Title

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Journal

Clinical Infectious Diseases, 76(3)

ISSN

1058-4838

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Publication Date

2023-02-08

DOI

10.1093/cid/ciac566

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

Transfusion-Transmitted Cache Valley Virus Infection in a Kidney Transplant Recipient With Meningoencephalitis

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Background. Cache Valley virus (CVV) is a mosquito-borne virus that is a rare cause of disease in humans. In the fall of 2020, a patient developed encephalitis 6 weeks following kidney transplantation and receipt of multiple blood transfusions.

Methods. After ruling out more common etiologies, metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid (CSF) was performed. We reviewed the medical histories of the index kidney recipient, organ donor, and recipients of other organs from the same donor and conducted a blood traceback investigation to evaluate blood transfusion as a possible source of infection in the kidney recipient. We tested patient specimens using reverse-transcription polymerase chain reaction (RT-PCR), the plaque reduction neutralization test, cell culture, and whole-genome sequencing.

Results. CVV was detected in CSF from the index patient by mNGS, and this result was confirmed by RT-PCR, viral culture, and additional whole-genome sequencing. The organ donor and other organ recipients had no evidence of infection with CVV by molecular or serologic testing. Neutralizing antibodies against CVV were detected in serum from a donor of red blood cells received by the index patient immediately prior to transplant. CVV neutralizing antibodies were also detected in serum from a patient who received the co-component plasma from the same blood donation.

Conclusions. Our investigation demonstrates probable CVV transmission through blood transfusion. Clinicians should consider arboviral infections in unexplained meningoencephalitis after blood transfusion or organ transplantation. The use of mNGS might facilitate detection of rare, unexpected infections, particularly in immunocompromised patients.

Keywords. Cache Valley virus; meningoencephalitis; kidney transplant; blood transfusion; transfusion-transmitted infection.

Cache Valley virus (CVV) is a single-stranded RNA mosquito-borne virus belonging to the Bunyamwera serogroup of the genus *Orthobunyavirus* [1, 2]. CVV was first isolated from *Culiseta inornata* mosquitoes in Cache Valley, Utah, in 1956 and since that time has been found in North America, Central America, and parts of South America [1]. Although the virus has been isolated from multiple mosquito species, the primary vector is unknown. In endemic areas, human seroprevalence estimates range from 1% to 19% [3, 4]. Clinically recognized infections, however, are rare. To date, only 6 cases of CVV disease in humans have been published, including 3 in patients with immunocompromising conditions. Five patients presented with meningitis or meningoencephalitis, and 3 cases were fatal. Here, we describe the first identified case of probable blood transfusion-transmitted CVV infection, which occurred in a patient following kidney transplantation.

METHODS

Diagnosis of CVV in Kidney Transplant Recipient

Following negative routine diagnostic testing for more common neuroinvasive infections in the kidney recipient, cerebrospinal fluid (CSF) was sent to the University of California–San Francisco (UCSF) for Clinical Laboratory Improvement Amendments-validated metagenomic next-generation sequencing (mNGS) [5, 6]. Confirmatory testing on the CSF with CVV reverse-transcription polymerase chain reaction (RT-PCR) and viral culture with subsequent whole-genome

Received 16 March 2022; editorial decision 26 April 2022; published online 27 July 2022

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Clinical Infectious Diseases® 2023;76(3):e1320–e7

https://doi.org/10.1093/cid/ciac566

sequencing was performed at the Centers for Disease Control and Prevention (CDC) Arboviral Diseases Branch Diagnostics Laboratory in Fort Collins, Colorado. CVV RT-PCR and plaque reduction neutralization test (PRNT) were conducted on pre-transplant serum and post-transplant whole blood, plasma, and a second CSF sample.

Virus Isolation

At the CDC, standard virus isolation methods were used to inoculate the CSF specimen onto confluent Vero cells in T25 flasks. Briefly, up to 200 µL of the CSF specimen was inoculated into 2 T25 flasks. Inoculated flasks were then incubated at 37°C and reviewed for viral-induced cytopathic effect daily. The harvested cell culture supernatant, which was exhibiting viral-induced cytopathic effects, was confirmed positive for CVV RNA by RT-PCR and sequenced using mNGS as previously described using the Ion Torrent GeneStudio S5 sequencing platform (ThermoFisher) [7]. A full-length, high-coverage sequence of the viral isolate was determined (GenBank accession OL555724-26). The genetic origin of each gene was determined using Bayesian inference [8].

Investigation of Organ Donor and Other Organ Recipients

The Organ Procurement Organization and Organ Procurement and Transplantation Network Disease Transmission Advisory Committee were notified of a possible organ donor–transmitted infection. Archived serum from the organ donor was tested using CVV RT-PCR and PRNT. Transplant teams were interviewed about the clinical status of the other recipients of organs from the common donor. Post-transplant sera from the other organ recipients were tested using CVV PRNT with or without RT-PCR.

Investigation of Blood Donors

To investigate the possibility of blood donor–derived infection, the blood collection organization initiated a traceback investigation of blood products received by the index kidney recipient prior to symptom onset. Blood donors were queried about mosquito exposures and presence of febrile illness within 1 month of donation and were asked to provide follow-up sera for CVV testing. The disposition of co-components from each donation was evaluated.

RESULTS

Kidney Transplant Recipient

A 60-year-old female from Illinois with end stage renal disease from complications of sickle cell disease (SCD) underwent a deceased donor kidney transplant in late fall 2020 following a living unrelated kidney transplant that had failed due to graft thrombosis 6 years prior. Alemtuzumab and rituximab were given for induction due to significant pre-transplant sensitization, followed by tacrolimus and mycophenolate for maintenance immunosuppression. Her post-operative course was notable for transient hypotension and slow graft function, but she was discharged by post-operative day (POD) 5.

From POD 6 to POD 19, the patient was hospitalized after a witnessed fall at home and an acute pain crisis related to her SCD. A computed tomography (CT) scan of her head was unremarkable. Hematology recommended initiation of monthly exchange transfusions for optimal management of SCD. During this admission, the patient was noted to have generalized weakness and sluggish cognition that was attributed to prolonged hospitalizations. On POD 43, the patient was readmitted with worsening generalized weakness, fatigue, weight loss, diarrhea, back pain, urinary frequency, and intermittent dysuria. She was treated for *Enterococcus faecalis* urinary tract and *Clostridioides difficile* infections but continued to exhibit weakness, most profound in her lower legs, and altered mental status with intermittent confusion and word-finding difficulty. The patient's spouse reported that she rarely left home due to her chronic illnesses and did not spend a notable amount of time outdoors. Her medications at the time included tacrolimus, mycophenolate, prednisone, sulfamethoxazole/trimethoprim, valganciclovir, aspirin, hydroxyurea, famotidine, and clonazepam. Clonazepam was held and tacrolimus was changed to cyclosporine and belatacept without improvement in mental status.

Physical examination was notable for hypophonia, bradyphrenia, impaired attention, and some perseveration. Cranial nerves were intact. Strength testing was limited by effort, especially proximally, but mild weakness was nonfocal. Reflexes were symmetrically brisk. Magnetic resonance imaging (MRI) of the brain showed multifocal and regionally confluent areas of increased T2 fluid attenuated inversion recovery (FLAIR) signal within bilateral white matter, attributed to chronic microvascular ischemic disease, and a stable small chronic lacunar infarct in the right cerebellum (Figure 1). Electroencephalography was consistent with moderate encephalopathy with no evidence of seizure activity. On POD 60, the patient developed recurrent fevers. Further infectious workup including blood and urine cultures; CT imaging of the chest, abdomen, and pelvis; and positron emission tomography/CT scan were all unremarkable. Because of persistent weakness and altered mentation, MRI of the brain was repeated and showed increased subtle T2/FLAIR hyperintensity in the left greater than right thalamus, suggestive of encephalitis (Figure 2).

The patient underwent 3 lumbar punctures for CSF analysis on POD 78, 99, and 114 (Table 1). Bacterial and fungal cultures; PCR testing for enterovirus, John Cunningham virus, herpes simplex virus, Epstein Barr virus, varicella zoster virus, human herpes virus 6, cryptococcal antigen, and Venereal Disease Research Laboratory antibody; an autoimmune encephalopathy panel; and a paraneoplastic panel were negative. Repeat MRI on POD 127 revealed progressive encephalitis (Figure 3). Ultimately, the CSF sample from POD 114 was found to have evidence of CVV infection by mNGS performed at UCSF (Figure 4). At the CDC, CVV RNA was detected by

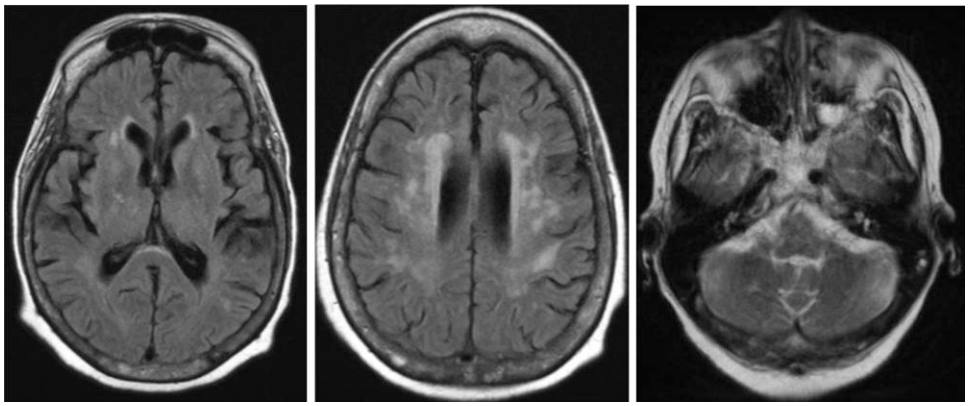

Figure 1. Index kidney recipient magnetic resonance imaging of brain with and without contrast 2 months post-transplantation. Multifocal and regionally confluent areas of abnormally increased T2 fluid-attenuated inversion recovery signal within subcortical, deep, and periventricular cerebral hemispheric white matter bilaterally. No pathologic enhancement of the brain or the meninges on post-contrast scans. A small chronic lacunar infarct is seen within the right cerebellum.

RT-PCR testing of CSF collected on the same day, and cytopathic effect was seen on viral culture, with CVV RNA detected in the supernatant. The CVV isolate was sequenced to high coverage. Both the CSF sample and cell culture isolate were intraspecies reassortants, with the small (Figure 5*A*) and medium (Figure 5*B*) segments falling in lineage II and the large (Figure 5*C*) segment corresponding to lineage I strains. Serum and plasma collected on POD 134 (8 days following the last belatacept infusion) had no detectable CVV RNA, and a low level of neutralization (slightly below the 90% threshold of 1:10) was observed on PRNT. No CVV RNA or neutralizing antibodies were detected in an archived serum specimen collected 19 days before transplantation (Table 2).

The patient's immunosuppression was held, and she was given monthly intravenous immune globulin (IVIG) without improvement in mental status. Three months later, she was readmitted to the hospital with new right hemiparesis, further decline in mental status, and fever. Repeat MRI demonstrated new areas of restricted diffusion and contrast enhancement, read as multiple ischemic events vs progressive infection (Figure 6). A serum specimen collected on POD 232 had detectable CVV neutralizing antibodies with a titer of 80. CSF collected from a repeat lumbar puncture was negative for CVV RNA by mNGS and RT-PCR but had a neutralizing antibody titer of 16 against CVV (Table 2).

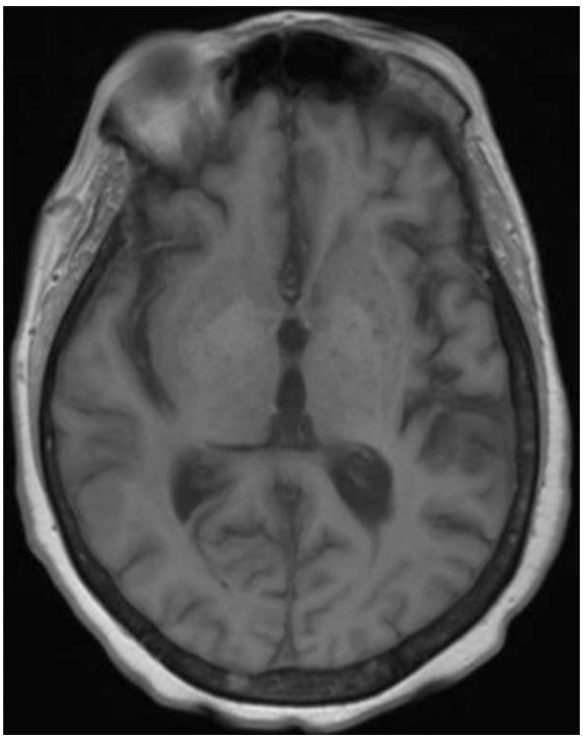

Figure 2. Index kidney recipient magnetic resonance imaging of brain with and without contrast 3 months post-transplantation. Interval subtle increase in fluid-attenuated inversion recovery hyperintensity at the left greater than right thalami; moderate central volume loss is similar to prior examination.

Table 1. Cerebrospinal Fluid Analyses of Index Kidney Recipient

	POD 78		POD 99	POD 114
Laboratory Tests	Tube 1	Tube 4	Tube 1	Tube 1
White blood cells (cells/μL)	2	2	2	0
Neutrophils (%)	30	70	32	0
Lymphocytes (%)	40	20	44	76
Monocytes (%)	30	10	24	20
Eosinophils (%)	0	0	0	4
Red blood cells (cells/μL)	14	1	34	91
Glucose (mg/dL)	71		65	82
Protein (mg/dL)	57		68	…

Abbreviation: POD, post-operative day.

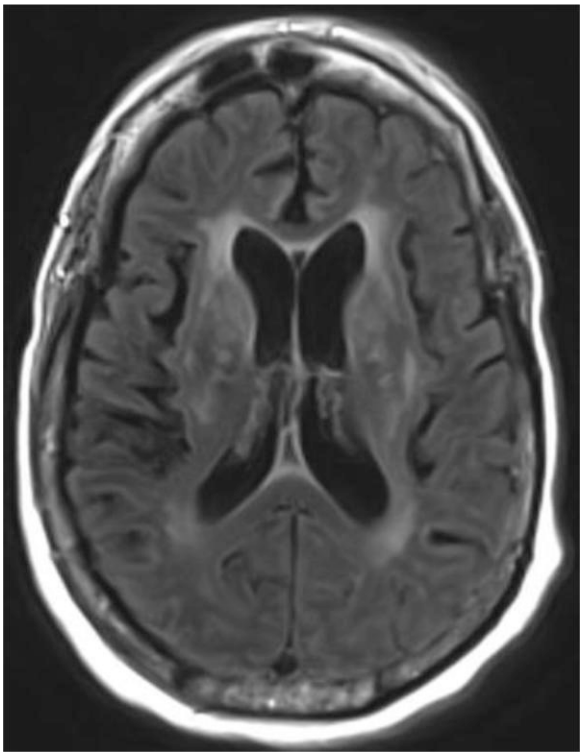

Figure 3. Index kidney recipient magnetic resonance imaging of brain with and without contrast 4 months post-transplantation. Advanced widespread abnormal fluid-attenuated inversion recovery signal in the periventricular white matter, thalami, and brain stem.

Organ Donor and Other Organ Recipients

The organ donor was a woman in her 40s who died following a subarachnoid hemorrhage in the fall of 2020. She received no blood transfusions during the 30 days prior to her death. Archived serum collected 3 days before organ procurement had no detectable CVV RNA or neutralizing antibodies. The other 4 recipients of organs from the same deceased donor, including the second kidney, heart, bilateral lungs, and liver, had no clinical findings suspicious for infection and no detectable CVV RNA or neutralizing antibodies in post-transplant sera. In addition, no CVV RNA was detected by RT-PCR testing of tissue from a routine post-transplant heart biopsy from the heart recipient (Table 2).

Blood Donor Investigation

During the transplant hospitalization, the index kidney recipient received 17 leukocyte-reduced additive-solution red blood cell (RBC) units from 17 donors. The patient had received no other blood transfusions at this center since 2014. RBCs were transfused due to therapeutic RBC exchange procedures required to reduce the risk of complications associated with SCD on preoperative day 0 (8 units) and on POD 1 (1 unit), POD 15 (1 unit), and POD 19 (7 units). At the time of the investigation, all tubing segments from the RBC units had been discarded according to standard protocol.

The 17 blood donors were residents of Wisconsin or Illinois; 16 donors were interviewed, and none reported a febrile illness within 1 month of donation. Several donors reported engaging in outdoor activities during the month prior to transfusion, but none specifically recalled mosquito bites. Thirteen blood donors provided follow-up sera. One donor from Illinois, a male in his 40s with no underlying medical conditions, had detectable CVV neutralizing antibodies at a titer of 10 in serum almost 8 months following the donation transfused into the kidney recipient. The donor provided a second serum specimen approximately 3 months later that showed the same CVV neutralizing antibody titer. The RBC unit from this blood donor was stored for 9 days before transfusion to the index kidney recipient on POD 0. The plasma co-component obtained from the same donation was transfused to a man in his 60s with underlying malignancy 2 months after donation. This recipient was asymptomatic following transfusion; neutralizing antibodies to CVV were detected at a titer of 80 in serum collected 7 months after transfusion (Table 2).

DISCUSSION

We report the first known CVV infection likely acquired via blood transfusion. The patient was a kidney transplant recipient who developed CVV neuroinvasive disease presenting with a chronic, progressive neurologic decline. Of the 6 previously published human CVV disease cases, 5 presented with meningitis or meningoencephalitis, 3 developed multiple organ dysfunction, and 3 died [1, 2, 10–13]. At least 3 of the 6 case patients were immunocompromised, including a man in his 60s with a history of thymectomy for malignant thymoma, a 34-year-old man with X-linked agammaglobulinemia, and a 58-year-old man receiving rituximab maintenance therapy for chronic lymphocytic leukemia. The latter 2 cases had more protracted clinical courses with progressive cognitive dysfunction dying 2 months to 3 years after their initial clinical signs and symptoms. In immunocompromised patients, illness progression can be delayed and detectable viremia from arboviral infections can be prolonged [1, 7, 12, 14–16].

Here, the patient's initial brain MRI and CSF profile were not clearly indicative of an infectious process, findings that are not atypical based on prior case reports of CVV-infected immunosuppressed individuals [12, 13]. Similar to findings reported for other CVV cases, serial MRI images showed progressive widespread abnormal T2/FLAIR signal in the periventricular white matter, thalami, and brain stem and moderate volume loss. A preliminary diagnosis for this case was provided by the UCSF mNGS test that has been validated for clinical use on CSF and found to have a sensitivity of 86.1% and specificity of 97.9% [6]. In this patient, culturable CVV was detected more

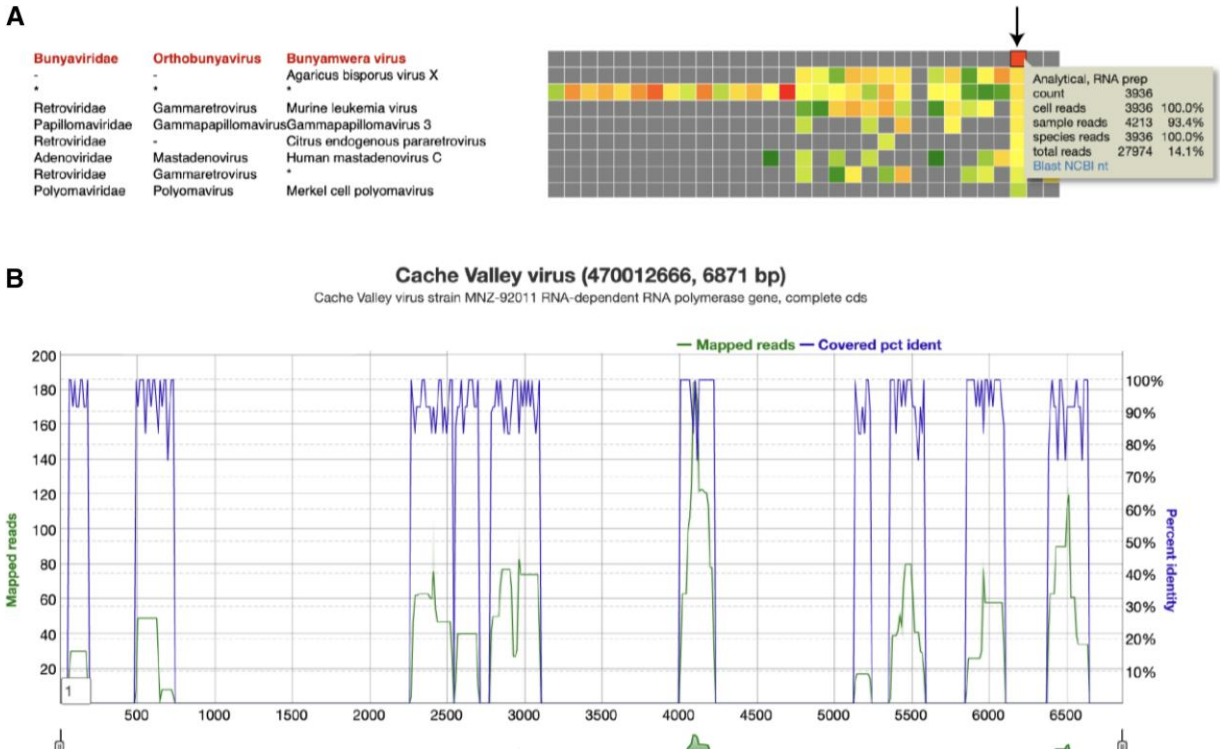

Figure 4. Metagenomic next-generation sequencing (mNGS) results for the index patient. *A,* Heat map of viral reads identified in the mNGS sequencing run. Each column of the heat map represents an individual patient cerebrospinal fluid sample, and the individual cells are color-coded based on viral read counts from green (minimum) to red (maximum), with gray denoting zero reads. The column corresponding to the index patient is highlighted with an arrow, and the read count data for the *Orthobunyavirus* (Cache Valley virus [CVV]) detection is displayed in a pop-up window. The highlighted cell shows that 3936 mNGS reads from the trisegmented bunyavirus genome are detected. Each row of the heat map represents taxonomic identification at the family (left), genus (middle), and species (right) levels, with asterisks denoting either the absence of a taxonomic designation in the reference database (eg, *Agaricus bisporus* virus X at the genus and family levels) or a read that is not specific at a given taxonomic level (eg, *Gammaretrovirus* at the species level). *B,* Coverage map of the bunyavirus reads from the index patient mapped to the closest identified viral reference sequence in the National Center for Biotechnology Information GenBank database (CCV MNZ-92011). A total of 775 nucleotides mapped CVV reads out of 3936 are observed to span the estimated 6871 bp L (large) segment. Automated heat and coverage maps were generated using the SURPI+ bioinformatics pipeline for pathogen identification [6, 9].
Abbreviations: NCBI, The National Center for Biotechnology Information; nt, nucleotide.

than 2 months after the patient's symptom onset and almost 4 months following the implicated blood transfusion. Notably, the CVV isolate generated from the patient's CSF appears to be a lineage I large segment intraspecies reassortant, similar to a recently documented CVV recovered from a non-neuroinvasive disease case in a Missouri resident with a history of thymoma [13].

While serology remains the mainstay of diagnosis for most neuroinvasive arboviral infections in immunocompetent patients, molecular diagnosis is often needed in immunocompromised patients who can have prolonged viremia and a delayed antibody response, as demonstrated here. However, CVV-specific neutralizing antibody testing was critical to CVV transmission tracing and identification of blood transfusion as the likely source. The blood transfusion is considered the probable source of infection as blood samples were not available from the blood donor or the plasma recipient prior to the donation or receipt of the blood product to know definitively the timing of infection for these individuals.

Transfusion-transmitted infection is well known for West Nile virus (WNV), leading to universal WNV blood donor testing in the United States [17]. Transfusion-transmitted infection has also occurred with Powassan virus in a kidney transplant patient [18] but has not previously been reported with CVV. Given the rarity of reported CVV disease cases, limited epidemiologic data, and lack of US Food and Drug Administration–approved screening tests for CVV, implementing blood donor screening is likely not feasible or cost-effective. Pathogen reduction technologies are available for plasma and platelets but are still under development for RBCs [19].

There are no proven therapies for CVV or other arboviral diseases. Compared with ribavirin, favipiravir (T-705) has demonstrated increased activity against several bunyavirus infections in vitro and against Punta Toro virus in animal models [20]. We were unable to obtain favipiravir, which was in short supply during the coronavirus disease 2019 pandemic. We tapered our patient off all immunosuppression and trialed IVIG; however, standard IVIG is unlikely to contain significant

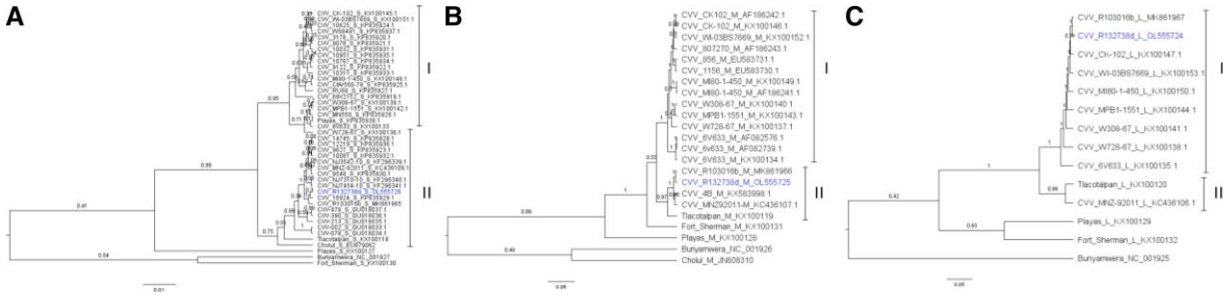

Figure 5. Bayesian phylogenetic inference of transfusion-associated CVV and select *Orthobunyaviruses*. Maximum credibility trees depicting the nucleotide open reading frames of the small (*A*), medium (*B*), and large (*C*) genomic segments. The virus sequenced in this study is highlighted in blue text. Viruses are labeled with virus name, isolate designation, and GenBank accession numbers. Strains corresponding to lineage I or II are grouped with brackets. Posterior probabilities are indicated on each branch, and the scale bar depicts nucleotide substitutions per site. Abbreviation: CVV, Cache Valley virus.

neutralizing antibody titers to CVV, and we did not observe any clinical improvement in our patient. As of most recent follow-up, the patient remains nonverbal and has retained allograft function off immunosuppression.

There were several limitations to the investigation. Although it remains possible that the patient acquired CVV via another mechanism, the limited outdoor exposure in the kidney recipient, lack of evidence of infection through organ transplantation, and seropositivity in a blood donor and another patient who received the co-component plasma from the same donor strongly implicate this case as a transfusion-transmitted infection. Conducting a thorough and expedient investigation into this transmission was also limited given the delay in clinical presentation and diagnosis of the index patient and follow-up needed for the multistate transplant and blood transfusion investigation. Finally, not all blood donors provided follow-up serum samples.

In summary, we report a case of CVV encephalitis in a kidney transplant recipient likely acquired through blood transfusion. This case highlights the potential role for broad-spectrum mNGS to facilitate the detection of rare, unexpected infections, particularly in immunocompromised patients. Clinicians should consider arboviral infections in cases of encephalitides following transfusion of blood products and investigate all

Table 2. Cache Valley Virus Testing in Organ Donor and Recipients, Blood Donor of Interest, and Recipient of Co-Component Plasma From the Index Blood Donation

			Results		
Patient	Sample	Collection Date	Metagenomic Next-Generation Sequencing	Reverse-Transcription Polymerase Chain Reaction (Culture)	Plaque Reduction Neutralization Test Titer
Right kidney recipient (index case)	Serum (pre-transplant)	9/2/2020	…	No RNA detected	<10
	CSF	1/13/2021	+CVV	+CVV RNA (+cytopathic effect)	…
	Blood	2/2/2021	…	No RNA detected	…
	Plasma	2/2/2021	…	No RNA detected	<10 (low-level neutralization slightly below threshold of detection)
	Blood	5/11/2021	…	No RNA detected	80
	CSF	5/8/2021	Negative	No RNA detected	16
Left kidney recipient	Serum	3/17/2021	…	No RNA detected	<10
Heart recipient	Serum	7/26/2021	…	…	<10
	Heart biopsy	9/28/2021	…	No RNA detected	
Bilateral lung recipient	Serum	3/4/2021	…	No RNA detected	<10
Liver recipient	Serum	5/20/2021	…	…	<10
Organ donor	Serum	9/18/2020	…	No RNA detected	<10
Blood donor A	Blood	4/22/2021	…	…	10
	Serum	8/4/2021	…	…	10
Recipient of frozen plasma from blood donor A	Serum	6/21/2021			80

$PRNT_{90}$ titer <10 = negative.

Abbreviations: CSF, cerebrospinal fluid; CVV, Cache Valley virus.

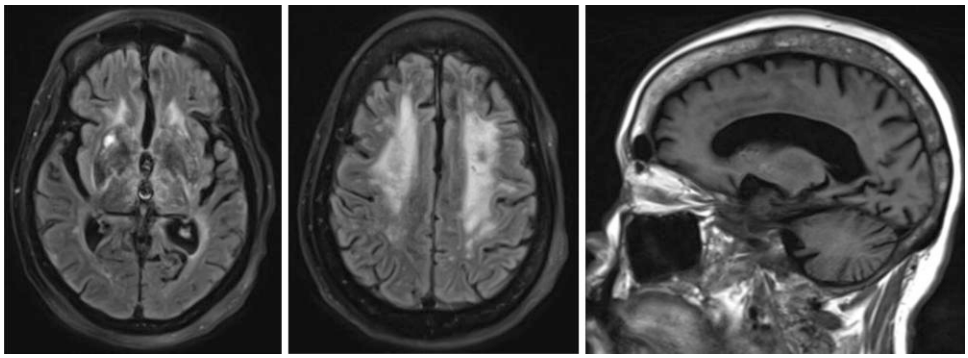

Figure 6. Index kidney recipient magnetic resonance imaging of brain with and without contrast 8 months post-transplantation. Progression of abnormalities particularly within the deep aspects of the cerebral hemispheres bilaterally as well as the basal ganglia and thalami and capsules, with new areas of diffusion restriction and enhancement compared with prior examination from 4 months post-transplantation.

relevant donor-recipient exposures, considering the seasonal and regional endemicity of arboviruses.

Notes

Acknowledgments. The authors thank Linda White, BS (Versiti Blood Center of Illinois); Caitlin Bonato, RN, BSN, Arlene Obias, and Laura O'Shaughnessy, MLS (American Society for Clinical Pathology certification)[CM] (Northwestern Medicine); Lisa Hinsdale, MBA (Gift of Hope Organ and Tissue Donor Network); Jennifer Crew, MD, and Fran Balster (Illinois Department of Public Health); Jennifer L. White, MPH (New York State Department of Health); Alexander T. Ciota, PhD, and Alan P. Dupuis II (Arbovirus Laboratory, Wadsworth Center, New York State Department of Health); Julie Coughlin (Iowa Department of Public Health); Anat R. Tambur, DMD, PhD, D[American Board of Histocompatibility and Immunogenetics] (Transplant Immunology Laboratory, Comprehensive Transplant Center, Northwestern University Feinberg School of Medicine); Susan Stramer, PhD (American Red Cross); Dulce Maria Ocampo (Loyola Medical Center); Kent Becker, MT (University of Iowa Health Care); Gregory D. Lewis, MD, and Meaghan Doucette, NP (Massachusetts General Hospital); and Katherine Dokus, MPH, and Lindsay Ryan (University of Rochester Medical Center) for their critical contributions to this multistate investigation.

Disclaimer. The findings and conclusions presented here are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. M. G. I. reports research support from National Center for Advancing Translational Sciences (UL1TR001422). None of the investigative work was funded by an outside source. M. R. W. reports the following support for this work: National Institute of Neurological Disorders and Stroke (K08NS096117). S. H. reports the following support for this manuscript: coordinated donor and other recipient investigations including education and retesting.

Potential conflicts of interest. M. G. I. reports research support, paid to Northwestern University, from AiCuris, GSK (RSV Vaccine), Janssen, and Shire and Plumocide (antifungal); is a paid consultant for Adagio, ADMA Biologics, Takeda, AlloVir, Celltrion, Cidara, Genentech, Roche, Janssen, Shionogi, and Viracor Eurofins; is a paid member of data and safety monitoring boards for Adamis, AlloVir, CSL Behring, Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, Talaris, and Vitaeris; and reports royalties paid to the author from UpToDate. C. Y. C. and S. M. have a patent on algorithms related to SURPI+ software, Pathogen Detection using Next-Generation Sequencing (PCT/US2016/052912). M. R. W. reports an unrelated research grant from Roche/Genentech; speaking honoraria from Takeda, Novartis, Genentech, and WebMD; payment for expert testimony from the Department of Justice; 1 patent, Method for High Percentage Recovery of Rare Cells (US-2020-0025783-A1), and 1 pending patent, Autoantibodies as a Biomarker of Paraneoplastic Encephalitis Associated with Testicular Cancer; and stock or stock options from VeriPhi Health. G. R. reports a leadership or fiduciary role as the chair of the College of American Pathologists Transfusion, Apheresis, and Cellular Therapy Committee. H. M. B. reports consulting fees from Idera (Novocure research), Myovant (Corea Therapeutics), and CARIS; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Guardant360; and support for attending meetings and/or travel from CARIS. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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