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Late-Onset BK Viral Nephropathy in a Kidney Transplant Recipient

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ABSTRACT

BK polyoma viral infection occurs as an asymptomatic infection in a high proportion of normal hosts without obvious sequelae. In the kidney transplant population, the virus is reactivated because of reduced immunity and, if not appropriately managed, can lead to BK viral nephropathy, which has emerged as a common cause of acute kidney injury and progressive chronic kidney disease in renal transplant recipients. BK viremia almost always occurs during the first 2 years after transplantation, when immunosuppressive therapy is high, or at other periods when immunosuppression is intensified. BK viremia is now detected by routine screening of transplant patients for the first few years, and BK viral nephropathy is considered to be high in the differential diagnosis of acute kidney injury in recently transplanted patients. We report a case of BK viral nephropathy developing 10 years after transplantation and present the challenges of managing advanced disease.

THE BK virus is a member of polyomavirus family that causes asymptomatic infection in a large proportion of the healthy population, particularly in childhood [1]. After a primary infection, the virus is dormant, but it becomes activated in some people with depressed immunity. This is particularly a common problem in kidney transplant recipients, with BK viremia reported in up to 20% of patients in the first few years after transplantation [2]. In these patients, BK viremia, if uncontrolled, leads to acute and then to chronic tubulointerstitial nephritis with progressive interstitial fibrosis, tubular atrophy, and eventually end-stage renal disease. The usual treatment strategy when BK viremia is detected before BK viral nephropathy is reduction in immunosuppression with selective use of agents thought to have anti-BK viral efficacy. The management is more challenging when patients present with advanced BK viral nephropathy. We report a case which presented as BK virus nephropathy 10 years after renal transplantation. Once diagnosed, a reduction in immunosuppression along with specific antiviral therapy substantially reduced viremia. However, despite therapeutic efforts, the residual allograft damage was significant.

CASE REPORT

A 50-year-old man with type 1 diabetes mellitus diagnosed at age 18 months and progressive chronic kidney disease underwent a combined deceased-donor kidney-pancreas transplant in October 2002. He was induced with antithymocyte globulin and transitioned to tacrolimus, mycophenolate mofetil (MMF), and prednisone

maintenance therapy. Although he had prompt pancreatic allograft function with adequate glycemic control, he had slow renal allograft recovery. His serum creatinine declined from a preoperative value of 4.1 mg/dL (estimated glomerular filtration rate [eGFR], 16 mL/min) to 1.8 mg/dL (eGFR, 42 mL/min) over 3 weeks. He was placed on infection prophylaxis according to our protocol. His ureteral stent was removed at 6 weeks without any complications.

Three months after transplantation, MMF was held for neutropenia. Ten days later he was admitted with flu-like symptoms, elevated blood sugar levels up to 500 mg/dL, and an increase in serum creatinine to 1.4 mg/dL. An allograft pancreas biopsy showed no histologic evidence of rejection, whereas an allograft renal biopsy showed borderline changes of acute cell-mediated rejection. MMF was resumed and he was treated with antithymocyte globulin along with insulin for glycemic control. In a matter of few days he became normoglycemic off insulin. By this time his serum creatinine had reached a nadir of 1.1 mg/dL (eGFR, 75 mL/min). Two years later, he continued to have excellent function of both allografts but developed progressive sensorineural hearing loss. There was no cause identified for his sensorineural deafness which ultimately needed cochlear implants. His tacrolimus level ranged from 5.5 to 8.6 ng/mL. His creatinine remained in the range of 0.9–1.1 mg/dL until April 2008 and rose to 1.5 mg/dL by early 2009. This was followed by a tacrolimus dose reduction, and the levels were maintained at a new therapeutic target of 3–6 ng/mL for the next 2 years.

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In the latter part of 2009 his creatinine had risen to 1.7 mg/dL, which was thought to be due to hypovolemia related to new-onset intermittent daytime diarrhea. Work up for diarrhea revealed mild nonspecific colitis on colonoscopy. He was empirically placed on pancreatic enzyme supplements, antimotility agents, and sulphasalazine, and the MMF dose was reduced. Following this, he had symptomatic improvement in diarrhea and creatinine reached a nadir of 1.4 mg/dL in 2010. In 2012 his creatinine progressively increased to 3 mg/dL. At this time he was noted to be BK viremic with 1.7 million copies of BK virus DNA per mL of plasma. Subsequent renal biopsy confirmed BK viral nephropathy with severe tubulointerstitial inflammation (Fig 1). MMF was stopped and leflunomide initiated. He was treated with 3 doses of cidofovir at weekly intervals and later given oral ciprofloxacin for 2 months. Following cidofovir, creatinine peaked at 8.9 mg/dL, although BK viral counts decreased to <5,000 copies per mL (Fig 2). In the following weeks his creatinine started to improve and reached a nadir of 3.9 mg/dL. At the time of writing, almost 2 years after the diagnosis of BK viral nephropathy and the subsequent therapy with cidofovir, he continued to be dialysis free, with creatinine 3.9–4.5 mg/dL (eGFR, 17–20 mL/min) and BK viral counts 1,800–2,800 copies per mL. His current immunosuppression included tacrolimus, leflunomide, and prednisone.

DISCUSSION

Epidemiology and Pathogenesis

The BK virus is a nonenveloped DNA virus, a member of polyomavirus family that was first described in 1971 [3,4]. In the normal host, BK viral infection is asymptomatic, usually in

childhood, with a prevalent seropositivity of up to 94% in healthy adults [1]. Primary infection is thought to be usually acquired via the respiratory tract, although infections can also occur through urinary shedding, semen, blood transfusion, and organ transplantation [5]. The natural history indicates that the virus is dormant after primary infection and reactivates during periods of reduced immunity. The reactivation manifests as BK viremia, BK viremia, and nephropathy, with incidences up to 40%, 20%, and 7%, respectively, after renal transplantation [2]. Factors (other than immunosuppressive therapy) associated with an increased risk of post-transplantation BK virus replication are older age, male sex, white race, diabetes mellitus, deceased-donor transplants, greater HLA mismatch, absence of HLA C-7 in donor and recipient, acute rejection, recipient BK virus seronegativity, donor BK virus seropositivity, high donor antibody titer, longer cold ischemia time, use of ureteral stents, delayed graft function, more recent transplantation year, lower center transplant volume, and poor cellular immune response [6–8]. Typically the infection occurs in the first 2 years after a kidney transplantation [2]. We report a case which presented as BK viral nephropathy 10 years after renal transplantation.

The virus, which has renal tropism, enters the cell via caveolin-1-mediated endocytosis and integrates with the host DNA [9]. The latter contributes to the dormant stage of the infection. When activated, its cytopathic effect initially manifests as swollen nuclei and cytoplasm. Subsequently, cell lysis occurs with release of virions, permitting

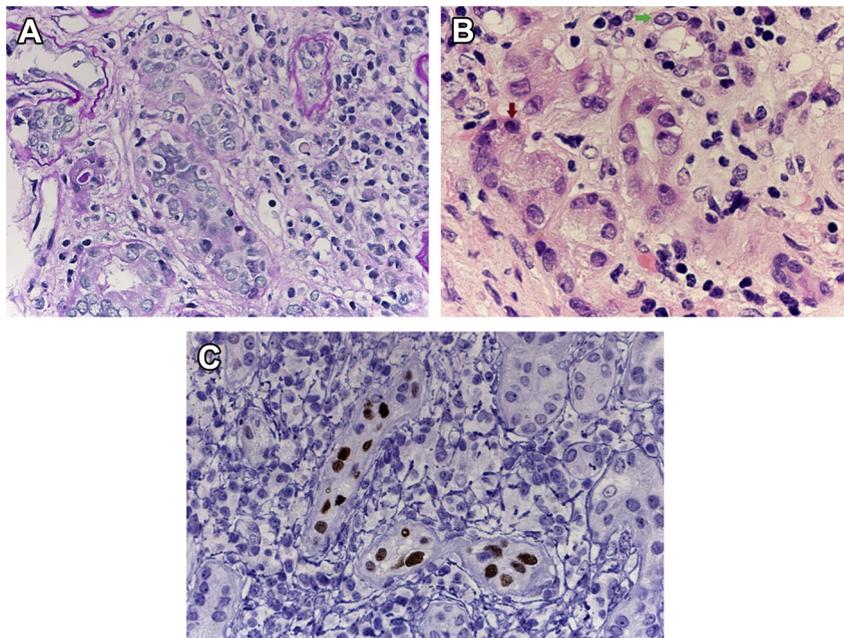


Fig 1. BK viral tubulointerstitial nephritis. **(A)** Periodic acid–Schiff staining of kidney biopsy, showing tubulitis and interstitial inflammation. The interstitial infiltrating cells are mononuclear lymphoplasmacytic cells. The tubular basement membranes are thickened. **(B)** Hematoxylin and eosin stain, showing marked virus-induced cytopathic changes, with features of acute tubular injury, prominent nuclear enlargement, and anisonucleosis consistent with polyomavirus-induced tubulopathy. *Red arrow:* nuclear homogeneous basophilic chromatin; *green arrow:* chromatin margination. **(C)** Immunoperoxidase stain of kidney biopsy with antibody to SV40 large T antigen, showing BK virus-infected tubular epithelial cells with polyomavirus staining the nuclei (*brown colored*).

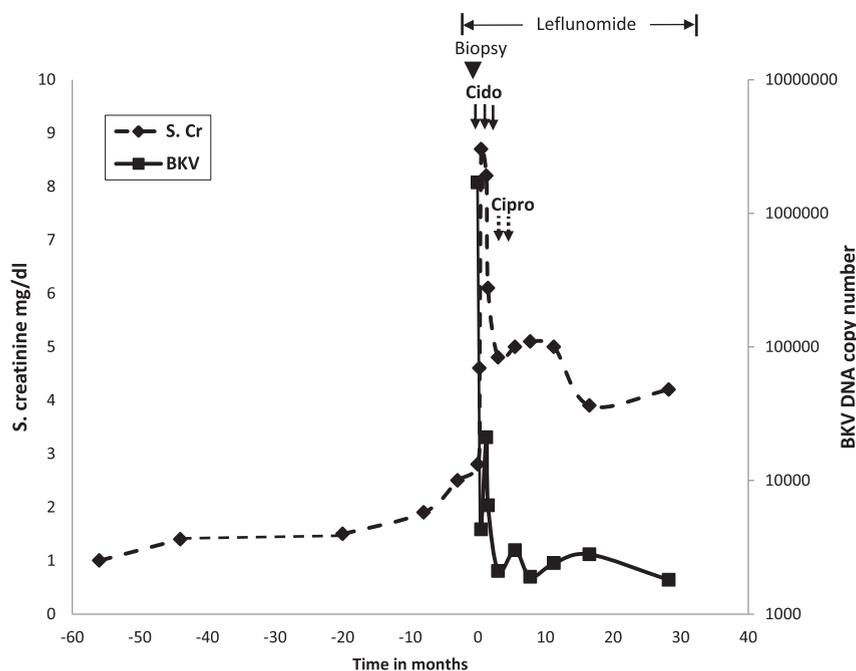


Fig 2. Laboratory parameters and associated treatments. Serial measurements of serum creatinine (S. Cr) and BK virus DNA copy number (BKV) are shown. Three separate doses of cidofovir (Cido) were given early in the course of treatment, and 2 months of ciprofloxacin (Cipro) were given right after.

local spread of the virus to adjacent renal tubular cells. The infection is propagated by a combination of cellular and humoral immune deficiencies along with poor immune surveillance [10]. Interestingly, the higher incidence of BK virus nephropathy in kidney transplants (compared with heart and liver transplants) raises suspicion of a potential role of alloactivation in the pathogenesis [10]. Cellular immunity seems to be the major defense against BK viral infection, with interferon- γ secreting T lymphocytes acting as the primary defense. The viral large T antigen and VP1 (viral structural protein 1) gene products are responsible for CD4 and CD8 cell activation [10]. Humoral immunity has a lesser role in the pathogenesis.

Clinical Features and Diagnosis

BK virus can cause primary infection as well as reactivation. Primary infection can manifest as hemorrhagic and non-hemorrhagic cystitis in the immunosuppressed host, particularly in bone marrow transplant patients. BK virus has also been described to cause encephalitis, hepatitis, pneumonia, inflammatory polyneuropathy, and tubulointerstitial nephritis. When the disease is due to secondary reactivation, it can manifest as ureteric stenosis, retinitis, meningoencephalitis, and desquamative interstitial pneumonia, as well as the usual presentation of tubulointerstitial nephritis [11,12]. Because the seroprevalence in North America is high, BK viral reactivation is seen more commonly than primary infection [13]. This usually presents in the first year after transplantation, though rarely cases have been reported as late as 5 years [14]. The infection is mostly asymptomatic and classically diagnosed during a work-up for increase in creatinine levels following renal transplantation. Today, BK viremia and BK

viral nephropathy often diagnosed by routine screening of blood and/or urine for BK virus by polymerase chain reaction or protocol biopsies after a renal transplantation.

Among renal transplant patients there are reports of BK viral infection manifesting as cystitis and ureteral stenosis with subsequent hydronephrosis. However, they are very uncommon compared with tubulointerstitial nephritis, probably because the urologic manifestations happen much later in the natural history of the disease. Although up to 40% of the renal transplant recipients have viruria, only ~10% develop nephropathy [15]. Shedding in urine of BK viral-infected cells (“decoy cells”) that have a large basophilic intranuclear inclusion are a classic pathognomonic feature of the BK viral infection. Although the sensitivity of decoy cells approaches 100%, the positive predictive value for BK viral nephritis is <30% [16]. Quantification of viral DNA in the blood and urine seems to be more specific and sensitive with a positive predictive value closer to 50%. There is a positive correlation between higher viral counts and incidence of BK viral nephritis. BK viruria precedes BK viremia by a median of 4 weeks, and BK viremia precedes histologically documented BK disease by a median of 12 weeks [16]. Renal biopsy is the standard criterion for BK viral nephropathy, with classic findings of tubular cytopathic changes along with nuclear inclusions that are more pronounced in the distal convoluted tubule and collecting duct. A viral specific stain such as for the SV40 T antigen increases the diagnostic accuracy.

Treatment

The principles of therapy are a reduction in immunosuppression and, in more advanced cases, the use of drugs

thought to have anti-BK virus efficacy, with close monitoring for change in renal function which may be secondary to subsequent allograft rejection, progressive BK viral nephritis, or drug nephrotoxicity. Generally, the antimetabolite (MMF or azathioprine) is first withdrawn and the intensity of other immunosuppressive therapy is reduced. Both cyclosporine and sirolimus has been shown to inhibit BK viral reactivation in vitro and therefore a conversion from tacrolimus to cyclosporine or sirolimus might be considered [17].

In early BK viral nephropathy, reduction of immunosuppression may be sufficient, 3-year graft survivals of 88%–100% being reported [17,18]. In those and other studies, viremia cleared in 92%–95% of patients, with a mean time to clearance of 54 days [18,19]. In contrast, rejection rates of up to 30% have been reported with reduction in immunosuppression alone, and allograft loss of 35%–50% despite reduction in total immunosuppression [20,21].

In late BK nephropathy with severe histologic changes and poor renal function, the pathology may continue to progress even if immunosuppression is reduced. However, some studies show that the rate of decline of GFR can be slowed by 40% with a reduction in immunosuppression alone [22]. On average, the burden of graft loss varies and may range from 15% in adults to 50% in the pediatric population [23].

Anti-BK virus therapies include the use of quinolones, cidofovir, leflunomide, and intravenous immunoglobulin, which are sometimes used alone or in combination. Cidofovir, which is a DNA polymerase inhibitor, inhibits BK virus (which paradoxically does not have any DNA polymerase) by restoring the function of p3 and pRB which are tumor suppressor genes and thereby permits BK virus-infected cell apoptosis [24]. Its use in doses of 0.25–1 mg/kg every 1–3 weeks has been shown to have a relative risk reduction of 70% [25]. However, cidofovir can by itself cause acute tubular injury, proximal tubular cell apoptosis, and Fanconi syndrome, with the effect typically peaking by the 7th day of therapy [26]. Quinolones have in vitro as well as in vivo effects on the BK virus. Observational studies have shown a reduction in the incidence of BK nephropathy with 1 month of ciprofloxacin therapy, and the “antiviral” effect seemed to persist even a year after the completion of treatment, suggesting that it can be used for the primary prevention of BK viral infection [27]. The clinical use of intravenous immunoglobulin has been limited owing to lack of clear benefit [28]. Leflunomide has been shown to have substantial antiviral effects in vitro and in vivo. Both observational studies and the only randomized controlled trial have shown a reduction in BK virus counts with leflunomide, although there was more rejection in the leflunomide arm [29,30].

In the present case, we could not be certain when BK viral replication began. We considered the possibility that this might have been a late primary infection, given the delayed presentation. It is unclear whether the colitis and the sensorineural hearing loss were, in fact, part of the primary BK viral infection. It is difficult to distinguish a primary

infection from secondary reactivation. Primary infections are more often described in bone marrow transplant patients where they can manifest as cystitis. The serology tests have a limited role in distinguishing primary infection from secondary reactivation in solid organ transplant patients. In the United States, where the seroprevalence of BK viral infection is very high, the likelihood of encountering a secondary reactivation is higher. Our case demonstrates that BK viral infections can be a cause of severe tubulointerstitial nephritis years after a renal transplant without intensification of immunosuppression as an antecedent event. Therefore, it needs to be considered in the differential diagnosis for worsening renal allograft function regardless of the time period after transplantation. A detailed literature search failed to identify any earlier reports of BK viral infection occurring this late after transplantation.

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