

BK Virus-Associated Nephropathy without Viremia in an Adolescent Kidney Transplant Recipient

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ABSTRACT

BK virus can reactivate in kidney transplant recipients leading to BK virus-associated nephropathy (BKVAN) and allograft dysfunction. Pathogenesis begins with viral replication, follows by viruria, viremia and nephropathy. Screening tools recommended for viral detection are urine and blood BK viral load. Viremia has higher positive predictive value than viruria, thus several guidelines recommend using viremia to determine whether renal biopsy, a gold standard for diagnosis of BKVAN is needed. We present a 16-year-old boy who developed BKVAN five months after deceased donor kidney transplantation. He had increased serum creatinine with negative blood BK viral load. BK nephropathy was diagnosed in kidney graft biopsy. The urine showed BK viruria. Immunosuppressant was reduced and ciprofloxacin given. Viruria disappeared and repeated graft biopsy was normal 4 months later. BK viremia was negative through 1 year follow up.

We conclude that BKVAN may occur even without viremia and BK viruria may be considered for screening tool.

Keywords: BKVAN; BK viremia; BK viruria; kidney transplantation (Siriraj Med J 2017;69: 297-299)

INTRODUCTION

BK virus-associated nephropathy (BKVAN) is an important cause of allograft dysfunction especially first year post transplantation. Incidence of BKVAN in pediatric kidney transplantation is 4-7%.¹ At present, there are no strategies for prevention of BK virus reactivation. Blood BK viral load which is pre-emptive surveillance recommendation is often used.^{2,3} We report an adolescent who developed BKVAN without viremia five months after deceased donor kidney transplantation (DDKT).

CASE REPORT

A 16-year-old boy with end stage renal disease from bilateral ureteropelvic junction obstruction underwent DDKT. He had a panel of reactive antibodies 0%, human leukocyte antigen (HLA) mismatch 2-1-1, and negative crossmatch. Both donor and recipient were cytomegalovirus (CMV) seropositive. The operation was uneventful. He received basiliximab and methylprednisolone for induction.

Maintenance immunosuppressive regimen was prednisone 60 mg/day, mycophenolic acid 500 mg every 12 hours (714 mg/m²/day), and tacrolimus 4 mg every 12 hours and adjusted to achieve therapeutic level of 10-12 ng/ml. Ureteric stent was retained for 22 days. His serum creatinine (Cr) upon discharge at 3 weeks was 1.2 mg/dL. Prednisolone was tapering to 15 mg/day at 1 month. One month later, he experienced CMV reactivation successfully treated with intravenous ganciclovir. Mycophenolic acid was further reduced to 250 mg every 12 hours (535 mg/m²/day) and tacrolimus level was maintained at 8-10 ng/ml. Blood BK viral load samples were taken monthly and were all negative.

At five months post transplantation, his Cr increased to 1.63 mg/dL. Physical examination was unremarkable. Doppler ultrasonography was normal. Serum CMV and BK viral loads were negative. Allograft biopsy demonstrated focal moderate interstitial mononuclear cell infiltration without viral inclusion bodies (Fig 1). However, immunostaining

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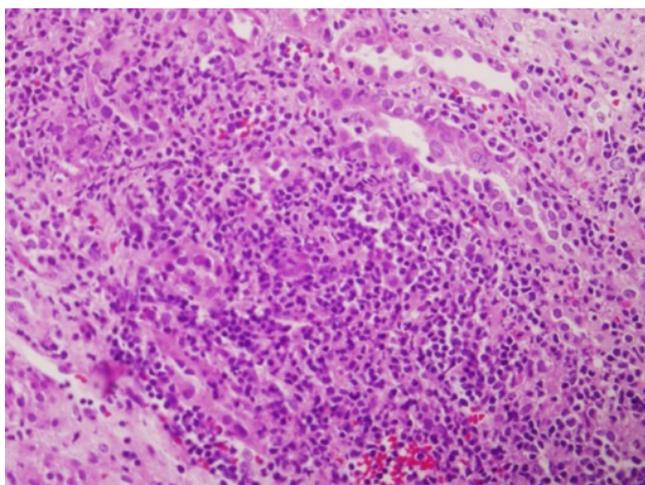


Fig 1. Interstitial inflammatory cell infiltration without viral inclusions identified in tubular cells (Hematoxyline & eosin).

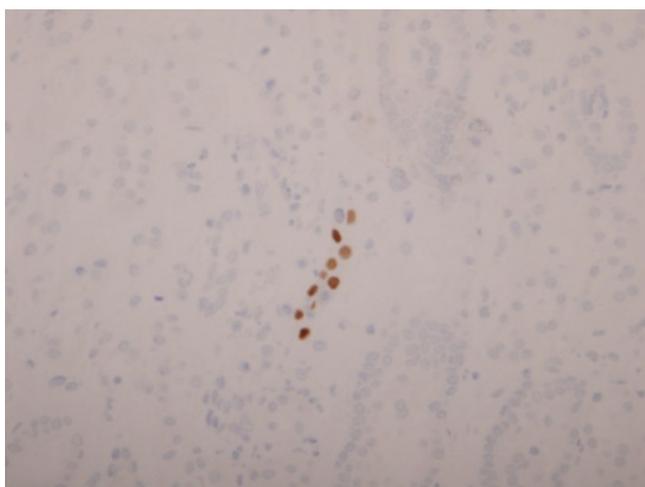


Fig 2. Occasional tubular cells positive for SV40 antibody indicating BK virus-associated nephropathy (Immunohistochemistry).

for SV40 was positive in occasional tubular cell nuclei (Fig 2). SV40 is a large T antigen commonly identified in polyomavirus group including BK virus. The pathologic diagnosis was BKVAN. MPA was further reduced to 357 mg/m²/day, trough level of tacrolimus decreased to 6-8 ng/mL, and ciprofloxacin 500 mg every 12 hours added. Urine BK viral load, examined after obtaining biopsy result, was 39,781,908 copies/mL. Serum BK viral loads were all negative during 9 months follow-up period. Urine BK viral loads declined and became undetectable at 4 months after treatment. Cr also returned to baseline and repeated renal pathology was normal. Fourteen months post transplantation, he remains clinically well with Cr 1.4 mg/dL.

DISCUSSION

BK virus is a non-enveloped double-stranded DNA virus, belonging to the polyomavirus group, which is a common opportunistic infection in post-transplant

patient. The first exposure to BK virus usually occurs during childhood, with average age 4-5 years.⁴ After primary infection, the virus resides latent in renal tubular epithelial cells and uroepithelium. The prevalence of seropositive at age 3, 10 and 20 years are 50, 60-90 and 80-90%.¹ In kidney-transplant recipients, the viral reactivation induces epithelial cell lysis and viruria. After that, BK virus manifolds in interstitium and invades peritubular capillaries, leading to viremia and finally causing nephropathy. Risk factors of BKVAN are unclear but intensive immunosuppressive agents is presumed to be a major factor.⁵ Other factors that may promote BKVAN are BK seronegative recipients, seropositive donors, male, elderly, HLA mismatching, prolonged cold ischemic time, ureteric stent placement and episode of acute rejection.^{6,7} Typical presentation is asymptomatic viruria, followed by viremia and then graft nephropathy with rising Cr. But BK reactivation in urogenital epithelium before development of BK viremia was proposed in some study.⁸ Definitive diagnosis of BKVAN requires renal biopsy, with confirmation of viral inclusion bodies or immunochemistry staining using SV40, with tubulointerstitial nephritis. SV40 can be positive in both BK and JC viral nephropathy but we think our patient had BKVAN because of several reasons. Firstly, BKVAN is much more common than JC virus nephropathy (incidence of BKVAN and JC virus nephropathy was reported as 5.5 and 0.9% of kidney transplant recipients).⁹ Besides, urine BK viral load in our patient was more than 10 million copies/mL and the incidence of co-detection rate between BK and JC viruria was very low at 1.5% because of inhibitory effects between JC and BK virus.¹⁰ The differential diagnosis between BK and JC virus nephropathy requires PCR and DNA sequencing to identify the viral genotype¹¹ which is not available in our hospital. Because there is no proven preventive strategy for BK viral reactivation, the best way to prevent BKVAN is early detection and intervention. Both viruria and viremia detected by polymerase chain reaction assay have a high sensitivity for BK virus screening. Urine BK viral load > 10⁷ and blood BK viral load > 10⁴ copies/mL are predictors for BKVAN. Several recommendations prefer BK viremia to viruria because of its higher positive predictive value for BKVAN.^{1,4,6,12} According to Kidney Disease Improving Global Outcomes (KDIGO), kidney transplant recipients should be screened for viremia monthly during the first 6 months then every 3 months for the first year after transplantation.²

This patient with BKVAN had elevated Cr and BK viruria without viremia. Risk factors were

immunosuppressive regimen, male gender and ureteric stent placement. The Blood BK viral load was sent monthly according to KDIGO² and the results were all negative. After BKVAN was diagnosed, urine BK viral load showed viruria. BKVAN without BK viremia were previously reported in ten cases. Six patients were male, 2 were female and 2 unidentified. Nine patients were adult and 1 was adolescent.^{8,13-17} The first case was reported in 2003.⁹ BKVAN was diagnosed in 5 cases by renal pathology with BK viruria, and viremia was undetectable, but there were no data of viremia afterward.¹³⁻¹⁴ Four cases of BKVAN, including one from Thailand, did not have BK viremia at the time of renal biopsy, but viremia occurred at 7 days and 3, 6 and 11 months later.^{8,15-16} One patient developed BKVAN without both viruria and viremia.¹⁷

When BK viremia is detected by screening, the intervention recommended is immunosuppressive reduction especially tacrolimus and mycophenolate.^{1,2,4,6,8} If BK viremia is not cleared and BKVAN develops, other drugs such as leflunomide, ciprofloxacin or cidofovir may be considered.^{1,3,4,6,12} MPA and tacrolimus were reduced and ciprofloxacin given in our patient.

CONCLUSION

This case confirmed that BKVAN can occur despite negative viremia. Screening only for viremia may not be enough. Screening for viruria may be considered for early detection and intervention in children.

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