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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 3 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. Here, we describe a probable instance of transfusion-transmitted Powassan virus infection.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Keywords

Powassan virus; encephalitis; renal transplant; blood transfusion

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 using immunoglobulin (Ig) M antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA), the 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 were 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 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 used from this donor were both lungs, which were allocated to a single recipient. Post-transplant serum from this lung recipient was tested for Powassan virus using 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 nontransfused plasma co-component from 1 donation was tested for Powassan virus using RT-PCR, MAC-ELISA, and PRNT. Co-components were not available for the other 2 donations. All 3 donors provided additional 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 at additional sites in the county of residence. Captured *I. scapularis* ticks were screened for Powassan virus RNA using RT-PCR.

RESULTS

Kidney Recipient

The patient, a woman in her thirties, developed severe frontal headache, fever, weakness, myalgias, and diarrhea 24 days after undergoing kidney transplantation at a Wisconsin hospital. 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 (Supplementary Table 1). Anti-infective therapy was initiated for meningitis. Magnetic resonance imaging (MRI) of the brain demonstrated nonspecific, an abnormal T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) signal in the cerebellum and pachymeningeal thickening and enhancement (Supplementary Figure 1A and 1E), the latter attributed to a 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 (Supplementary Figure 1B and 1F). Extensive testing revealed no evidence of a specific pathogen, malignancy, or autoimmune disorder (Supplementary 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 9 showed decreased cerebellar enhancement (Supplementary 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 in 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 2 months later showed near complete resolution of cerebellar enhancement (Supplementary 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

During her transplant hospitalization, the patient had received red blood cell transfusions from 3 blood donors on postoperative days 1, 2 and 5. Donor 2, who was from Wisconsin, reported working in the woods in northern Wisconsin and removed an embedded tick 1 month prior to blood donation. This donor provided a single unit of packed red blood cells to the kidney recipient on postoperative day 2, 22 days before symptom onset (Supplementary Figure 2). RT-PCR testing performed at the CDC on the plasma co-component from this blood donation revealed a low level of Powassan virus RNA (cycle threshold value, 36.5), with 1 of 3 primer sets positive in duplicate (Table 1). Powassan virus IgM and neutralizing antibodies were not detected in this sample; however, repeat testing 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 2 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 1 prior report of Powassan virus encephalitis in an organ transplant recipient [5]. In Europe, where a highly related tick-borne encephalitis virus circulates, 3 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 5 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 US blood supply is currently screened for 2 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 US Food and Drug Administration–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 nonendemic regions, as demonstrated here. Immunocompromised patients are at risk of severe disease or less grave, but persistent, neurologic symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of Powassan Virus Testing of Renal Transplant Recipient, Organ Donor, Second Organ Recipient, and 3 Blood Donors

Individual	Day of Collection Relative to Implicated Transfusion	Day of Collection Relative to Symptom Onset	Specimen	Results of Powassan Virus Testing[a]		
				IgM[b]	PRNT (titer)	RT-PCR
Renal	−3	−25	Serum	Negative	Negative	Negative
transplant	14	−8	Serum	Negative	Negative	Negative
recipient	35	13	Cerebrospinal fluid	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[c]
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[d]	Negative	Negative	Inconclusive[e]
		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 Arboviral Diseases Branch.

Abbreviations: IgM, immunoglobulin M; n.t., not tested; PRNT, plaque reduction neutralization test; RT-PCR, reverse transcription-polymerase chain reaction.

[a] Negative result defined as: PRNT value <10, or no IgM detected by IgM-antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), or no viral nucleic acid detected by RT-PCR.

[b] Assayed by MAC-ELISA.

[c] All PCR reactions performed in duplicate.

[d] Remaining plasma co-component from index blood donation.

[e] One of 3 primer sets positive.