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Case Report

Is Cauda Equina Involvement Related to BK Virus in Patients with Combined Immunodeficiency?

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Abstract

The BK virus, an unenveloped double-stranded DNA virus, infects up to 90% of the population, The virus often remains dormant but can reactivate and cause illness under conditions of impaired cellular immunity. It can cause progressive multifocal leukoencephalopathy and has been implicated in a variety of conditions, including encephalitis, nephritis, cystitis, and retinitis. This report explores neurological symptoms linked to the BK virus, focusing on its potential role in spinal cord pathology in patients with combined immunodeficiency by presenting and analyzing two distinct case studies. Although not commonly associated with neurological disorders, there are rarely reports of BK virus involvement in central nervous system diseases.

Keywords
- BK virus
- combined immunodeficiency
- spinal cord

Introduction

The BK virus, an unenveloped double-stranded DNA virus with icosahedral capsids, also known as *Polyomavirus hominis* 1, infects as many as 90% of the population. Nevertheless, notable clinical symptoms are infrequent and only detected in people with compromised immune systems.[1] The BK virus, responsible for causing progressive multifocal leukoencephalopathy (PML) as a central nervous system (CNS) demyelinating disorder, was initially discovered in 1971 from a urine collection of a patient who had received a kidney transplant.[2] It causes several conditions, including encephalitis (regardless of whether the patient is immunosuppressed or immunocompetent), nephritis, ureteric stenosis, hemorrhagic and nonhemorrhagic cystitis, retinitis, upper respiratory tract infection, pneumonitis, vasculopathy, hepatitis, delirium, and multiorgan failure.[1,3] Furthermore, it is associated with autoimmune disorders and may be malignancies.[1] Several potential pathways for BK virus transmission, including the respiratory system (the most probable mode), transplacental passage, urine and blood, sexual transmission, dissemination through oral ingestion of infected substances, and the transplantation of organs, specifically kidney grafts, have been proposed.[1,3]

After the first infection, the BK virus persists in the urinary system and kidneys as the predominant locations, followed by the brain being the second most commonly documented site of latent infection. In addition to the kidney and brain, the eye, lung, and liver have been suggested as potential locations for

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BK virus–related diseases, including both initial infections and reactivations.[3] Under circumstances of either partial or complete impairment of cellular immune function, the virus has the potential to reactivate and induce illness, as seen in HIV-infected individuals and transplant patients.[3] It is commonly not linked to neurological disorders; nevertheless, there have been reports of BK contribution in people with CNS disease. Herein, we seek to analyze the neurological symptoms associated with the BK virus and focus on the potential BK virus involvement in the spinal cord in patients with combined immunodeficiency by presenting two unique cases.

Case Reports

Case 1

An 8-year-old male patient with a history of eosinophilic esophagitis, warts, and ganglioneuroma was admitted with weakness of bilateral lower extremities while being monitored for nephropathy. He had a sibling who died due to a homozygous DOCK8 defect. The patient, before the transplantation plan due to the DOCK8 defect, was found to have high levels of BK virus shedding in his urine (more than 1 million copies/mL) and 245,200 copies/mL in his blood. Also, cytomegalovirus (CMV) antigen was found positive (1,105 copies/mL), and varicella zoster virus (VZV) and herpes simplex virus (HSV) antigens were found negative. Craniospinal magnetic resonance imaging (MRI) revealed brain atrophy, contrast enhancement of the cauda equina and pial spinal cord surface, and subtle T2 hyperintensity in the conus medullaris (►**Fig. 1**). Following intravenous immunoglobulin and leflunomide treatments, BK viremia and BK virus shedding in the urine decreased, and limb weakness improved.

Case 2

A 9-year-old male patient with parental consanguinity presented with recurrent oral ulcers, lymphadenopathy, and

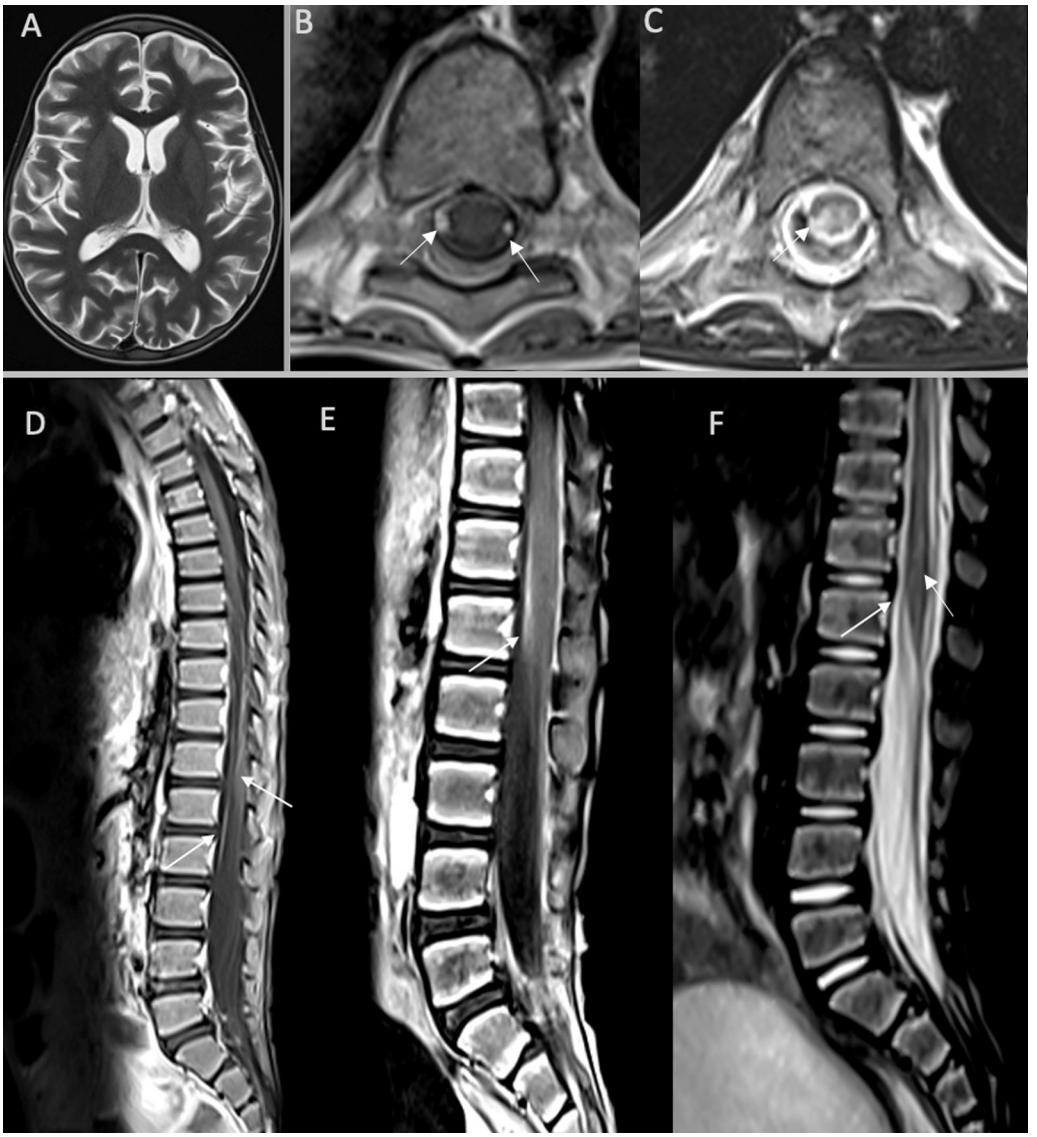

Fig. 1 Brain and spinal magnetic resonance imaging of case 1. Axial T2-weighted (T2W) brain image shows cerebral atrophy (**A**). Postcontrast axial (**B**) and sagittal (**D, E**) T1W images pial and cauda equina contrast enhancement (arrows). Axial (**C**) and sagittal (**F**) T2W spinal images show hyperintense cord lesion consistent with myelitis (arrows).

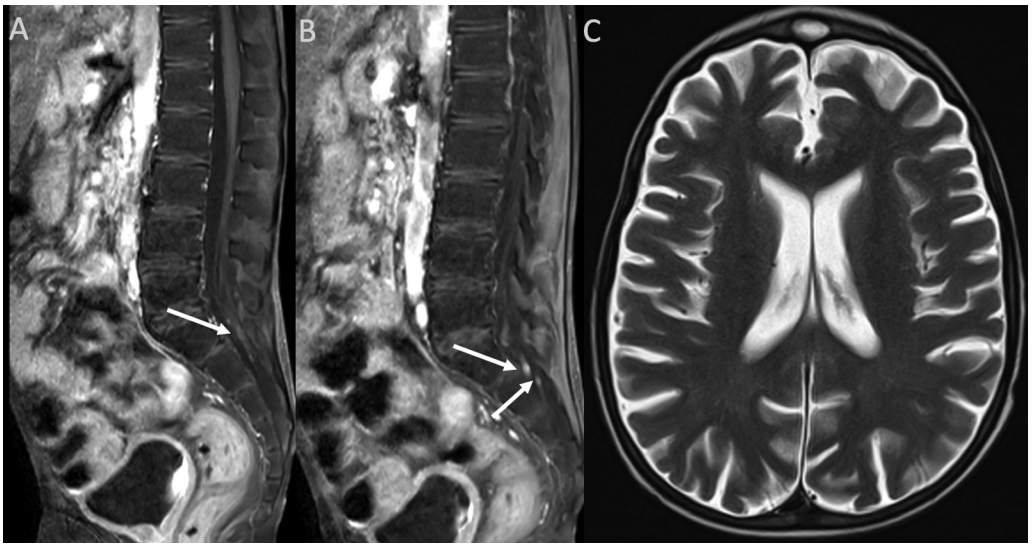

Fig. 2 Brain and spinal magnetic resonance imaging of case 2. After contrast, sagittal T1W images (**A, B**) show contrast enhancement in the sacral nerve roots (arrows). Axial T2W image (**C**) shows cerebral atrophy.

hepatosplenomegaly. Genetic testing revealed a homozygous RAG1 defect, and the patient underwent hematopoieticstem cell transplantation from a human leukocyte antigen (HLA)–matched sibling. While being monitored for chronic graft-versus-host disease (GVHD), the patient developed progressive weakness in the lower extremities. Laboratory tests revealed negative results for VZV and HSV and a positive result for the COVID-19 antigen test. BK virus antigen was positive in the urine (more than 1 million copies/mL) and blood (702,500 copies/mL). Craniospinal MRI showed brain atrophy and contrast enhancement involving several cauda equina nerve roots at the S1-2 level (►**Fig. 2**). The patient is currently receiving dialysis treatment for BK nephropathy.

Discussion

So far, CNS involvement due to BK virus in immunocompetent patients has primarily been reported as encephalitis. Lopes da Silva's study (2011)[4] included all documented cases of CNS involvement due to BK virus. We expanded upon this by incorporating additional reported cases, creating an updated literature review of CNS involvement caused by BK virus (►**Table 1**). According to our literature review, spinal cord involvement by BK virus has not been documented in the literature, highlighting the significance of the two cases we present.

PML, a fatal CNS condition in immunosuppressed patients, affects the cerebral hemispheres, cerebellum, brain stem, and spinal cord. JC viremia, rarely BK viremia, is detectable in such cases, likely spreading to the CNS hematogenously. The spinal cord's apparent sparing in most PML cases may stem from underrecognition of spinal lesions or the virus's preference for the brain. Alternatively, the immune system may more effectively clear the virus in the spinal cord. Notably, a case of JC virus–associated PML lesions in the spinal cord was reported in an AIDS patient.[5] A 64-year-old Japanese man with lymphocytopenia was diagnosed with PML, showing demyelinating lesions in the spinal cord, cerebral white matter, cerebellum, and brain stem, presenting a unique PML distribution. All segments had demyelinating lesions of varying intensity, with JC virus protein detected via immunostaining.[6] The PML lesions primarily occur in the cerebral white matter; nonetheless, they can also be observed to a lesser extent in the brain stem, the cerebellum, and, less frequently, the spinal cord, as in the previous case. A 21-year-old man with common variable immunodeficiency and PML was described following JC virus infection, causing dysplastic ganglion-like changes in the infected neurons. During the autopsy, there was significant demyelination and necrosis found in the white matter of the cerebrum, cerebellum, brain stem, and spinal cord.[7] Hence, medical practitioners need to consider that, apart from the brain, PML can also impact the white matter of the medulla spinalis. Therefore, they must take into account this condition while evaluating individuals who are susceptible to PML as part of the differential diagnosis.

In the first recorded instance of PML in a patient with common variable immunodeficiency, a 38-year-old man was found to have both JCV and CMV infections simultaneously.[8] A further case of meningoencephalitis attributed to a BK virus infection in a 26-year-old male AIDS patient[9] had concurrent viremia with CMV. Hence, it is plausible to predict that the BK virus may have relevant interactions with CMV in the CNS, lungs, and kidneys.[1,9] Case 1 had a concurrent CMV infection along with the BK virus, and we observed that as the BK virus load decreased, there was an improvement in strength loss. Also, the BK virus load was higher than the CMV virus load when the extremity weakness occurred (►**Fig. 3A**).

Similarly, case 2 had COVID-19 infection simultaneously with BK virus (►**Fig. 3B**). COVID-19-associated myelitis was reported in the medical literature, and nearly all patients had classic symptoms of COVID-19, such as fever and headache, before developing neurological deficits. Our patient, however, did not exhibit any symptoms related to COVID-19 infection.[10]

Both patients had more prominent contrast enhancement of the cauda equina rather than the cord involvement. CMV

Table 1 Summary of the patients with CNS involvement by BKV

References	Age	Gender	Background	Neuroradiology	Laboratory	Neurological symptoms
O'Kelly et al (2021)[12]	48	M	HIV infection	CT—hypodensity in the left temporoparietal region MRI—a hypointense lesion on T1, hyperintense on T2	CSF: JCV −, BKV+ Serum: BKV−	Progressive right arm weakness, right leg weakness, dysarthria
Ayvacıoglu et al (2019)[13]	29	F	Postpartum 2 wk	MRI—T2/FLAIR positive lesion with some Gad enhancement	CSF: BKV +, JCV−	Left hemiparesis, hyperreflexia, progressing to loss of consciousness
Melis et al (2018)[14]	60	F	SLE	MRI—T2 hyperintensity in the left frontal lobe with extension on the right frontal and parietal lobes with periventricular extension and on the corpus callosum genu	CSF: BKV +, JCV− Urine: BKV− Brain: BKV+	Confusion, personality change, weakness of lower limbs bilaterally
Darbinyan et al (2016)[15]	29	M	NEMO deficiency and ectodermal dysplasia	MRI—multiple scattered foci of increased T2 FLAIR signal, restricted diffusion, and contrast enhancement, predominantly within the right occipital lobe, small foci of increased T2 FLAIR signal within the left frontal lobe, left thalamus, left pons	CSF: BKV +, JCV− Brain: BKV +, JCV−	Left homonymous hemianopsia and headache, without significant motor, sensory, or cognitive impairment
Daveson et al (2013)[16]	71	F	B-cell NHL, Sjogren's, hypogammaglobulinemia	MRI—two areas of abnormality in the posterior left frontal lobe in the subcortical and the periventricular regions	CSF: BKV+ JCV− Urine: BKV+ Brain: BKV+ JCV−	Ataxia, 2 wk of right-sided neglect
Lopes da Silva (2011)[17]	48	F	Bone marrow transplantation	MRI: predominant involvement of the pons and around the third ventricle	CSF: BKV+ Urine: BKV+ Brain: BKV+	Dysarthria, altered mental status, headache
Kinnaird et al (2010)[18]	48	M	HIV infection	MRI—multifocal and infratentorial foci of abnormally high T2 and FLAIR signal	Urine: BKV+	Ataxia, cognitive deficit, dysarthria
Behre et al (2008)[19]	NA	NA	Bone marrow transplantation	MRI—T2-weighted imaging showed an encephalopathy with edema parieto-occipital in the cerebral white matter and less pronounced in the cerebellum	CSF: BKV+	Seizure
Ferrari et al (2008)[20]	NA	NA	Lymphoma	NA	CSF: BKV+	Confusion
Vidal et al (2007)[21]	43	M	HIV infection	MRI—increased signal intensity of the periventricular white matter	CSF: BKV+	Headache, speech, gait, and memory disturbances
Friedman et al (2006)[22]	38	M	Bone marrow transplantation	MRI—widespread increased signal intensity on T2	Brain biopsy: BKV+	Progressive mental status changes, lethargy, psychomotor slowing, dysarthria
Cabrejo et al (2005)[23]	70	M	Long-term steroid therapy and sarcoidosis	MRI—right parieto-occipital (T1 hypo, T2/Gad enhancement hyperintense)	CSF: BKV +, JCV− Urine: BKV +	Progressive left-sided neurologic defects, homonymous hemianopia
Hix et al (2004)[24]	54	M	Renal transplantation	MRI—bilateral frontal encephalomalacia and gliosis	CSF: BKV +, JCV− Urine: BK+	Oligoanuric renal failure, aggressive, lethargy, confusion

Table 1 (*Continued*)

References	Age	Gender	Background	Neuroradiology	Laboratory	Neurological symptoms
Jørgensen et al (2003)[25]	35	M	HIV infection	NA	CSF: BKV+ Brain biopsy: BKV+	Mental status changes; visual impairment
Behzad-Behbahani et al (2003)[26]	5	F	Bone marrow transplantation	NA	CSF: BKV +	None
	3	M	Bone marrow transplantation	NA	CSF: BKV +	Irritability
	5	F	Immunocompetent	NA	CSF: BKV +	Lethargic, irritability,
	16	M	Immunocompetent	NA	CSF: BKV +	Confusion
	13	F	Immunocompetent	NA	CSF: BKV +	Headache, diplopia
	24	F	Immunocompetent	MRI—diffuse white matter lesions, chiefly in the parietal region	CSF: BKV+ Serum: anti-BKV+	Seizures
	30	F	Immunocompetent	NA	CSF: BKV+	Headache, lethargy
	32	M	Immunocompetent	NA	CSF: BKV+	Mental status change
	29	M	Immunocompetent	NA	CSF: BKV+	Fever, headache
	26	F	Immunocompetent	NA	CSF: BKV+	Headache, left hemiparesis, drowsiness
Stoner et al (2002)[27]	40	M	Leukemia	NA	CSF: BKV+ Urine: BKV +	Headache, altered mental status
Garavelli et al (2002)[28]	37	M	HIV infection	NA	CSF: BKV +	Altered mental status
Lesprit et al (2001)[29]	44	M	HIV infection, NHL	MRI—diffuse areas of increased signal intensity of the periventricular white matter	CSF: BKV+	Paraplegia
Bratt et al (1999)[30]	26	M	HIV infection	MRI—increased meningeal contrast enhancement and increased meningeal thickness	CSF: BKV+	Progressive hearing loss, visual impairment
Voltz et al (1996)[31]	34	M	Recurrent herpes labialis	MRI—diffuse white matter involvement on T2-weighted images	CSF: BKV+	Headache, fever, generalized and complex partial seizures, hallucinations, delusions
Vallbracht et al (1993)[32]	27	M	Hemophilia type A and HIV infection	CT—internal hydrocephalus with periventricular lucencies	Brain: BKV+	Headache, frequent tenesmus, vomiting, disturbances of coordinative, mnemic functions

Abbreviations: BKV, BK virus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; Gad, gadolinium; JCV, JC virus; MRI, magnetic resonance imaging; NA, not available; NEMO, nuclear factor-kappa B essential modulator; NHL, non-Hodgkin lymphoma; SLE, systemic lupus erythematosus.

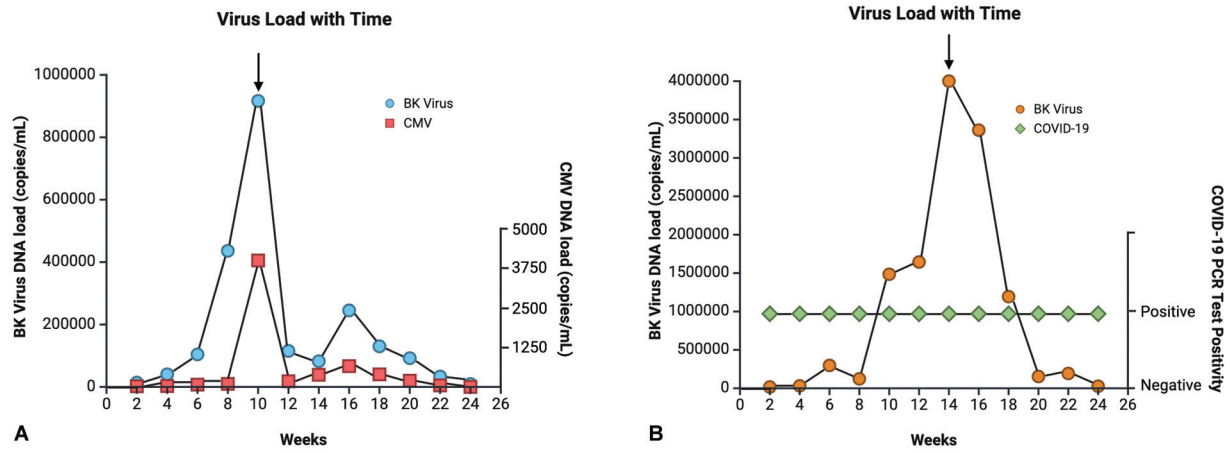

Fig. 3 The graphs show the BK virus and CMV virus loads over time, along with COVID-19 positivity for case 1 (**A**) and case 2 (**B**). The arrows indicate the onset times of neurological deficits.

has been shown to cause contrast enhancement in cauda equina nerve roots with other pathogens.[11] COVID-19 can cause myelitis secondary to infections and may also cause contrast enhancement in cauda equina nerve roots.[33] In the literature, only one case with the BK virus–induced polyneuropathy was reported in a renal transplant recipient, but there is no information regarding a contrast enhancement of the cauda equina in the spinal cord MRI.[34]

These cases offer substantial evidence of a robust correlation, but not definitive verification of a cause-and-effect link, between these disease processes and the BK virus, although the neurologic symptoms improved after treatment targeting the BK virus. There might be an association among the BK virus, SARS-CoV-2, and CMV infections rather than a direct BK virus cause. Our findings indicate that the human polyomavirus BK is likely accountable for a severe opportunistic infection involving the medulla spinalis associated with primary immunodeficiencies not previously documented.

Conclusion

Based on current understanding, there is a link between the infection of the BK virus and JC virus and the involvement of the spinal cord. However, as far as we know, this is the first report demonstrating the presence of neurological deficits with BK viremia and spinal cord involvement that may be related to the BK virus. Subsequently, understanding the neurological signs attributed to the BK virus is of top priority, as in PML and possibly infrequent instances of spinal cord involvement, since individuals with compromised immune systems are vulnerable to BK disease affecting several organs. Additional inquiries, however, are necessary to elucidate the importance and mechanism of the BK virus infections affecting the spinal cord in individuals with inborn errors of immunity.

Patient Consent

Informed consent was obtained from the families for publication of this report.

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Conflict of Interest

None declared.

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