Nephroquiz 4: A 43-Year-Old Woman With Kidney Allograft Dysfunction Due to BK Virus Nephropathy

Fatemeh Yassari,[1] Mahmood Parvin,[2] Pedram Ahmadpoor[3]

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[1]Department of Dialysis, Razi Hospital, Ghaem-Shahr, Mazandaran, Iran
[2]Department of Pathology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Division of Nephrology, Department of Medicine, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

CASE

A 43 years-old woman was admitted to hospital because of kidney allograft dysfunction. She had received a living kidney donation 8 months earlier, after 5 months of hemodialysis, and the early posttransplant course was excellent. The cause of her kidney failure was unknown, but her kidneys were bilaterally small with no extrarenal presentations. Her serum creatinine was 1.5 mg/dL 1 month earlier, but rose to 2.4 mg/dL. There were no complaints of febrile episodes, cough, dyspnea, diarrhea, or localized pain. Blood pressure was 140/80 mm Hg, and physical examination was unremarkable expect for mild pedal edema. Her drug history was cyclosporine A, 200 mg/d, mycophenolate mofetil, 2 g/d, and prednisolone, 10 mg/d. Laboratory data were as follows: hemoglobin, 13 g/dL; platelet count, 240 × 10^9/L; leukocyte count, 8.5 × 10^9/L; blood urea nitrogen, 32 mg/dL; serum creatinine, 2.4 mg/dL; serum sodium, 141 mmol/L; serum potassium, 4.8 mmol/L; fasting blood glucose, 68 mg/dL; serum uric acid, 5.8 mg/dL; creatine phosphokinase, 180, U/L; serum calcium, 8.8 mg/dL; serum phosphate, 4.3 mg/dL; serum alanine transferase, 32 U/L; cyclosporine trough level, 130 ng/mL; and urine leukocyte count, 5 to 10 per high-power field. Other urinalysis parameters and urine culture were unremarkable. Antihuman leukocyte antigen antibody and cytomegalovirus antigen were negative.

On ultrasonographic and Doppler examinations of the allograft, there was no evidence of hydronephrosis. The renal vein was normal and the resistive index was 0.7. Renal scintigraphy revealed mildly impaired function and preserved perfusion. Urine cytology was positive for presence of decoy cells (Figure 1). Result of plasma BK virus detection by polymerase chain reactive assay was positive. An allograft biopsy was taken with the impression of BK virus nephropathy and for ruling out a rejection episode. Measurement of BK viral load was not available for this patient. Examination of biopsy specimens of the patient revealed patchy infiltration and flattening of the epithelial cells and denudation of the basement membrane along with flattening of the lining epithelium, bulging of epithelium tubular cells inside the tubules, and cytopathic changes and nuclear enlargement (Figures 2 and 3).

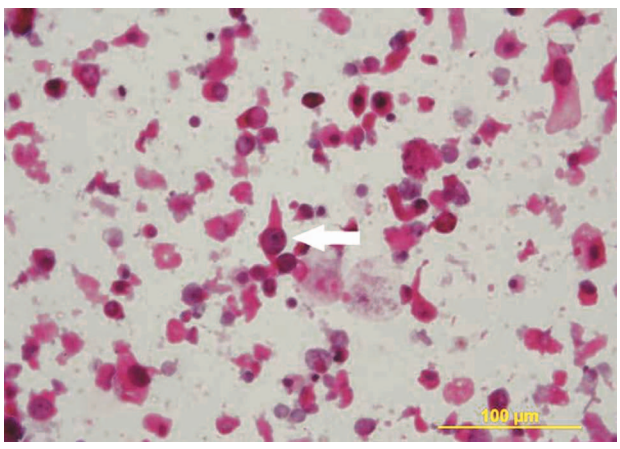

Figure 1. Detection of decoy cells (arrow) has a sensitivity close to 100%, but the positive predictive value is 20%. The predictive value increases if more than 10 decoy cells per high-power field is detected. Decoy cells can be seen in JC, BK, cytomegalovirus, and adenovirus infections and sometimes resemble shedding cells in renal cell carcinoma.

NEPHROQUIZ

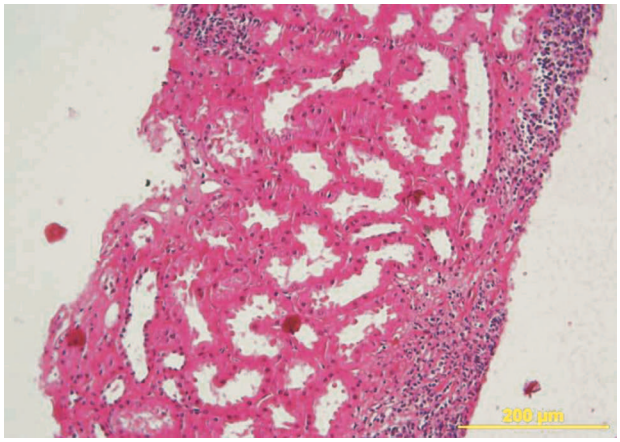

Figure 2. Patchy infiltration and flattening of tubular epithelial cells.

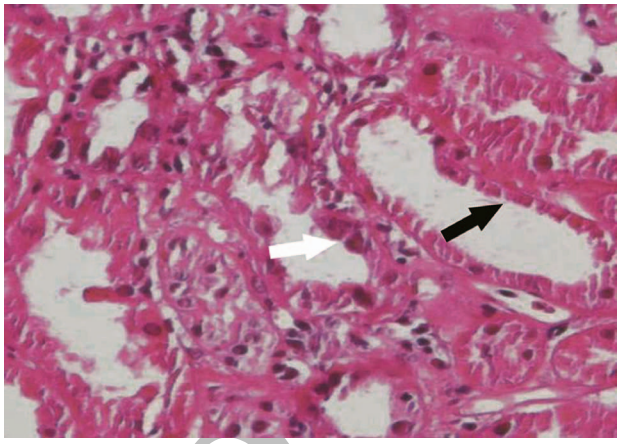

Figure 3. Viral cytopathic changes (white arrow) and flattening and denudation of tubular basement membrane (black arrow).

QUIZ
How Should BK Nephropathy be Screened and Treated?

In 1971, the two classical human polyoma viruses, BK virus and JC virus, were concurrently reported.[1] They named with the initials of the patients from whom the viruses were first isolated. The human polyoma viruses share 64% to 75% DNA sequence homology with SV40. They cause clinical disease only in immunocompromised patients. The major diseases caused by BK virus are tubulointerstitial nephritis and ureteral stenosis in kidney transplant recipients and hemorrhagic cystitis in bone marrow transplant recipients. The prevalence of BK virus-induced nephritis in kidney transplant recipients is estimated to be 5% to 8%.

There are multiple screening tests for detection of BK virus. Examination of urine sediment for decoy cells is an inexpensive test, but decoy cells are neither sensitive nor specific for BK virus infection, because they can be confused with other viruses such as cytomegalovirus and adenovirus (positive predictive value, 20%). Specificity of 71% for decoy cells was noted in a prospective report of 78 kidney transplant recipients. Cytologic study of urine may be normal when other tests that directly detect BK virus in urine are positive.[2] Thus, the absence of decoy cells does not rule out the disease. Serum antibodies against the BK virus are not helpful in the diagnosis of BK-associated nephropathy, because they are commonly positive in the general population.

Another method is identification of BK virus DNA in plasma or urine with polymerase chain reaction assay. The presence of BK virus DNA in plasma as examined with this method reported in 78 kidney transplant patients was associated with a sensitivity and specificity of 100% and 88%, respectively, for diagnosis of BK virus nephropathy.[2]

Measuring BK viral load may increase specificity and predictive value of BK viremia for diagnosis of BK-associated nephropathy. A plasma viral load of more than 10 000 copies per milliliter was associated with biopsy-proven BK-associated nephropathy in almost all of the patients. Although specificity increased by using a cutoff level of 16 000 copies per milliliter.[3]

It is recommended that all kidney transplant recipients be screened for BKviremia in plasma as follows: (1) monthly for 3 to 6 months, and then every 3 months during the first year posttransplant, or alternatively BK viruria be screened every 3 months up to 2 years; (2) when allograft dysfunction (unexplained rise in serum creatinine level) is noted; (3) when allograft biopsy is performed; and (4) after treatment of acute rejection. A positive screening result should be confirmed in less than 4 weeks and evaluated by quantitative assays (eg, BK virus DNA load in plasma or urine) with a threshold for presumptive disease (plasma DNA load more than 10 000 copies per milliliter, urine DNA load more than 10^7 copies per milliliter, urine VP-1mRNA load greater than 6.5×10^5 copies per milligram of total RNA. If one of the above tests is positive, kidney allograft biopsy should be obtained to diagnose BK-induced nephropathy definitely.[4] BK virus-associated nephropathy can be diagnosed only with kidney allograft biopsy and

requires demonstration of BK virus replication in kidney allograft tissues. However, sensitivity may be less than 100% due to the multifocal nature of the disease. Measurement of BK virus DNA level may provide a wider dynamic range and could be a better choice for determining the extent of viral content.[3] A plasma viral titer greater than 10 000 copies per milliliter is presumptive of BK virus nephropathy, even in the absence of histologic evidence on biopsy.[4]

There is a correlation between an increased incidence of BK virus infection in kidney transplant recipients and an increased degree of immune suppression. No strong association has been found between a particular immunosuppressive drug and BK-induced nephropathy. Therapeutic approaches for BK-induced nephropathy are largely based upon anecdotal cases and small series. Since specific antiviral therapy does not currently exist, the cornerstone of therapy is to decrease immunosuppressive medication.[5] The effectiveness of this strategy has not been evaluated systematically. Only retrospective studies and case series have evaluated the efficacy of decreasing overall immune suppression. In a study on 24 patients,[6] reduced doses of mycophenolate mofetil and tacrolimus resulted in a successful elimination of viremia in a mean period of 6 months and improved allograft survival in 23 patients at a mean follow-up period of 31 months. BK-induced nephritis was presented in 16 patients and viremia was presented in 8 patients without evidence of nephritis on biopsy. At the time of diagnosis, the mean plasma BK virus DNA load was 460 409 copies per milliliter. The mean reductions of mycophenolate mofetil and tacrolimus doses were 44% and 41%, respectively. Decline in the viral load was noticed within 15 to 30 days with successful elimination of viremia over a mean period of 5.8 months. Reduction in immunosuppressive therapy resulted in development of acute rejection in 3 patients. After a mean follow-up period of 43.5 months, all of the 24 patients were alive and 23 had a functioning graft. Seventeen patients had stable or improved graft function.[6]

Alternative approaches also may be efficacious against BK-induced nephropathy,[1] such as changing from tacrolimus to low-dose cyclosporine that concurrently reduces the effect of the calcineurin inhibitor and mycophenolic acid level. Replacing a calcineurin inhibitor with rapamycin with or without discontinuation of the antimetabolite has the advantage of avoiding the long-term calcineurin inhibitor-related nephrotoxic effect.[7] Lowering the dose of the calcineurin inhibitor may slow down the loss of kidney function.[8] No studies have directly assessed one strategy versus another.

Antiviral therapy is the other step in patients with progressive allograft dysfunction despite a maximal decrease in immunosuppressive therapy after several weeks. There are several drugs that may have efficacy against BK-induced nephropathy.[9] Ciprofloxacin (a quinolone antibiotic) may have anti-BK virus effects. In one study on patients with hematopoietic stem cell transplantation, administration of standard-dose ciprofloxacin was associated with decreased urinary BK viral load.[10] Another agent that has been examined is intravenous immunoglobulin, with limited information available concening its efficacy. One advantage of this agent in patients with BK-induced nephropathy is that the drug may treat both BK virus infection and allograft rejection. In a single-center study of 8 affected patients, a reduction of immunosuppretion dose plus intravenous immunoglobulin saved allograft in 7 patients after a 15-month follow-up.[11]

The third agent is leflunomide. It is a prodrug and its antimetabolite, A771726, has both immunosuppressive and antiviral activities.[12] Its mechanism of action against BK virus is unclear. There is suggestive evidence of efficacy of leflunomide in BK-induced nephropathy. In a case series, there was improvement or stabilization in 23 of 26 patients with BK-induced nephropathy after discontinuation of mycophenolate mofetil, targeting tacrolimus level to 4 ng/mL to 6 ng/mL, maintaining prednisone at 5 mg/d to 10 mg/d, and replacing mycophenolate mofetil with leflunomide with a target level of 80 µg/mL to 100 µg/mL (or A771726 > 40 µg/mL). However, the correlation between level and outcome is unclear.[13] There are some limitations that preclude routine use of leflunomide in the treatment of BK-induced nephropathy, such as the absence of any control group of leflunomide compared to reduction in immunosuppression, the wide interpatient A771726 level variability, the potential hematologic and hepatic toxicity, and the limited availability of A771726 levels.

Cidofovir is another drug that may have

efficacy against BK-induced nephropathy. A few uncontrolled studies have evaluated the use of cidofovir in BK-induced nephropathy. In a nonrandomized retrospective study on 21 patients treated with cidofovir, all the allografts survived in a median period of 25 months. By comparison, 9 of 13 allografts of patients without cidofovir were lost at a median period of 8 months.[14] Cidofovir induces proteinuria and kidney failure in 20% of patients. In addition, this agent has caused at least 1 case of subacute intenestitial nephritis, which leads to end-stage renal disease.[15] Cidofovir should only be used when all other interventions have failed after a period of 3 month. Recently, a lipid-bound cidofovir is being developed that may make cidofovir safer and more effective.

Additional agents that may have anti viral activity against BK virus include retinoic acid, which needs further studies on its efficacy.[16]

Overall, the initial management of BK-induced nephropathy is immunosuppressive dose reduction, and in those with no response, antiviral therapy may be indicated. The optimal agent is unclear. Quinolone can be the initial therapy because of its low costs and ease of administration. Another step is the use of leflunomide, and in refractory cases, cidofovir or intravenous immunoglobulin can be tried.

REFERENCES

1. Mantyjarvi RA, Arstila PP, Meurman OH. Hemagglutination by BK virus, a tentative new member of the papovavirus group. Infect Immun. 1972;6:824-8.
2. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med. 2002;347:488-96.
3. Costa C, Bergallo M, Astegiano S, et al. Monitoring of BK virus replication in the first year following renal transplantation. Nephrol Dial Transplant. 2008;23:3333-6.
4. Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation. 2005;79:1277-86.
5. Celik B, Shapiro R, Vats A, Randhawa PS. Polyomavirus allograft nephropathy: sequential assessment of histologic viral load, tubulitis, and graft function following changes in immunosuppression. Am J Transplant. 2003;3:1378-82.
6. Saad ER, Bresnahan BA, Cohen EP, et al. Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. Transplantation. 2008;85:850-4.
7. Wali RK, Drachenberg C, Hirsch HH, et al. BK virus-associated nephropathy in renal allograft recipients: rescue therapy by sirolimus-based immunosuppression. Transplantation. 2004;78:1069-73.
8. 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.
9. Josephson MA, Williams JW, Chandraker A, Randhawa PS. Polyomavirus-associated nephropathy: update on antiviral strategies. Transpl Infect Dis. 2006;8:95-101.
10. Leung AY, Chan MT, Yuen KY, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2005;40:528-37.
11. Sener A, House AA, Jevnikar AM, 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.
12. Chong AS, Zeng H, Knight DA, et al. Concurrent antiviral and immunosuppressive activities of leflunomide in vivo. Am J Transplant. 2006;6:69-75.
13. Josephson MA, Gillen D, Javaid B, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006;81:704-10.
14. Kuypers DR, Vandooren AK, Lerut E, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant. 2005;5:1997-2004.
15. Vandercam B, Moreau M, Goffin E, Marot JC, Cosyns JP, Jadoul M. Cidofovir-induced end-stage renal failure. Clin Infect Dis. 1999;29:948-9.
16. Talmage DA, Listerud M. Retinoic acid suppresses polyoma virus transformation by inhibiting transcription of the c-fos proto-oncogene. Oncogene. 1994;9:3557-63.

Correspondence to:
Pedram Ahmadpoor, MD
Department of internal Medicine, Shahid Labbafinejad Medical Center, 9th Boustan St, Pasdaran Ave, Tehran, Iran
Tel: +98 21 2258 0333
Fax: +98 21 2258 0333
E-mail: pedram.ahmadpoor@gmail.com