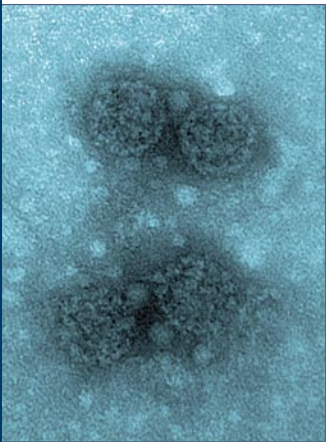


BK Virus Overview

ABOUT THE VIRUS

BK is a member of the Polyomaviridae family, which are small, nonenveloped viruses with a closed, circular double-stranded DNA genome. Polyomaviruses are ubiquitous in nature and can be isolated from a number of species. BKV and JCV make up the members of the human polyomaviruses. BK virus was first isolated in 1971 from the urine of a renal transplant patient who developed ureteral stenosis postoperatively. The virus was named after the initials of this first patient. Primary infection with BKV typically occurs in childhood, probably as a mild upper respiratory infection. Studies suggest over 90% of the population has been infected with BK virus by the age of ten years. Following primary infection, the virus establishes latency in the urogenital tract where it remains for life. Reactivation of the virus can occur spontaneously or, more commonly, in an immunocompromised host.



Polyomavirus viewed at 340,000x (negative staining) by transmission electron micrograph. Image courtesy of UMICH.

CLINICAL MANIFESTATIONS

BK virus associated renal allograft nephropathy (BKVAN) has emerged as a major cause of renal allograft dysfunction worldwide since the early 1990s. This emergence seems to have coincided with the widespread availability of potent immunosuppressive drugs. BKVAN can be a difficult clinical problem with a prevalence rate of 1-10% and a graft loss rate of 10-80%, depending on the center's BK screening program and use of immunosuppression.

In renal allograft recipients, BK reactivation most frequently manifests itself as a nephropathy. However, in hematopoietic stem cell transplant (HSCT) patients, hemorrhagic cystitis is frequently seen. Less common presentations of BKV reactivation include echogenic mass, interstitial nephritis and ureteric stenosis. Pediatric renal transplant patients that are seronegative at the time of transplantation seem to be at particularly high risk of BKVAN, although this requires further study for confirmation. These patients may present with a viral prodrome consisting of low grade fever, myalgia and mild gastroenteritis prior to onset of allograft dysfunction.

Despite recent advances in BK diagnostics, it remains unclear why only a small number of renal transplant patients, the majority of who are seropositive for BKV, develop full

blown renal disease. Several efforts have been made to identify risk factors for development of BKVAN. Specific immunosuppressive agents, such as tacrolimus and mycophenolate mofetil (MMF), are generally believed to be associated with a higher incidence of BKVAN. However, BKVAN has been observed with all immunosuppressive regimens. It may be more plausible that patients whose immunosuppression is maintained at a higher total level, rather than with a specific agent, have an increased incidence of BKVAN. Other risk factors that have been associated with an increased risk of BKVAN include: HLA mismatch, the use of corticosteroid pulses to treat graft rejection, cell injury due to acute rejection or cold ischemia, male gender and BKV serology. However, many other studies have contradicted these associations. Recently, host and viral genomic variation have also been correlated with development of BKVAN. DNA sequence variations in several putative transcription factor binding sites in the noncoding control region (NCCR) of the BK genome and polymorphisms of several cytokine genes have been proposed to play a role in the pathogenesis of BKVAN. The effect of mutations within the BKV genome on therapy outcome is unknown at this time. It seems that BKVAN is promoted by the concurrent presence of several risk factors, among which immunosuppression appears to be a prerequisite.

LABORATORY DIAGNOSIS

The key to confirming the diagnosis of BKVAN remains the recognition of BKV inclusions in tubular and glomerular epithelial cells in renal allograft biopsy specimens. Viral inclusions in BKVAN are often associated with variable mononuclear interstitial infiltrates and focal tubulitis, which closely resembles acute rejection.

Because of the focal nature of BKV replication in the kidney, negative biopsy results cannot rule out BKVAN. Interestingly, the diagnosis of BKVAN is often preceded by a diagnosis of acute rejection episode(s) in many patients. These episodes are, or tend to gradually become, nonresponsive to conventional therapy. It is unclear if these rejection episodes may be early stages of BKVAN, prior to the viral inclusions becoming conspicuous on biopsy. Thus, a high index of suspicion is needed for diagnosis of BKVAN, especially in patients who present an unexplained rise in serum creatinine or have episodes of acute rejection that are refractory to steroid therapy.

Molecular detection methods, such as real-time PCR, provide a sensitive and noninvasive means to detect BKV in urine and blood. Molecular detection of BKV allows patients to be placed on a regular monitoring program that allows detection of the virus prior to development of nephropathy (and therefore kidney damage). There are numerous studies in the literature demonstrating rising BK urinary loads, by real-time quantitative PCR, prior to presentation with full blown BKVAN. Such a scenario can often predict and predate BKVAN by several weeks to several months. Urinary viral load of more than 10,000,000 copies/ml has now been proposed to be a significant risk factor for BKVAN. A rising titer of several log orders can also be of clinical significance. Besides the role of urinary BKV viral load in BKVAN management, especially in early stages, real-time PCR analysis of blood samples to detect and quantify BKV DNA is rapidly becoming the test of choice for confirming diagnosis and monitoring progression of active BKVAN. The sensitivity of DNA PCR is considered to be 100% and the specificity approximately 85%. The interdisciplinary panel of BKV experts that met in Basel, Switzerland in October 2003 proposed a titer of > 10,000 copies/ml in plasma (or serum) to be a significant marker of BKVAN with a specificity of $\geq 93\%$. The panel recommended renal allograft recipients be screened for BKV replication in the urine every three months for the first two years following transplant and annually thereafter until the fifth year post-transplant, in addition to performing urinary screening whenever an allograft biopsy is performed, whether it be for allograft dysfunction or surveillance biopsy.

To view the panel's recommendation in further detail go to: *Transplantation*; Volume 79, Number 10, May 27, 2005

TREATMENT

Although various therapeutic strategies have been tried for BKVAN, the results are variable with graft loss rate ranging from 10 to 80%. In most centers, BKVAN is initially treated by lowering immunosuppression and sometimes additionally by discontinuing drug regimens containing tacrolimus. These therapeutic attempts can result in good clinical success if BKVAN is diagnosed during an early stage, thus emphasizing the need for regular monitoring. Several centers have reported significantly improved graft survival rates upon initiation of a monitoring program. If lowering of immunosuppression does not result in resolution of nephropathy, a consideration for the institution of additional therapy should be made in an expeditious manner. Currently, specific antiviral strategies for BKVAN are poorly defined, although low dose cidofovir (0.25-1 mg/kg without probenecid) has been successful in a number of cases. Additionally, there have been reports of successful use of leflunomide in resolving BKVAN.

CONCLUSION

There remains much to be learned regarding risk factors, both viral and recipient, as well as in treatment and prevention strategies. There is a critical need for development of antiviral drugs that will inhibit the replication of BK virus.

Selected References

Hirsch HH, Brennan DC, Drachenburg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation*. 2005;79(10):1277-1286.

Knipe D, Howley P. *Fields Virology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

Limaye AP, Jerome KR, Kuhr CS, et al. Quantitation of BK virus load in serum for the diagnosis of BK virus-associated nephropathy in renal transplant recipients. *J Infect Dis*. 2001;(183):1669-1672.

Nickeleit V, Klimkait T, Binet IF, et al. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. *N Engl J Med*. 2000;(342):1309-1315.

Scantlebury V, Randhawa P, Shapiro R, et al. Cidofovir: A Method of Treatment for BK Virus-Associated Transplant Nephropathy. *Graft*. 2002;5(suppl):S82-S87.

Vats A, Shapiro R, Scantlebury V, et al. BK Virus associated nephropathy and cidofovir: long term experience. [abstract]. *Am J Transplant*. 2003;3(suppl 5):A190.

