Published in final edited form as:

J Pediatr. 2007 August ; 151(2): 215–217.

BK VIRUS–INDUCED TUBULOINTERSTITIAL NEPHRITIS IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Hiroto Inaba, MD, PHD, Deborah P. Jones, MD, Lillian W. Gaber, MD, Jerry L. Shenep, MD, Sandra K. Call, PharmD, Ching-Hon Pui, MD, and Bassem I. Razzouk, MD

From the Departments of Oncology, Infectious Diseases, and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee; and Departments of Pediatrics and Pathology, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee

Abstract

We report a case of BK virus–induced tubulointerstitial nephritis in a child with acute lymphoblastic leukemia. Primary BKV infection was exacerbated by chemotherapy-induced immunodeficiency. Careful administration of chemotherapy and anti-viral therapy prevented further damage. This diagnosis should be considered in children who experience renal dysfunction during cancer treatment.

BK virus (BKV), a human polyomavirus, was first isolated from the urine of kidney transplant recipient B.K.¹ Primary BKV infection is common during childhood, and 70%–80% of adults are seropositive.^{2,3} Latent BKV can be reactivated in the setting of immunosuppression, causing tubulointerstitial nephritis and ureteral stenosis in up to 8% of patients after renal transplantation or clinically overt hemorrhagic cystitis in up to 15% after hematopoietic stem cell transplantation.²⁻⁴ We describe BKV-induced tubulointerstitial nephritis in a child treated for newly diagnosed acute lymphoblastic leukemia (ALL).

CASE REPORT

A 5-year-old girl was found to have ALL with a t(12;21) translocation in September 2003. There was no personal or family history of kidney disease or immunodeficiency. She was treated on the St. Jude Children's Research Hospital Total XV protocol.⁵ She had a complete response to remission induction chemotherapy with methotrexate, prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, and mercaptopurine. Induction and consolidation (high-dose methotrexate and mercaptopurine) therapy were completed uneventfully; methotrexate was promptly cleared and serum creatinine values remained stable at 0.4 mg/dL. After week 44 of continuation therapy with daily mercaptopurine and weekly methotrexate plus pulses of dexamethasone and vincristine every 4 weeks, she became anemic and moderately neutropenic, requiring monthly transfusion and frequent hospitalization for febrile neutropenia and for *Klebsiella pneumoniae* and *Streptococcus pneumoniae* bacteremia. Her dosages of mercaptopurine and methotrexate were reduced by 25% and 30%, respectively. Her thiopurine S-methyltransferase genotype was wild-type.

Reprint requests: Hiroto Inaba, MD, PhD St. Jude Children's Research Hospital 332 North Lauderdale Memphis, TN 38105-2794
Phone: 901-495-3300; Fax: 901-521-9005; E-mail: hiroto.inaba@stjude.org.
Dr. Razzouk is now at the Children's Center for Cancer and Blood Diseases, St. Vincent Children's Hospital, Indianapolis, Indiana
Edited by TRW and WFB

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

During week 77, she was admitted for fever and neutropenia and treated with vancomycin and cefepime. Her serum creatinine concentration was 0.7 mg/dL, creatinine clearance was 32 mL/min/1.73m², and vancomycin clearance was delayed. Urinalysis showed a low specific gravity (1.006); no blood, protein or leukocyte esterase was detected and no white blood cells were found on microscopic examination. Her urine contained 8,721 µg of β2-microglobulin per gram of creatinine (normal, ≤160 µg/g), consistent with renal tubular dysfunction. Serum antistreptolysin O and antinuclear antibody titers and C3 and C4 concentration were within normal limits. Her creatinine level continued to increase, reaching 1.8 mg/dL at week 91, when she underwent renal biopsy.

Microscopically, the biopsy sample showed diffuse, extensive interstitial inflammation with tubular epithelial atypia in the renal medulla and deep cortex (Figure 1A). Tubular epithelial cells (particularly their nuclei) were enlarged; many had intranuclear inclusions morphologically typical of BKV infection and immunohistochemically positive for SV40 antigen (also typical of BKV infection; Figure 1B). Tubulitis was prominent, with extensive necrosis, sloughing, and reactive proliferation of tubular cells. The glomeruli appeared normal. No leukemic infiltration was observed. Her peripheral blood showed no B cells, decreased T cells (0.470×10⁹/L), and low serum IgG concentration (331 mg/dL) prior to therapy with IVIG. BKV DNA was detected in her urine (8.1 log₁₀ copies/mL) and plasma (4.2 log₁₀ copies/mL).

Anti-BKV therapy was initiated with cidofovir (0.25-1 mg/kg IV weekly, without probenecid), leflunomide (10 mg PO daily), and IVIG (1 g/kg monthly) simultaneously. Chemotherapy was continued with a 50% reduction of mercaptopurine and a 65% reduction of methotrexate (given with leucovorin rescue) dosage. Dexamethasone was discontinued to reduce immunosuppression. Creatinine concentration ranged from 0.9 to 1.2 mg/dL and plasma BKV DNA values from 3.6 to 4.2 log₁₀ copies/mL during the remaining weeks of continuation chemotherapy (Figure 2).

After completion of chemotherapy (week 120), BKV DNA copy number rose markedly with the increase of absolute lymphocyte counts, and ciprofloxacin was added to the anti-viral regimen. Four months later, when CD19-positive B cells, immunoglobulin production, and a decreased BKV DNA copy number were observed, a repeat kidney biopsy showed significant interstitial fibrosis consistent with chronic tubulointerstitial nephritis. At least 50% of the glomeruli showed global sclerosis, but none showed immune complex deposition. In situ hybridization showed no BKV. Anti-viral therapy was discontinued, the patient's creatinine concentration remained stable between 0.9 and 1.1 mg/dL, and BKV DNA copy number continued to decline in blood and urine (Figure 2). On the last follow-up, 1 year after completion of chemotherapy and 8 months after discontinuing anti-viral therapy, her creatinine was 1.1 mg/dL and plasma BKV DNA level was below the quantitative limit of the assay (<2.3 log₁₀ copies/mL). Serum IgG level (857 mg/dL), CD19 counts (0.530×10⁹/L), and CD3 counts (1.610×10⁹/L) were normalized. She also had a normal CBC, blood pressure, and growth pattern. Retrospective PCR analysis showed no BKV DNA in plasma obtained at presentation or in bone marrow sampled at week 48 of continuation therapy, but BKV DNA was present in bone marrow sampled at week 67, before serum creatinine concentrations began to rise. The St. Jude Institutional Review Board approved, and parents consented to, retrospective studies of these banked samples.

DISCUSSION

Renal dysfunction during continuation therapy for ALL is extremely rare⁶, and BKV nephritis has never been reported among patients with ALL. Biopsy is necessary for definitive diagnosis of BKV nephropathy and typically reveals cellular necrosis of the tubules and collecting ducts, interstitial inflammation, and extensive BKV replication,^{2,3} as in our case. The repeat biopsy

showed chronic tubulointerstitial nephritis, which is often seen in the late stage of BKV nephropathy.³

Treatment of BKV nephropathy is challenging in the setting of renal transplantation or leukemia. Immunosuppression or chemotherapy can be reduced to decrease the viral load, but only at the risk of renal graft rejection^{2,3} or leukemia relapse, respectively. We judiciously modified our patient's dosage of mercaptopurine and methotrexate and monitored her serum drug levels and hematologic and renal measures. We also administered cidofovir, leflunomide, IVIG and ciprofloxacin to suppress BKV replication. Cidofovir, a cytosine-phosphate analogue, exerts modest anti-polyomavirus activity in vitro and can prolong kidney graft survival and stabilize graft function.⁷ The immunosuppressant active metabolite of leflunomide, A77 1726, shows substantial anti-BKV activity when its blood level is maintained above 40 µg/mL,⁸ as achieved in our patient. Continuation therapy for ALL, especially when pulses of glucocorticoid are given, usually produces profound B-lymphocytopenia and low IgG and IgM concentrations.⁹ Immunoglobulin replacement has produced favorable outcomes in renal allograft recipients with BKV infection.¹⁰ Ciprofloxacin has shown activity against BKV after hematopoietic stem cell transplantation.⁴

Persistence of BK virus in the peripheral blood following infection is controversial, but detection of BK virus in peripheral blood does not seem to be prevalent in immunocompetent adults, especially older adults; however, BK virus does seem to be prevalent in immunocompromised adults, and would be expected in an immunocompromised child.^{11,12} Thus, although reactivation of latent infection cannot be definitively excluded, the absence of BKV DNA during the early phase of chemotherapy and its appearance shortly before the elevation of serum creatinine indicate that primary infection occurred during continuation chemotherapy in our patient and progressed to nephritis in the setting of chemotherapy-induced immunodeficiency. BKV-seronegative kidney transplant recipients, especially children, are at increased risk of BKV interstitial nephritis.³ Tubular epithelial injury, which is considered an essential cofactor of interstitial nephritis,^{2,3} could have been caused in our patient by chemotherapy agents or urinary tract infection during neutropenia. We recommend that plasma and urine BKV DNA PCR and, if feasible, kidney biopsy be performed when an immunocompromised patient develops renal dysfunction. A higher index of suspicion should result in earlier diagnosis, which may translate into improved renal outcome secondary to earlier treatment with anti-viral medications and more judicious exposure to potentially nephrotoxic agents.

Acknowledgements

Supported in part by Cancer Center Core grant CA 21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities.

REFERENCES

1. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. *Lancet* 1971;1:1253–7. [PubMed: 4104714]
2. Fishman JA. BK virus nephropathy--polyomavirus adding insult to injury. *N Engl J Med* 2002;347:527–30. [PubMed: 12181409]
3. Hirsch HH. BK virus: opportunity makes a pathogen. *Clin Infect Dis* 2005;41:354–60. [PubMed: 16007533]
4. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* 2005;40:528–37. [PubMed: 15712075]
5. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006;354:166–78. [PubMed: 16407512]

6. Krawczuk-Rybak M, Kuzmicz M, Wysocka J. Renal function during and after treatment for acute lymphoblastic leukemia in children. *Pediatr Nephrol* 2005;20:782–5. [PubMed: 15782299]
7. Kuypers DR, Vandooren AK, Lerut E, Evenepoel P, Claes K, Snoeck R, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. *Am J Transplant* 2005;5:1997–2004. [PubMed: 15996251]
8. Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, et al. Leflunomide for polyomavirus type BK nephropathy. *N Engl J Med* 2005;352:1157–8. [PubMed: 15784677]
9. Caver TE, Slobod KS, Flynn PM, Behm FG, Hudson MM, Turner EV, et al. Profound abnormality of the B/T lymphocyte ratio during chemotherapy for pediatric acute lymphoblastic leukemia. *Leukemia* 1998;12:619–22. [PubMed: 9557622]
10. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. *Transplantation* 2006;81:117–20. [PubMed: 16421486]
11. Dolei A, Pietropaolo V, Gomes E, Di Taranto C, Ziccheddu M, Spanu MA, et al. Polyomavirus persistence in lymphocytes: prevalence in lymphocytes from blood donors and healthy personnel of a blood transfusion centre. *J Gen Virol* 2000;81:1967–73. [PubMed: 10900035]
12. Azzi A, De Santis R, Ciappi S, Leoncini F, Sterrantino G, Marino N, et al. Human polyomaviruses DNA detection in peripheral blood leukocytes from immunocompetent and immunocompromised individuals. *J Neurovirol* 1996;2:411–6. [PubMed: 8972423]

Figure 1. Photomicrographs of renal biopsy sections. (A) Cytologic atypia of the tubular epithelial cells, including enlarged nuclei and large basophilic intranuclear viral inclusions (hematoxylin and eosin $\times 200$). (B) Immunohistochemical staining reveals SV40 antigen (typical of BK virus infection) in the nuclear inclusions ($\times 200$).

Figure 2.

Serum creatinine concentration and BK virus DNA copy number. (A) Serum creatinine concentrations after week 67 of continuation therapy. Values increased during week 77 (0.7 mg/dL), reached 1.8 mg/dL during week 91, when the patient underwent renal biopsy, and ranged from 0.9 to 1.2 mg/dL during and after anti-viral therapy. (B) BKV DNA copy number in plasma remained stable during chemotherapy, rose briefly after the completion of chemotherapy, and then dramatically decreased with the recovery of CD19-positive B cells and immunoglobulin production (* indicates below the quantitative limit of the assay: $<2.3 \log_{10}$ copies/mL).