## CASE REPORT

# BIOPSY-PROVEN BK VIRUS NEPHROPATHY WITHOUT DETECTABLE BK VIREMIA IN A ONE-YEAR POST-KIDNEY TRANSPLANT RECIPIENT

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**Abstract.** BK virus nephropathy (BKVN) is an important clinical problem in kidney transplant (KT) recipients. The sequence of disease is usually viruria, viremia and then nephropathy. Diagnosis of BK virus (BKV) infection includes checking BKV DNA in the urine, in the plasma and histology on renal biopsy. This last method is used to diagnose BKVN. We describe a KT patient with BKVN without detectable BK viremia. A 62-year-old female with hypertensive nephropathy underwent renal transplant from a living relative donor in December 2011. Fourteen months after transplantation, her serum creatinine(SCr) rose up from 1.2 to 1.6 mg/dl with biopsy-proven acute antibody-mediated and cellular rejection. After pulse methylprednisolone, plasmapheresis and intravenous immunoglobulin, her SCr decreased to baseline but she subsequently developed cytomegalovirus infection with pancytopenia and transaminitis. The SCr rose to 1.9 mg/dl despite ganciclovir treatment. Renal ultrasound and antegrade pyelogram showed partial obstruction of the proximal ureter with moderate hydronephrosis. A quantitative polymerase chain reaction (PCR) assay for BKV DNA was negative (less than 10 copies/ml). A renal biopsy was performed and the pathology revealed viral cytopathic changes in the tubular epithelium with interstitial inflammation. The renal biopsy also showed BKV nucleic acid sequences by in-situ hybridization confirming BKVN. Immunosuppression regimen was changed to cyclosporine, low-dose prednisolone and leflunomide. A temporary percutaneous nephrostomy was performed. Her renal function improved within one week. The diagnosis of BKVN should be considered in a KT recipient with a rising SCr with or without BK viremia and should be made by renal biopsy.

**Keywords:** BK virus, nephropathy, PCR, sensitivity, viremia

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## INTRODUCTION

BK virus (BKV) is an important cause of polyomavirus-associated nephropathy, known as BK virus nephropathy (BKVN). BKVN is a common viral complication after kidney transplantation with prevalence

rates of 1% to 10% (Costa and Cavallo, 2012). The nephropathy usually begins 10 to 13 months post-transplantation, but may occur as early as 6 days post-transplantation and as late as five years post-transplantation (Randhawa *et al*, 1999).

Primary BK infection usually occurs in childhood and remains latent in different organs, particularly the urogenital epithelium (Drachenberg and Papadimitriou, 2006; Viscount *et al,* 2007). Reactivation may occur in kidney transplant (KT) recipients and is associated with immunosuppressive medications (Yeo *et al*, 2008). The typical course of BKVN is an asymptomatic period of viruria followed within weeks by viremia with no change in renal function (Ramos *et al,* 2009). Viral replication and high viremia lead to deterioration in graft function and graft loss in 10%-80% in KT recipients (Ramos *et al*, 2009). The pathological findings in BKVN include tubulointerstitial nephritis and rarely ureteral stenosis (Gupta *et al*, 2003). Patients with BKVN who develop interstitial nephritis usually present with an asymptomatic acute or slowly progressive rise in the serum creatinine (SCr) with or without hematuria (Vasudev *et al*, 2005). A definitive diagnosis of BKVN requires finding the characteristic cytopathic changes on kidney biopsy along with a positive immunohistochemistry test for antibodies directed specifically against cross-reacting simian virus 40 (SV40) large-T antigen or a positive polymerase chain reaction **(**PCR) assay for BKV (Wiseman, 2009). We describe here a case of BKVN.

## CASE REPORT

A 62-year-old woman underwent a KT from a living related donor in December 2011. The cause of her renal failure was hypertensive nephropathy. She received basiliximab for induction therapy and was treated with triple therapy consisting of tacrolimus, mycophenolic acid and prednisolone for maintenance immunosuppression. Her SCr was 1.1 mg/dl one month post-transplantation. Six months post-transplant her SCr was increased to 1.4 mg/dl and a kidney biopsy was performed which showed acute cellular rejection. She received treatment with intravenous methylprenisolone 2,000 mg over 3 days; her SCr then returned to 1.1 mg/dl.

Fourteen months post-transplant her SCr rose from 1.2 to 1.6 mg/dl, a repeat biopsy was performed showing acute cellular and antibody-mediated rejection. She was treated with methylprednisolone 2,000 mg over 3 days, plasmapheresis for 7 sessions and a total of 115 g intravenous immunoglobulin. She developed pancytopenia by fifteen months post-transplant. Laboratory studies revealed: a hemoglobin of 9 g/dl, a white blood cell count of 3,200/$mm^3$ with 56% neutrophils and 27% lymphocytes; her platelet count was 95,000/ $mm^3$, her AST was 100 U/l, and her ALT was 60 U/l. A blood test for CMV viral load showed 10,923 copies/ml. She was diagnosed as having cytomegalovirus infection with pancytopenia and elevated transaminases. Intravenous ganciclovir was started, but her SCr continued to rise to 1.9 mg/dl. A kidney biopsy was again performed.

The biopsy specimen when examined with light microscopy showed slightly enlarged renal tubular cells with ground-glass intra-nuclear inclusions and extensive cytoplasmic vacuolization (Fig 1). There was focal interstitial fibrosis and edema without evidence of tubulitis. The glomeruli had slightly increased mesangial cells and mild vascular arteriosclerosis. An *in situ* hybridization was strongly

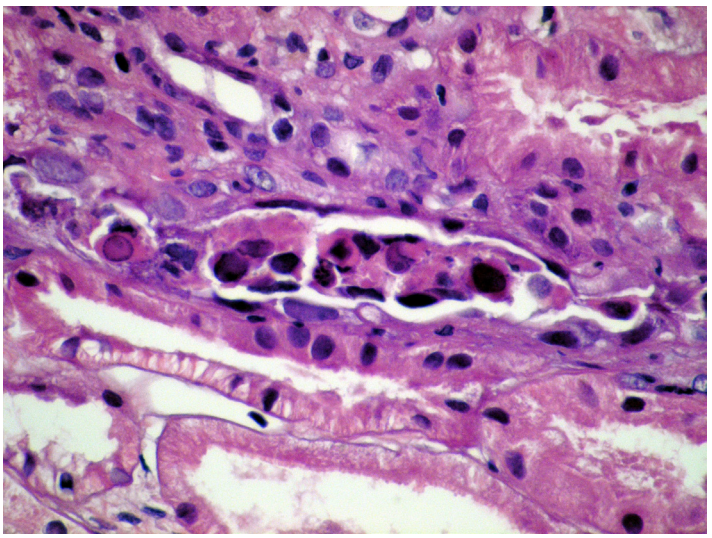

Fig 1–Light microscopy demonstrating renal tubular cells with groud-glass intra-nuclear inclusions and extensive cytoplasmic vacuolation.

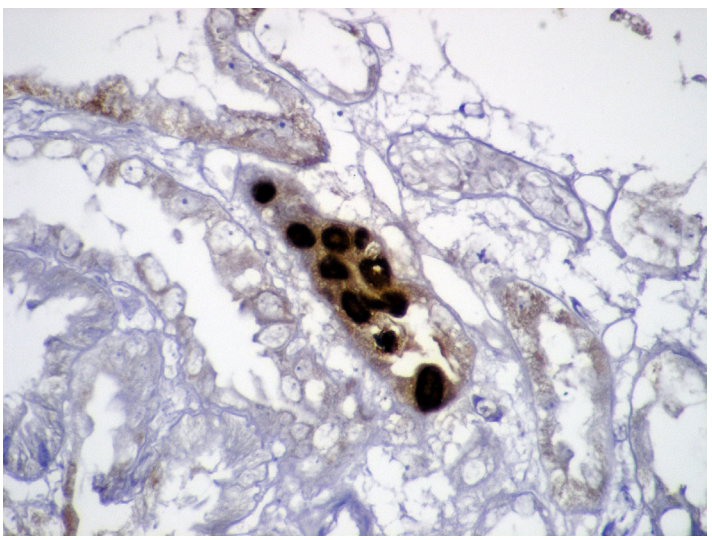

Fig 2–In-situ hybridization positive for BK viral DNA in renal tubular epithelial cells.

positive for BK viras infection localized to the renal tubules (Fig 2). Immunohistochemistry for CMV viral particles showed weakly positive staining in the renal tubular cells. The patient's serum was tested for BKV with a quantitative multiplex real-time PCR assay: the report showed it was undetectable at fewer than 10 copies/ml. Partial ureteric obstruction was diagnosed by renal ultrasonography and an antegrade pyelogram demonstrated delayed excretion at the proximal ureter with moderate hydronephrosis. Because of the BKVN and ureteral stenosis, the immunosuppressive regimen was changed to cyclosporine, low dose prednisolone, and leflunomide. A temporary percutaneous nephrostomy was performed and her SCr remained at 2.2 mg/dl. The patient developed BK viremia with 304,549 copies/ml seen three months after the histological diagnosis of BKV nephropathy. Immunosuppressive medications were further reduced and the patient's SCr remained at 2.4 mg/dl.

## DISCUSSION

BKV is an urotheliotropic virus that becomes latent in the urinary tract after primary infection and is recognized as an important cause of graft failure in kidney transplant recipients (Shinohara *et al*, 1993). Viral replication begins early after transplantation and progresses in a usual sequence: viruria, viremia, then nephropathy (Brennan *et al*, 2005). When the infection increases, the markers of viral replication also increase. A screening test for BKV replication is urine cytology for decoy

cells or urine BKV DNA load. BKVN is suspected when finding a urine BKV DNA load of $>10^7$ copies/ml or a plasma BKV DNA load of $>10^4$ copies/ml (Costa and Cavallo, 2012). BKVN is confirmed by renal biopsy with the pathology showing typical basophilic intranuclear inclusion bodies in the tubular epithelial cells with tubulointerstitial inflammation along with finding SV40 large-T antigen on immunohistochemical staining (Drachenberg and Papadimitriou, 2006). The BKV DNA viral load is determined with a quantitative multiplex real-time PCR assay which has a sensitivity ranging from 72% to 100% (Randhawa *et al*, 2004; Viscount *et al*, 2007; Boudreault *et al*, 2009; Bechert *et al*, 2010; Rubio *et al*, 2010; Stellrecht *et al*, 2013). Previous studies have found the accuracy of using the BKV DNA viral load detected with a quantitative multiplex real-time PCR assay depends on the use of standardized reference materials, PCR primers and probes (Hoffman *et al*, 2008).

We reported here a patient with BKVN detected 14 months post-kidney transplant who had an elevated SCr but no detectable BK viremia. A previous report found BK viremia can appear several weeks to months after kidney transplantion prior to the histopathological changes of BKVN (Bressollette-Bodin *et al*, 2005). The mean BK viral load in plasma is significantly higher in patients with biopsy-proven BKVN than in patients without histologic evidence of nephropathy (Hirsch *et al*, 2002). The correlation between the viral load and allograft involvement suggests BKV viremia is due to replication in the transplanted organ. This theory is supported by the rapid drop in BK viral load among patients who underwent nephrectomy (Limaye *et al*, 2001). Screening for BKV viruria and viremia with PCR is useful for identifying patients at risk for BKVN, since immunosuppressive therapy in such patients can be tailored for those with viremia. However, BK viruria and viremia are not predictive of BKVN (Bressollette-Bodin *et al*, 2005). BK viremia was not quantitatively related to BK viruria (Leung *et al*, 2002). One study found 2 out of 7 patients with biopsy proven BKVN had BK viremia 6-11 month later (Renoult *et al*, 2010). This could reflect independent BKV reactivation in different tissue (Leung *et al*, 2002). In our patient, BKVN was observed without detectable BK viremia, which might be due to BKV reactivation in the urogenital epithelium before the development of BK viremia. A limitation in this case report is the patient was not tested for BK viruria.

Patients who receive intense immunosuppression, such as the aggressive treatment of rejection, need to have BK virus monitoring. In suspected cases with a rising SCr, even though the PCR assay for BKV DNA viral load is negative, a kidney biopsy should be considered since not finding BK viremia does not exclude the possibility of developing BKVN (Knight *et al*, 2013).

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