal transplant recipient, organ donor, second organ recipient, and three blood donors

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Individual	Day of collection relative to implicated transfusion	Day of collection relative to symptom onset	Specimen	Results of Powassan virus testing[a]		
				IgM	PRNT (titer)	RT-PCR
renal transplant recipient	-3	-25	serum	negative	negative	negative
	14	-8	serum	negative	negative	negative
	35	13	CSF	positive	negative	negative
	35	13	serum	positive	positive (10)	negative
	40	18	serum	positive	positive (320)	negative
Individual	**Day of transplant or transfusion relative to symptom onset**		**Specimen**	**Results of Powassan virus testing[a]**		
				IgM	**PRNT (titer)**	**RT-PCR[b]**
organ donor	-24		pre-procurement serum	negative	negative	negative
			pre-procurement plasma	n.t.	n.t.	negative
lung recipient	—		post-transplant serum	negative	negative	n.t.
blood donor 1	-23		post-donation serum	n.t.	negative	n.t.

blood donor 2	-22	archived plasma[c]	negative	negative	inconclusive[d]
		post-donation serum	positive	positive (40)	n.t.
blood donor 3	-19	post-donation serum	negative	negative	n.t.

Testing performed at the Centers for Disease Control and Prevention (CDC) Arboviral Diseases Branch. Abbreviations: immunoglobulin M (IgM), assayed by IgM-antibody capture enzyme-linked immunosorbent assay (MAC-ELISA); n.t., not tested; plaque reduction neutralization test (PRNT); reverse transcription-polymerase chain reaction (RT-PCR).

[a]Negative result defined as: PRNT value <10, or no IgM detected by MAC-ELISA, or no viral nucleic acid detected by RT-PCR.

[b]All PCR reactions performed in duplicate. [c]Remaining plasma co-component from index blood donation.

[d]One of three primer sets positive.