Case Report

Encephalitis with coinfection by Jamestown canyon virus (JCV) and varicella zoster virus (VZV)

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ABSTRACT

We present the case of a 59-year-old Midwestern farmer who presented with altered mental status, dysarthria, urinary incontinence, and a right-sided L5 dermatomal rash; he had recently received a course of oral corticosteroids for treatment of radicular low back pain. Lumbar puncture revealed the presence of varicella zoster virus (VZV) and IgM antibodies against a California-group encephalitis virus, later confirmed as Jamestown Canyon virus (JCV). Unfortunately, the patient's health declined despite aggressive treatment, developing progressive subarachnoid hemorrhage. He died after withdrawal of supportive care following 3 weeks in the intensive care unit. To our knowledge, this is the first documented case of encephalitis associated with coinfection by VZV and JCV. While the relative contributions of these viral pathogens to the patient's illness are difficult to ascertain, the clinical features of this case are consistent with co-pathogenesis, possibly driven by antecedent corticosteroid use. This case highlights the emerging role of viral coinfections in the etiology of viral illnesses.

Introduction

Acute viral encephalitis is a potentially devastating infection of the brain associated with a variety of viral pathogens. Herpes Simplex Virus 1 (HSV-1) is the most common etiology, although other human herpesviruses including varicella-zoster virus (VZV) and arthropod-borne viruses are also occasional causes. VZV is a neurotropic virus that commonly infects unvaccinated children, manifesting as chickenpox after primary infection. Following infection, the virus is transported in a retrograde axonal fashion to neuronal cell bodies where it enters a latent phase. Reactivation from viral latency, often in the setting of advancing age, immunosuppressing treatments, and/or psychological stress, results in a painful dermatomal rash, known as zoster [1];

however, viral reactivation from latency can cause a variety of less common clinical syndromes, including encephalitis and CNS vasculopathy [1]. Mortality from VZV encephalitis is 9–20 %, occurring almost exclusively in elderly or immunocompromised individuals [2].

Arthropod-borne viruses (arboviruses) represent a second important category of encephalitis pathogens. The most common of these infections in the United States is West Nile Virus, although considerable annual variation occurs [3]. The California encephalitis virus group of bunyaviruses represents the second most common etiology of arboviral encephalitis and includes several related viruses such as La Crosse (LACV), California, and Jamestown Canyon (JCV) viruses. JCV is uncommonly diagnosed, but is most frequently seen in the upper Midwest; there have been 181 cases reported to date in the United States [4]. Infected individuals complain of nonspecific constitutional symptoms that can progress to neuroinvasive features such as meningismus, altered mental status, and/or coma in two-thirds of cases [5]. Death has only been reported in only 3 patients so far in the USA [4].

We report a unique case of acute encephalitis associated with VZV and JCV coinfection. Viral coinfections represent an emerging area of interest in clinical infectious disease and are increasingly being identified due to sensitive diagnostic techniques [1,2]. Coinfections have the potential to result in atypical manifestations of infection, potentially including worsened morbidity and/or

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Abbreviations: CNS, Central Nervous System; CSF, Cerebrospinal Fluid; CT, Computed Tomography; DHZ, Disseminated Herpes Zoster; EEEV, Eastern Equine Encephalitis Virus; HSV-1, Herpes simplex virus 1; HZAE, Herpes Zoster-Associated Encephalitis; ICU, Intensive Care Unit; JCV, Jamestown Canyon Virus; LACV, La Crosse Virus; MRI, Magnetic Resonance Imaging; SVT, Supraventricular Tachycardia; VZV, Varicella Zoster Virus.

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mortality, and represent an opportunity for greater understanding of the pathogenesis of viral disease.

Case description

A 59-year-old Caucasian male famer, who resided in rural southwest Michigan presented to the emergency department with confusion, incoherent speech, and a fall at home. Aside from intermittent episodes of low back pain, he had previously been healthy, although he did not have a primary care physician due to a lack of health insurance. Approximately 6 weeks prior to presentation, he noted the onset of low back pain. The pain was severe, located on the lower lumbar spine, and associated with numbness and tingling of the right leg radiating to the ankle. The patient had regular chiropractic treatments for 4 weeks without improvement, and as a result, the patient was referred to a primary care physician. A 10-day course of prednisone was prescribed, ending 7 days prior to presentation, and only provided transient improvement. A few days after initiating the corticosteroid course, the patient's wife noted the onset of painful fluid-filled blisters on his right lower extremity that were most pronounced over the right anterior ankle and along the webbed spaces between his second and third toes; these blisters subsequently became hemorrhagic and scabbed over by the time of presentation. Three days prior to presentation, the patient was noted to begin intermittently slurring his speech and having episodes of urinary incontinence. On the day of presentation, the patient attempted to use the bathroom but instead opened the door to the basement, consequently falling and prompting presentation to the emergency department (ED). No history of fevers, headache, or seizures were elicited from the patient or his family.

In the ED, physical exam revealed confusion (Glasgow Coma Scale score of 14 due to confused responses to questions), dysarthric speech, fresh abrasions to his bilateral knees, and scabbed-over cutaneous lesions along the L5 dermatome of the right lower extremity (Fig. 1). Social history was significant for long days spent working outdoors, including exposure to heavily wooded areas, frequent mosquito bites, a tick bite 3 months ago, exposure to dogs and goats, and no recent travel.

Initial laboratory studies revealed hyponatremia (128 mmol/L), hemoconcentration (hemoglobin 17.7 g/dL), and hypochloremia (94 mmol/L), and urinalysis was positive for nitrites, bacteria, and pyuria. A urine culture grew *Escherichia coli*. The patient was diagnosed with a urinary tract infection and treated with ceftriaxone, as well as intravenous (IV) hydrocortisone due to concern for adrenal insufficiency.

On hospital day 2, acute kidney injury was noted, with elevation of serum creatinine from 1.1 mg/dL on presentation to 1.8 mg/dL. Renal ultrasound revealed bilateral hydronephrosis, and a urinary catheter was placed; following this, some improvement in the patient's confusion was noted. However, the patient was unable to complete an MRI of his lumbar spine due to agitation. Incomplete images revealed L5-S1 disc protrusion with possible L5 nerve root compression. Neurosurgery was consulted and initiated dexamethasone while awaiting MRI of the spine with sedation. On hospital day 3, the patient's confusion and slurred speech worsened. MRI of the spine with IV contrast performed under general anesthesia again showed L4-L5 disc extrusion and L5 nerve root compression but was also remarkable for diffuse leptomeningeal enhancement and CSF signal abnormality concerning for elevated protein concentration. MRI of the brain demonstrated abnormal signal of the bilateral medial frontal cortices, left insula, medial temporal lobe, amygdala, and hippocampus, and also found abnormal enhancement of lepto- and pachymeninges (Fig. 2). Due to these findings he was transferred to the ICU.

Fig. 1. Right Lower 1 Extremity Dermatomal Rash.

Fig. 2. MRI Brain.

Empiric treatment for CNS infection was initiated with ceftriaxone, vancomycin, ampicillin, and IV acyclovir. A lumbar puncture was performed, which revealed markedly elevated protein concentration, a mononuclear pleocytosis, xanthochromia, and normal glucose. A multiplex meningitis/encephalitis PCR panel (BioFire FilmArray, BioMérieux) revealed the presence of VZV DNA (Table 1). Given the patient's outdoor exposures, peripheral serology for arboviruses was also performed, and

Table 1
CSF Analysis.

Glucose	93 mg/dL
Protein	>2000 mg/dL
Color	Red-Orange
Description	Cloudy
Xanthochromia	3+
RBC	43,800 cells/μL (tube 1)
	24,500 cells/μL (tube 4)
WBC	5300 cells/μL (tube 1)
	1360 cells/μL (tube 4)
Differential	5% polymorphonuclear
	95 % mononuclear
	(tubes 1 & 4)
Multiplex CSF pathogen PCR[a]	VZV+
California Encephalitis Virus IgM	Positive
Jamestown Canyon Virus PRNT	1:512
LACV IgM	Negative

[a] Negative for: *Cryptococcus neoformans/gattii*, cytomegalovirus, enterovirus, *Escherichia coli* K1, *Haemophilus influenzae*, Herpes Simplex Virus 1, Herpes Simplex Virus 2, Human Herpesvirus 6, Human Parechovirus, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*.

found to be positive for California encephalitis IgG, at a titer of 1:256; IgM for California encephalitis was negative, as was testing for West Nile Virus, St Louis Encephalitis Virus, and both Western and Eastern Encephalitis viruses (EEEV). These peripheral serologies became available on hospital day 16, and prompted further testing of CSF at the CDC Division of Vector-borne Diseases (Ft. Collins, CO). These results, received approximately 5 months following the lumbar puncture, revealed capture ELISA positivity for Jamestown Canyon Virus CSF IgM, which was confirmed by plaque reduction neutralization test at a neutralizing antibody titer of 1:512. CSF testing for presence of EEEV and LACV IgM was negative by microsphere immunofluorescence assay and ELISA, respectively.

Antibacterial therapy was stopped 6 days after initiation, and treatment with IV acyclovir for 3 weeks was recommended following the discovery of VZV DNA in the CSF. Repeated attempts to wean ventilator support were unsuccessful, and the patient remained unresponsive after sedation was weaned. At no point during the patient's hospitalization did he develop a fever, and an electroencephalogram demonstrated only diffuse, generalized slowing, without epileptiform discharges. On hospital day 20, dilated, minimally reactive pupils were noted on exam. A computed tomography (CT) of the head with and without IV contrast demonstrated ongoing diffuse leptomeningeal enhancement, as well as layering of blood products in the occipital horns of the lateral ventricles with moderate ventriculomegaly. After a palliative care consultation, comfort care measures were initiated, and the patient died the following day.

Discussion

We present a case of viral encephalitis associated with co-infection by VZV and JCV in a Midwestern farmer with a history of extensive outdoor exposure and recent corticosteroid treatment. The diagnosis of viral encephalitis in this case was delayed by the presence of alternative potential explanations for the patient's encephalopathy, namely urinary retention and urinary tract infection, and by the absence of fever and headache. Unfortunately, despite treatment with acyclovir, the patient's condition relentlessly declined, and he ultimately succumbed to this infection.

Encephalitis is one of several possible manifestations of VZV reactivation, which most commonly manifests as a dermatomal rash known as herpes zoster. Encephalitis in the setting of active or recent herpes zoster has been termed herpes zoster-associated encephalitis (HZAE) and may also accompany disseminated herpes zoster (DHZ). Use of corticosteroids may precipitate VZV reactivation [9–11], raising the possibility that the use of corticosteroids in this case may have contributed to progression from dermatomal zoster to invasive CNS disease. HZAE is a rare complication of zoster with an incidence of 1–2 per 10,000 zoster episodes and presents with delirium within days of the appearance of the rash [6,7]. However, as seen in our patient, the appearance of a skin rash has occasionally been noted to precede the onset of HZAE by several weeks [8]. While DHZ following steroid therapy may be refractory to antiviral treatment [9], HZAE is not typically fatal, particularly in the non-elderly and immunocompetent, even before the advent of acyclovir; mortality of HZAE is approximately 10 % [7,8].

VZV vasculopathy is another CNS manifestation of VZV reactivation that may be relevant in explaining the features of this case. VZV vasculopathy occurs as a result of the ability of VZV to replicate within the arterial wall, potentially causing ischemic or hemorrhagic sequelae. Such patients can present with fever, headache, seizure, incoherent speech, aphasia, or facial paralysis, which can appear clinically similar to a stroke [7]. Although the entity is not well-studied, multiple cases of intracerebral hemorrhage, aneurysm formation, and cerebral infarctions in the setting of varicella zoster vasculopathy have been reported [10,11]. This patient's initial CSF was notable for marked xanthochromia, and he subsequently developed further subarachnoid hemorrhage (SAH) later in his ICU course; however, no discrete foci of intraparenchymal or subarachnoid hemorrhage were identified on neuroimaging in this case. Nonetheless, VZV vasculopathy may have contributed to the xanthochromia and markedly elevated protein noted in this patient's CSF and to subsequent progressive SAH.

In contrast to VZV, JCV is an orthobunyavirus of the California serogroup, a group that includes the more common LACV and causes 70–100 cases of encephalitis per year. First isolated in 1961 from Culiseta mosquitoes in Jamestown, Colorado, the incidence of this virus has been historically low, likely due to the lack of commercially available tests and rarity of severe disease: increased surveillance in an endemic region yielded a 4.5-fold increases in cases [12]. JCV has been isolated in at least 26 species of mosquitoes with various ecological breeding patterns, raising the concern for a diverse, broad transmission pattern [12]. White-tailed deer are thought to serve as an amplifier host, but large mammals like sheep, cattle, and horses are also susceptible to infection [13]. A sample of Michigan residents in 1986 showed that 27.7 % of the population had JCV neutralizing antibodies with a geographical distribution that correlated with the density of the white-tailed deer population in the state [13].

JCV infection in humans was historically understood to cause a mild viral syndrome in Midwestern forest workers [14]. Symptoms generally develop between 2 days and 2 weeks after being bitten by an infected mosquito, and include fever, headache, nausea, and vomiting, with some patients also developing respiratory symptoms such as sore throat, runny nose, and cough. However, likely due to a lack of testing outside of critically ill patients, the rate of CNS disease is quite high, with reports of meningitis or meningoencephalitis as high as 54–79 % of those infected [5]. Despite the high incidence of neurological sequela, mortality is surprisingly rare, with only 3 total deaths reported in the US [4].

Diagnosis is initially serologic, from peripheral blood and/or CSF specimens. However, confirmation of positive serology via PRNT or PCR testing is only currently available in a reference lab setting [12]. As there is currently no specific pharmacotherapy for JCV, treatment is supportive. While vaccine development has shown promise in animal models, none are currently available for human clinical use [15].

Two plausible etiologies of this patient's CNS infection were identified but determining the degree to which VZV and JCV contributed to his illness is difficult. Certainly, the dermatomal rash, xanthochromia, CSF PCR positivity, and subsequent subarachnoid hemorrhage point to a prominent role for VZV in the pathogenesis of this patient's illness. However, HZAE is not typically fatal, particularly in previously healthy individuals treated with acyclovir, and therefore, a role for JCV in explaining the severity of illness in this case should be entertained. This is particularly so given the presence of IgM with JCV plaque-neutralizing activity confirmed in CSF, which is diagnostic of invasive CNS infection. Intriguingly, 2019 also saw a remarkable increase in the incidence of human EEEV infections in Southwest Michigan. While Aedes and Ochlerotatus mosquitoes are thought to be the primary vectors of human infection by JCV, Culiseta also may act as a vector for both pathogens, suggesting a potential ecological link between the two viruses [12]. From a diagnostic standpoint, this case highlights the importance of maintaining a broad differential even when initial diagnostic data are suggestive of a particular diagnosis, and highlights coinfections as a possible explanation for more severe disease outcomes. As our patient was previously healthy and had no known immunocompromising conditions aside from a recent course of a glucocorticoid, this case also suggests clinical caution in steroid prescribing, and could provide an impetus for larger-scale studies of adverse outcomes after steroid courses.

Informed consent

Written informed consent was obtained from the patient's legally acceptable representative for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Consent was obtained by the patient's wife for the publication of this case report and images associated with the patient.

Author contribution

NV: Conceptualization and acquisition of data, analysis, and interpretation of the draft; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted.

NN: Conceptualization and acquisition of data, analysis, and interpretation of the draft; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted.

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CRediT authorship contribution statement

Nathan VanderVeen: Conceptualization, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Nikki Nguyen:** Writing - review & editing. **Kenny Hoang:** Writing - review & editing. **Jason Parviz:** Writing - review & editing. **Tahuriah Khan:** Writing - review & editing. **Andrew Zhen:** Writing - review & editing. **Brett W. Jaggera:** Conceptualization, Investigation, Validation, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

These authors deny any conflicts of interest.

Acknowledgements

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