

# Hemorrhagic Cystitis and Possible Neurologic Disease from BK Virus Infection in a Patient with AIDS

A.N. Kinnaird, G.M. Anstead

## Abstract

BK virus (BKV)-associated hemorrhagic cystitis occurs in bone marrow transplant recipients but is rare among other immunosuppressed patients. We present a rare case of BKV-associated hemorrhagic cystitis in a 48-year-old man with AIDS and previously diagnosed progressive multifocal leukoencephalopathy.

Infection 2010; 38: 124–127  
DOI 10.1007/s15010-009-9201-5

## Background

BK virus (BKV) is a human polyomavirus that has been implicated as an etiology of hemorrhagic cystitis in bone marrow transplant (BMT) recipients and as a significant cause of tubulointerstitial nephritis, vasculopathy, and allograft dysfunction in renal transplant patients [1–5]. However, in HIV-infected patients, BKV clinical syndromes have been limited to case reports of tubulointerstitial nephritis, interstitial pneumonitis, interstitial desquamative pneumonitis, subacute meningitis, retinitis, and encephalitis [6–11]. As for BKV-associated hemorrhagic cystitis in HIV-infected patients, there are only two other reported cases: a 41-year-old man with cytomegalovirus (CMV) antigenemia who had been treated with cyclophosphamide for a large B cell lymphoma 9 days before the onset of hemorrhagic cystitis and a 29-year-old man with HIV [12, 13]. We present a rare case of BKV-associated hemorrhagic cystitis in a 48-year-old man with AIDS and previously diagnosed progressive multifocal leukoencephalopathy.

## Case History

A 48-year-old African-American man with AIDS (CDC Stage C3) was admitted for gross hematuria of one week's duration. The patient had a CD4 count of 68 cells/mm<sup>3</sup> (16%), with a viral load of <50 copies/mL on an antiretroviral regimen consisting of emtricitabine-tenofovir and lopinavir-ritonavir. He had been admitted several times for hematuria in the preceding 5 months. Repeat CD4 counts and HIV viral loads were not obtained during each admission. He had received an extensive evaluation for hematuria, including computed tomographic urogram,

percutaneous ureteronephroscopy, intravenous pyelogram, and nephrotomography. All of these tests were unrevealing for a structural cause of the hematuria.

The patient's past medical history included HIV infection and a clinical diagnosis of progressive multifocal leukoencephalopathy (PML; a demyelinating neurodegenerative disease due to infection by the JC virus [JCV]). He was diagnosed with HIV and concurrent PML 18 months prior to admission, with a CD4 nadir of 44 cells/mm<sup>3</sup> (12%) and a baseline viral load of 174,000 copies/mL. At the time of diagnosis, he was started on emtricitabine-tenofovir and lopinavir-ritonavir and his HIV viral load became undetectable within 8 months. At the time of his first undetectable HIV viral load, his CD4 count had risen to 59 cells/mm<sup>3</sup> (11%).

The patient's presumptive diagnosis of PML was based on ataxia and cognitive and speech deficits. At the time of presentation of the neurological deficits, magnetic resonance imaging (MRI) of the brain with gadolinium contrast was performed, which showed multifocal and infratentorial foci of abnormally high T2 and FLAIR signal, not typical for PML. Furthermore, a polymerase chain reaction (PCR) assay of the cerebrospinal fluid (CSF) was negative for the presence of the JCV. Nevertheless, a brain biopsy revealed positive immunohistochemical staining with antibodies against simian virus 40 (one of the polyomaviruses). Thus, the patient was diagnosed with PML on the basis of clinical presentation and immunohistochemical staining of the brain biopsy specimen, despite the negative PCR and inconsistent MRI findings.

During the current admission to the hospital, physical examination was unremarkable except for prior cognitive deficits and suprapubic tenderness. Laboratory data were unremarkable except for a mild normocytic anemia. A Foley catheter was

---

### A.N. Kinnaird

Dept. of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

### G.M. Anstead

Dept. of Medicine, Division of Infectious Diseases, South Texas Veterans Healthcare System, San Antonio, TX, USA

### G.M. Anstead

Dept. of Medicine, Division of Infectious Diseases, University of Texas Health Science Center at San Antonio, Office of Educational Programs, San Antonio, USA

### A.N. Kinnaird (corresponding author)

4903 Edgemoor Ln., Apt. 802, Bethesda, MD 20814, USA;  
Phone: (+1/706) 8362812,  
e-mail: akinnairdmd@gmail.com

Received: June 10, 2009 · Revision accepted: September 21, 2009

Published online: March 2, 2010

placed with passage of gross blood. Computed tomography (CT) of the pelvis demonstrated concentric bladder wall thickening and slight mucosal enhancement consistent with hemorrhagic cystitis (Figure 1) [14]. Cytological examination of the urine revealed transitional cells with enlarged, deeply staining basophilic nuclei that were suggestive of ‘decoy cells.’ Cultures of urine specimens were negative for bacteria, CMV, and adenovirus. PCR assays of urine samples yielded results positive for BKV and negative for JCV. The patient was started on continuous bladder irrigation and his urine cleared after 3 days. The patient was discharged and, at follow-up, has remained asymptomatic for 18 months.

### Discussion

Sites of BKV-associated disease, both primary and reactivated, in the non-HIV-infected population include the kidney, lung, liver, eye, and brain. In HIV-infected patients, BKV clinical syndromes have been associated with infections in the same organs and are limited to case reports of tubulointerstitial nephritis, interstitial pneumonitis, interstitial desquamative pneumonitis, subacute meningitis, retinitis, encephalitis, and the other reported cases of hemorrhagic cystitis (Table 1) [6–13, 15, 16]. A detailed discussion of these cases has been presented elsewhere [16].

The significance of BKV detection in the cerebral tissue of HIV-infected patients is uncertain. Two different studies have detected BKV by PCR in the cerebral tissue of 3–6% of HIV-infected patients both with and without neurological symptoms [17, 18]. In another study, CSF samples from 400 immunocompromised patients with neurological symptoms were negative for BKV by PCR [10]. When it is associated with clinical disease, the virus seems to have a predilection for the ventricular and pial surfaces of the brain parenchyma [9–11]. Although BKV infections of the central nervous system are seemingly rare in HIV-infected patients, there seems to be sufficient

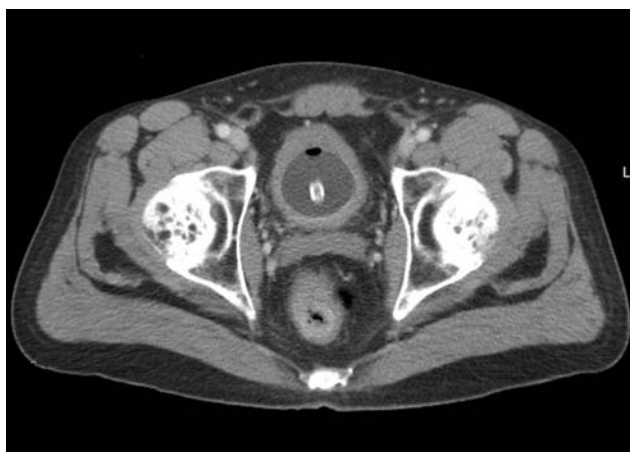
evidence to warrant its consideration, especially in patients with concurrent central nervous system and renal or urinary tract disease.

As for BKV-associated hemorrhagic cystitis, while it is relatively common in patients following BMT, it is rarely reported for other immunocompromised patients [2, 19]. Herein, we present the third reported case of BKV-associated hemorrhagic cystitis in an HIV-infected patient. Previous cases of BKV-associated hemorrhagic cystitis in both BMT patients as well as HIV-infected patients have relied on urine cytology and/or electron microscopy and PCR for the detection of viruria [2, 12, 13, 20, 21]. In our case, urine cytology for ‘decoy cells’ was suggestive of BKV infection, while PCR was positive for BKV. Positive PCR alone has been shown to be sufficient for the diagnosis of polyomaviruses, being both more sensitive and specific than cytology [22]. At the laboratory that performed our urine PCR for BKV, the limit of detection is 390 copies/mL and the PCR is specific to BKV when tested in the presence of JCV, herpes simplex virus-1, herpes simplex virus-2, varicella zoster virus, CMV, Epstein–Barr virus, and adenovirus.

It has been suggested that BKV-associated hemorrhagic cystitis in HIV-infected patients is related to immune reconstitution following the initiation of effective antiretroviral therapy [16]. In our case, the patient had his first episode of hematuria 3 months after his HIV viral load first became undetectable and at that time his CD4 count had also begun to rise. This is suggestive of an association between the onset of BKV-associated hemorrhagic cystitis and immune reconstitution. Although the patient’s rise in absolute CD4 count was modest, immune reconstitution inflammatory syndrome can also occur as a result of HIV viral load reduction and the redistribution of memory CD4 lymphocytes [23].

Interestingly, this case provides more direct evidence for the ability of BK viruria to cause hemorrhagic cystitis in an HIV-infected patient due to the lack of confounding variables present in one of the other reported cases: concomitant immunosuppression by CMV and non-Hodgkin’s lymphoma and prior cyclophosphamide administration [12].

Another question is whether or not this patient’s neurologic disease may have been secondary to BKV infection. The MRI scan of the brain in this patient did not show the findings typical for PML (hyperintense T2-weighted signal in the white matter adjacent to the cortex) [24]. These atypical MRI findings could not be explained by immune reconstitution because the patient had not yet been started on antiretroviral therapy at the time that his PML was diagnosed. Also, the PCR for JCV was negative; this test has a reported sensitivity of about 75% [24]. The brain biopsy specimen gave positive immunohistochemical staining with anti-SV40 antibody, but this would be cross-reactive with both JCV or BKV infection. Unfor-



**Figure 1.** Computed tomography (CT) of the patient’s pelvis demonstrating concentric bladder wall thickening and mucosal enhancement consistent with hemorrhagic cystitis.

Table 1  
Clinical presentations, patient characteristics, and radiographic and pathologic findings of BK virus (BKV) infection in HIV-infected patients.

Case	Clinical presentation	CD4 count (mm <sup>-3</sup> )	On HAART	Radiographic/pathologic findings	Reference
1	Hemorrhagic cystitis	23	Yes	Cystitis by cystoscopy; bladder mucosal lymphocytic infiltrate; BKV by urine PCR	Glück et al. [13]
2	Hemorrhagic cystitis	Unknown	Yes	Thickened bladder by CT scan; BKV by urine PCR; decoy cells in urine; IHC-positive decoy cells; polyomavirus in decoy cells by EM	Barouch et al. [12]
3	ARDS	0	Unknown	Interstitial pneumonia and chronic interstitial nephritis; BKV by EM, IHC, and PCR-positive type II pneumocytes and renal tubular epithelial cells	Cubukcu-Dimopulo et al. [8]
4	Tubulointerstitial nephritis	< 50	Yes	Neutrophilic and lymphocytic interstitial nephritis; BKV by renal tissue PCR; polyomavirus in tubular epithelial cells by EM, IHC-positive tubular epithelial cells	Smith et al. [6]
5	Acute kidney injury	10	Yes	Tubulointerstitial fibrosis with lymphocytic and monocytic infiltrates; BKV by renal tissue PCR; polyomavirus in tubular epithelial cells, parietal epithelial cells, endothelial cells by EM; IHC-positive tubular epithelial cells	Nebuloni et al. [7]
6	Retinitis, meningoencephalitis, and tubulointerstitial nephritis	100	Yes	Renal interstitial fibrosis with edema, monocytic infiltrate, tubular epithelial desquamation; fibrotic leptomeninges with macrophage and lymphocytic infiltrate; BKV by brain, eye, CSF, urine, and peripheral mononuclear cell PCR; IHC-positive tubular epithelial cells and periventricular/ependymal cells	Bratt et al. [10]
7	Encephalitis	65	Unknown	BKV by blood, bone marrow, kidney, bladder, stomach, mesenteric lymph nodes, lymphoma cells, and CSF PCR; IHC-positive ependymal lining, leptomeninges, subpial parenchyma and choroids plexus, tubular epithelial necrosis; polyomavirus in tubular epithelial cells by EM	Lesprit et al. [11]
8	Meningoencephalitis	37	Yes	Leptomeningeal lymphocytic infiltrate; BKV by CSF and cerebral tissue PCR	Vidal et al. [15]
9	Subacute meningoencephalitis and normal pressure hydrocephalus	Unknown	Unknown	Tubulointerstitial nephropathy, interstitial desquamative pneumonitis, meningoencephalitis; IHC-positive renal tubular epithelium, pneumocytes, choroid plexus, ventricular ependyma, leptomeninges	Vallbracht et al. [9]

HAART: highly active antiretroviral therapy; BKV: BK virus; PCR: polymerase chain reaction; IHC: immunohistochemistry; EM: electron microscopy; ARDS: acute respiratory distress syndrome; CSF: cerebral spinal fluid

unately, the patient was lost to follow-up at the time this manuscript was submitted and further CSF studies could not be performed.

Prior case reports have suggested a role for cidofovir in the treatment of BKV-associated hemorrhagic cystitis; however, the patients in these reports had mixed results [12, 20, 21]. As for other therapeutic options, currently, the most effective treatment for the other polyomavirus infection in HIV, PML, is immune reconstitution by

highly active antiretroviral therapy (HAART) [25, 26]. Cidofovir does not have survival benefit in the treatment of JCV infection in AIDS patients [27]. It is unknown if HAART is effective for other polyomavirus-induced complications of HIV.

### Conclusions

This report provides additional evidence that BK virus (BKV)-associated hemorrhagic cystitis can occur in

immunosuppressed patients other than transplant patients, specifically those with HIV. More investigation will be required to determine whether this condition is truly rare or simply underdiagnosed.

## References

1. Reploeg MD, Storch GA, Clifford DB: BK virus: a clinical review. *Clin Infect Dis* 2001; 33: 191–202.
2. Arthur RR, Shah KV, Baust SJ, Santos GW, Saral R: Association of BK viraemia with hemorrhagic cystitis in recipients of bone marrow transplants. *N Engl J Med* 1986; 315: 230–234.
3. Randhawa PS, Finkelstein S, Scantlebury V, Shapiro R, Vivas C, Jordan M, Picken MM, Demetris AJ: Human polyoma virus-associated interstitial nephritis in the allograft kidney. *Transplantation* 1999; 67: 103–109.
4. Nickleleit V, Klimkait T, Binet IF, Dalquen P, del Zenero V, Thiel G, Mihatsch MJ, Hirsch HH: Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. *N Engl J Med* 2000; 342: 1309–1315.
5. Petrogiannis-Haliotis T, Sakoulas G, Kirby J, Koranik IJ, Dvorak AM, Monahan-Earley R, de Girolami PC, de Girolami U, Upton M, Major EO, Pfister A, Joseph JT: BK-related polyomavirus vasculopathy in a renal-transplant recipient. *N Engl J Med* 2001; 345: 1250–1255.
6. Smith RD, Galla JH, Skahan K, Anderson P, Jr Linnemann CC, Ault GS, Ryschewitsch CF, Stoner GL: Tubulointerstitial nephritis due to a mutant polyomavirus BK virus strain, BKV(Cin), causing end-stage renal disease. *J Clin Microbiol* 1998; 36: 1660–1665.
7. Nebuloni M, Tosoni A, Boldorini R, Monga G, Carsana L, Bonetto S, Abeli C, Caldarelli R, Vago L, Costanzi G: BK virus renal infection in a patient with the acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1999; 123: 807–811.
8. Cubukcu-Dimopulo O, Greco A, Kumar A, Karluk D, Mittal K, Jagirdar J: BK virus infection in AIDS. *Am J Surg Pathol* 2000; 24: 145–149.
9. Vallbracht A, Löhler J, Gossmann J, Glück T, Petersen D, Gerth H, Gencic HJ, Dörries K: Disseminated BK type polyomavirus infection in an AIDS patient associated with central nervous system disease. *Am J Pathol* 1993; 143: 29–39.
10. Bratt G, Hammarin AL, Grandien M, Hedquist BG, Nennesmo I, Sundelin B, Seregard S: BK virus as the cause of meningoencephalitis, retinitis and nephritis in a patient with AIDS. *AIDS* 1999; 13: 1071–1075.
11. Lesprit P, Chaline-Lehmann D, Authier FJ, Ponnelle T, Gray F, Levy Y: BK virus encephalitis in a patient with AIDS and lymphoma. *AIDS* 2001; 15: 1196–1199.
12. Barouch DH, Faquin WC, Chen Y, Koranik IJ, Robbins GK, Davis BT: BK virus-associated hemorrhagic cystitis in a human immunodeficiency virus-infected patient. *Clin Infect Dis* 2002; 35: 326–329.
13. Glück TA, Knowles WA, Johnson MA, Brook MG, Pillay D: BK virus-associated hemorrhagic cystitis in an HIV-infected man. *AIDS* 1994; 8: 391–392.
14. Kuhlman JE, Browne D, Shermak M, Hamper UM, Zerhouni EA, Fishman EK: Retroperitoneal and pelvic CT of patients with AIDS: primary and secondary involvement of the genitourinary tract. *Radiographics* 1991; 11: 473–483.
15. Vidal JE, Fink MC, Cedeno-Laurent F, Delbue S, Ferrante P, Dauar RF, Filho FB, Nogueira RS, Calore EE, Pannuti CS, Trujillo JR, de Oliveira ACP: BK virus associated Meningoencephalitis in an AIDS patient treated with HAART. *AIDS Res Therapy* 2007; 4: 13.
16. Hirsch H, Steiger J: Polyomavirus BK. *Lancet Infect Dis* 2003; 3: 611–623.
17. Vago L, Cinque P, Sala E, Nebuloni M, Caldarelli R, Racca S, Ferrante P, Trabattoni G, Costanzi G: JCV-DNA and BKV-DNA in the CNS tissue and CSF of AIDS patients and normal subjects. Study of 41 cases and review of the literature. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 12: 139–146.
18. Moret H, Guichard M, Katlama C, Hauw JJ, Huraux JM, Ingrand D: Presence of BK virus in brain tissues of four AIDS patients, detected by polymerase chain reaction (PCR). The IXth International Conference on AIDS, Berlin, Germany, June 1993.
19. Kwak EJ, Vilchez RA, Randhawa P, Shapiro R, Butel JS, Kusne S: Pathogenesis and management of polyomavirus infection in transplant recipients. *Clin Infect Dis* 2002; 35: 1081–1087.
20. Held TK, Biel SS, Nitsche A, Kurth A, Chen S, Gelderblom HR, Siegert W: Treatment of BK virus-associated hemorrhagic cystitis and simultaneous CMV reactivation with cidofovir. *Bone Marrow Transplant* 2000; 26: 347–350.
21. González-Fraile MI, Cañizo C, Caballero D, Hernández R, Vázquez L, López C, Izarra A, Arroyo JL, de la Loma A, Otero MJ, San Miguel JF: Cidofovir treatment of human polyomavirus-associated acute haemorrhagic cystitis. *Transpl Infect Dis* 2001; 3: 44–46.
22. Boldorini R, Zorini EO, Vigano P, Nebuloni M, Mena M, Monga G: Cytologic and biomolecular diagnosis of polyomavirus infection in urine specimens of HIV-positive patients. *Acta Cytol* 2000; 44: 205–210.
23. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, Hamill RJ: Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005; 19: 399–406.
24. Spudich SS, Price RW: Neurological disease. In: Dolin R, Masur H, Saag M (eds) *AIDS therapy*. Churchill Livingstone, Elsevier, Philadelphia 2008, pp 314.
25. Albrecht H, Hoffmann C, Degen O, Stoehr A, Plettenberg A, Mertenskötter T, Eggers C, Stellbrink H: Highly active antiretroviral therapy significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. *AIDS* 1998; 12: 1149–1154.
26. Gasnault J, Taoufik Y, Goujard C, Kousignian P, Abbed K, Boue F, Dussaix E, Delfraissy JF: Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *J Neurovirol* 1999; 5: 421–429.
27. Kraemer C, Evers S, Nolting T, Arendt G, Husstedt IW: Cidofovir in combination with HAART and survival in AIDS-associated progressive multifocal leukoencephalopathy. *J Neurol* 2008; 255: 526–531.