A Rare Cause of Encephalopathy Post Renal Transplant: BK Polyoma Virus Encephalitis

Abstract

BK polyoma virus (BKV) belongs to Polyomaviridae family. It is a double-stranded DNA virus. Only a few cases of BKV–associated neurological disease in renal transplant recipients have been reported. BKV related central nervous system (CNS) infection may often remain unrecognized in immunocompromised patients. Here, we are reporting a case of BKV encephalitis post renal transplantation for the awareness of all physicians regarding this entity.

Keywords: *BK polyoma virus, encephalitis, Post transplant*

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Introduction

BK polyoma virus (BKV) is a double-stranded DNA virus belonging to Polyomaviridae family. BKV related disease is encountered in immunosuppressed individuals such as those with acquired immunodeficiency syndrome (AIDS) and those who undergo renal or bone marrow transplantation. BKV can also infect the central nervous system (CNS).[1] BKV-related CNS infection may often be overlooked and underdiagnosed in immunocompromised patients. Only a few cases of BKV-associated neurological disease in kidney transplant recipients have been reported so far.[2] We are reporting this case to spread awareness among all physicians, so as to intervene early in a patient with BKV encephalitis. Early intervention can reduce the mortality significantly.

Case Presentation

A 20-year-old boy with end-stage renal disease underwent living donor renal transplantation in our center. He was given antithymocyte globulin as induction. The maintenance immunosuppressive therapy was comprised of tacrolimus, mycophenolate mofetil (MMF), and steroids. His hospital stay after transplant was uneventful, and the graft function was normal (1.2 mg/dl) at the time of discharge. One year post transplantation, his graft function remained stable (creatinine 1.4 mg/dl). He was lost to follow-up for 7 months and he presented to us with worsening of graft function (S. creatinine 2.2 mg/dl). There was no proteinuria, tacrolimus trough level was 7 ng/dl, and graft Doppler showed good global perfusion. He was admitted for renal biopsy. A day after renal biopsy, he developed generalized tonic clonic seizures followed by altered sensorium. On evaluation, he was found to have acute hyponatremia (S. sodium 124 mEq). Hyponatremia workup was suggestive of syndrome of inappropriate hypersecretion of antidiuretic hormone (SIADH; urine sodium 31mmol/l, S. uric acid 3.5mg/dl, urine osmolarity >100 mOsm/kg). There was no improvement in sensorium despite correction of hyponatremia and he had to be mechanically ventilated. There were no demonstrable signs of meningeal irritation. Magnetic resonance imaging (MRI) brain with venogram was normal. Cerebrospinal fluid (CSF) analysis showed the following: no cells, protein 43 mg/dl, sugar 91 mg/dl. Electroencephalogram (EEG) was suggestive of encephalopathy. A CSF viral panel (polymerase chain reaction [PCR] was positive for BKV, with a viral load of 700 copies/ml. Plasma quantitative real-time BKV PCR showed a viral load of 4366 copies/ml. Even though quantitative PCR of blood samples not showing significant viremia, but CSF fluid PCR was showing evidence of BKV, and hence We started him on Intravenous immunoglobulin (2g/kg) and leflunomide.

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Antimetabolite (MMF) was withheld and the dose of calcineurin inhibitor was reduced to a target a level of 4-6 ng/dl. In the meantime, renal biopsy was reported as BKV nephropathy class 2 (pvl3 cl 1). SV40T antibody confirmed viral inclusions [Figure 1]. Gradually, the patient improved, and he was extubated and discharged in a stable condition. At 1 month follow-up, the patient remains asymptomatic with stable graft functions.

Discussion

BKV is widely distributed in the population.[2] Primary asymptomatic infection occurs during childhood via respiratory tract. Latent infection is then established in renal epithelial cells and possibly other tissues (including brain).[2] BKV nephropathy is a serious complication of kidney transplantation. BK viremia may present in 10%–30% of renal transplant recipients, but nephropathy is seen in approximately 2% of cases.[3] Nephropathy is most common early after renal transplantation when immunosuppression is at its peak.[4] Patients are often asymptomatic, and the diagnostic standard is biopsy.[4] Risk factors for BKV nephropathy include donor seropositivity, greater mismatching, extremes of age, Caucasian race, male sex, diabetes, lymphocyte-depleting induction, ureteral stents, and tacrolimus or mycophenolate-based regimens.[5]

The clinical presentation of BKV nephropathy varies from asymptomatic state of viremia, hematuria, interstitial nephritis to ureteral stenosis.[6] BKV nephropathy can simulate acute rejection.[3] The onset of disease occurs at an average period of 10-13 months post transplantation; however, the onset may occur early (6 days after transplantation) or may be delayed (5 years after transplantation).[7] CNS manifestations of BKV include headache, seizures, progressive mental deterioration, dysarthria, hallucinations, and visual disturbances.[8] In pediatric age, irritability and lethargy are the main manifestations.[8]

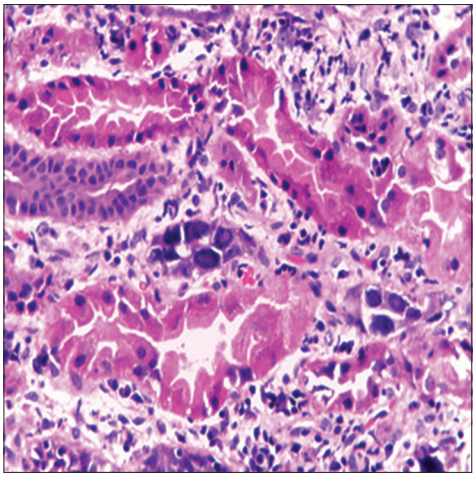

Figure 1: BKV inclusions. BKV: BK polyoma virus

Diagnosis of BKV encephalitis has usually been established by PCR of the CSF, complemented by BKV PCR of the brain biopsy specimen.[9] Since most of the reactivation occurs in AIDS and transplant recipients, it is reasonable to suspect meningoencephalitis in a patient who shows neurological symptoms, with a positive result for BKV PCR in CSF/brain tissue.[2]

It is difficult to define absolute levels of serum sodium above or below which seizures are likely to occur.[10] Usually, seizures occur in severe and rapidly evolving hyponatremia if serum sodium is <115 mEq/L.[11] Persistence of altered sensorium after correction of hyponatremia prompted further investigation. On evaluation, initial EEG showed gross slowing of background activity (2-3 Hz). After 4 days, a repeat EEG was done and showed improvement in background activity (6-7 Hz), but asymmetric slowing was noted over the right hemisphere with periodic lateralized epileptiform discharges (PLEDS). CSF BKV PCR was found to be positive (700 virions/ml). PLEDS in EEG can be associated with ischemic cerebral infarction, hemorrhagic cerebral infarction, CNS infection, traumatic brain injury, CNS vasculitis, tumor, cerebral venous thrombosis, and limbic encephalitis.[12] The sensitivity limit of BKV PCR–enzyme-linked immunosorbent assay (ELISA) was found to be six copies of the BKV genome.[13] Detection of BKV DNA in the CSF of the patients suspected to have either meningitis or encephalitis suggests BKV may have an etiological role. Two cases of BKV in CSF have been reported in renal transplant recipients from other parts of world [Table 1].[14,15] MRI brain may show limbic encephalitis or diffuse T2 hyperintensities with diffusion restriction in white matter.[16]

There is no standard recommendation of treatment for BKV encephalitis and BKV nephropathy. Early intervention can be lifesaving in BKV encephalitis, and a delay in diagnosis leads to high mortality rate.[17] Reduction in immunosuppression is the cornerstone of the treatment.[18] Some centers discontinue antimetabolites (MMF or azathioprine) completely, whereas others reduce the dose of antimetabolites.[18] Tacrolimus can inhibit anti-BK–specific T cells, which is essential for viral clearance, hence the dose of tacrolimus must be reduced by 25%-50%.[19] Several agents have been used in treatment, including intravenous immunoglobulin, leflunomide and ciprofloxacin. Intravenous immunoglobulins have high titers of neutralizing antibodies to BKV and can expedite virus clearance (0.25 - 2g/kg).[20] Leflunomide can be used following discontinuation of MMF (100mg daily for 3-5 days and then 20-60 mg once daily).[20] Treatment must be continued until viremia is cleared.

Conclusion

There are no specific symptoms or imaging findings for BKV encephalitis. A high index of suspicion is needed to make

Table 1: Comparison between our case and two other cases of BKV encephalitis

	Clinical manifestations	CSF analysis	MRI	Treatment and outcome
Our case	Seizure	Analysis: No cells Protein: 43mg/dl Sugar: 91mg/dl PCR: BKV +	Normal	Stopped MMF, reduced CNI Immunoglobulin (IV Ig) :2g/kg Leflunomide 100mg for 1 day followed by 20 mg daily Recovered
Hix *et al*.[15]	Confusion lethargy	Analysis Not reported PCR: BKV +	Bilateral frontal and temporal encephalomalacia and gliosis	Stopped MMF, prednisolone tapered down to 7.5 mg daily Leflunomide: 40mg daily Recovered
Rocha *et al*.[16]	Headache and fever (pediatric)	Analysis: Cells – WBC112 Protein: 66 mg/dl PCR: BKV+	Not reported	Stopped MMF, CNI dose reduced IVIg: 500mg/kg Cidofovir: 0.25mg/kg Recovered

BKV: BK virus, CNI: calcineurin inhibitor, CSF: cerebrospinal fluid, MMF: mycophenolate mofetil, MRI: magnetic resonance imaging, PCR: polymerase chain reaction, WBC: white blood cell

the diagnosis of BKV encephalitis in patients who present with neurological symptoms after transplantation. BKV nephropathy can lead to graft loss, but BKV encephalitis has excellent prognosis if intervened early in the course of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Replog MD, Storch GA, Clifford DB. BK virus: A clinical review. Clin Infect Dis 2001;33:191-202.
2. De Silva RL. Polyoma BK. Virus: An emerging opportunistic infectious agent in immunocompromised of the human central nervous system, Review article. Braz J Infect Dis 2011;15;276-84.
3. Vasudev B, Hariharan S, Hussain SA, Zhu YR, Bresnahan BA, Cohen EP. BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. Kidney Int 2005;68:1834-9.
4. Hirsch HH, Randhawa P. AST infectious diseases community of practice: BK polyomavirus in solid organ transplantation. Am J Transplant 2013;13(Suppl 4);179-88.
5. Hrisch HH, Babel N, Comoli P, Friman V, Gineveri F, Jardine A, *et al*. European Perspective of human polyoma virus infection, replication and disease in solid organ transplantation. Clin Microbiol Infect 2014;20 (Suppl 7):74-88.
6. Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, *et al*. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol 2002;13:2145-51.
7. Randhawa PS, Finkelstein S, Scantlebury V, Shapiro R, Vivas C, Jordan M, *et al*. Human polyoma virus-associated interstitial nephritis in the allograft kidney. Transplantation 1999;67:103-9.
8. Behzad –Behbahani A, Klapper PE, Valley PJ, Cleator GM, Bonington A. BKV DNA and JCV DNA in CSF of patients with suspected meningitis or encephalitis. Infection 2003;31:374-8.
9. Stoner GL, Alappan R, Jobes DV, Ryschkewitsch CF, Landry ML. BK virus regulatory region rearrangements in brain and cerebrospinal fluid from a leukemia patient with tubulointerstitial nephritis and meningoencephalitis. Am J Kidney Dis 2002;39:110212.
10. Castilla-Guerra L, del Carmen Fernández-Moreno M, López-Chozas JM, Fernández-Bolaños R. Electrolytes disturbances and seizures. Epilepsia 2006;47:1990-98.
11. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. J Clin Neurol 2016;12:21-33.
12. Garcia-Morales I, Garcia MT, Galan-Davila L, Gomez-Escalonilla C, Saiz-Diaz R, Martinez-Salio A, *et al*. Periodic lateralized epileptiform discharges: Etiology, clinical aspects, seizures, and evolution in 130 patients. J Clin Neurophysiol2002;19:172-77.
13. Behzad-Behbahani A, Klapper PE, Vallely PJ, Cleator GM. BK virus DNA in CSF of immunocompetent and immunocompromised patients. Arch Dis Child 2003;88:174-5.
14. Hix JK, Braun WE, Isada CM. Delirium in a renal transplant recipient associated with BK virus in the cerebrospinal fluid. Transplantation 2004;78:1407-8.
15. Rocha A, Faria S, Costa T, Marques L, Freitas C, Mota C. BK virus nephropathy complicated with meningoencephalitis after kidney transplantation. Pediatr Transplant 2014;18:E48-51.
16. Chittick P, Williamson JC, Ohl CA. BK virus encephalitis: Case

report, review of the literature, and description of a novel treatment modality. Ann Pharmacotherapy 2013;47:1229-33.
17. Horger M, Beck R, Fenchel M, Ernemann U, Nägele T, Brodoefel H, *et al*. Imaging findings in tick-borne encephalitis with differential diagnostic considerations. AJR Am J Roentgenol 2012;199:420-7.
18. Hirsch HH, Babel N, Comoli P, Friman V, Ginevri F, Jardine A, *et al*. European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. Clin Microbiol Infect 2014;20(Suppl 7):74-88.
19. Egli A, Köhli S, Dickenmann M, Hirsch HH. Inhibition of polyomavirus BK-specific T-Cell responses by immunosuppressive drugs. Transplantation 2009;88:1161-8.
20. Sharma R, Zachariah M. BK Virus nephropathy: Prevalence, impact and management strategies. Int J Nephrol Renovasc Dis 2020;13:187-92.