

BK virus nephritis after renal transplantation

S Hariharan¹

¹Division of Nephrology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

BK viremia and nephritis are increasing problems in renal transplant recipients. The exact cause of the increasing prevalence of this condition remains poorly understood. Increasing prevalence has been correlated with newer immunosuppressive agents and the decline in acute rejection rates in recent years. The clinical manifestation varies from the asymptomatic state of viremia and nephritis to clinical renal dysfunction. The diagnosis of this infection is based on the combination of the presence of urinary decoy cells, virus in the urine/blood, and typical renal histological findings of interstitial nephritis. Routine post-transplant screening for BK viremia and viruria prior to the occurrence of nephritis and the reduction in immunosuppressive therapy for subjects with viremia appear to be attractive approaches. The treatment of BKV nephritis (BKVN) consists of reduction in immunosuppressive therapy and antiviral therapy with cidofovir or leflunomide or a combination of both. Approximately 30–60% of subjects with BKVN experienced irreversible graft failure. However, in recent years, the combinations of early detection, prompt diagnosis, and appropriate reduction in immunosuppressive therapy have been associated with better outcome. The pathogenesis of BK virus infection in renal transplant recipients needs to be explored. The source of BKV infection (donor as opposed to recipient), the role of host humoral, and cellular immunity to BKV, and the role of alloimmune activation in renal graft to the occurrence of nephritis are discussed in this review.

Kidney International (2006) **69**, 655–662. doi:10.1038/sj.ki.5000040; published online 4 January 2006

KEYWORDS: BKV-nephritis; renal transplantation; diagnosis; treatment; pathogenesis

VIROLOGY

BK virus belongs to the virus family polyomaviridae. Human polyoma viruses are of two types: JC manifests as viral encephalopathy and BK as viral nephritis. JC and BK represent initials of patients in whom they were first detected. There are other types of polyoma: a murine form that is known as murine polyoma virus and a simian form that is known as simian virus (SV)40. Viruses of the family polyomaviridae contain a 5000 base-pair genome composed of double-stranded deoxyribonucleic acid (DNA) that replicates in the host nucleus. Each polyoma virus encodes three capsid proteins, viral protein (VP)1, VP2, and VP3. VP1 is the only VP exposed on the outer shell of the virion, and contains a small groove that interacts with cellular receptors. BKV is classified into four major sero/genotypes: group I encodes the prototype strain Dunlop (Dun), MM, and GS; group II encodes the SB strain; group III encodes the AS strain; and group IV encodes the MG strains. The BK viral genome has a region that contains the origin of replication, transcriptional enhancer regions, and transcriptional promoter regions called the noncoding control region (NCCR).

HISTORY OF BKV NEPHRITIS

The terminology of BK virus originated from a renal transplant patient, initial BK, in whom it was first detected as a clinical disease in 1971.¹ There were no reported cases of this disease for the next 24 years, until Purighalla and co-workers observed their first case in early 1995.² Subsequently, there has been a surge of BKV nephritis (BKVN) cases from many transplant centers across US, including ours.^{3–8} The key factor associated with this increasing incidence remains unclear. Introduction of immunosuppressive agents such as mycophenolate mofetil (MMF) and Tacrolimus (Tac) has been thought to play a causative role in BKVN. However, this infection is also seen in patients who have never received the above combinations of immunosuppressive agents, as well as those receiving sirolimus, and those with steroid avoidance protocols. Thus, in recent years, the incidence of this infection has increased in renal transplant recipients and now poses a threat to improving graft survival.^{6,7}

PREVALENCE OF BKV INFECTION

Approximately 80% of the general population has a detectable antibody to BKV, which appears early in life and remains elevated throughout life.^{9,10} Antibodies to antigen

Correspondence: S Hariharan, Division of Nephrology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, Wisconsin 53226, USA. E-mail: hari@mcw.edu

Received 9 July 2005; accepted 13 September 2005; published online 4 January 2006

VP1 crossreact with SV40, BKV, and JCV;¹¹ however, a specific monoclonal antibody can be used to differentiate various viruses. The prevalence of this virus in the end-stage renal disease population, kidney donors, and transplant recipients has not been well defined.

The prevalence of BK viremia, viremia, and nephritis after renal transplantation has been estimated at 30, 13, and 8%, respectively.¹² The overall prevalence of BKVN at the Medical College of Wisconsin from 1996 to 2004 is 4.2%, that is, 48 out of 1139 renal transplants. Viremia and viruria are also seen in liver, heart, and lung transplant recipients, but with a lower prevalence than in renal transplant recipients. Although reported, the incidence of clinical native renal BKVN is rare following other solid organ transplant recipients such as liver, heart, and lung. Clinical BKVN has occasionally been seen in immunosuppressed human immunovirus patients as well as in individuals with immunodeficiency syndromes, and rarely in other immunosuppressed individuals with systemic lupus erythematosus.^{13,14}

CLINICAL FEATURES, DIAGNOSIS, RISK FACTORS, AND OUTCOME

Clinical features

Most renal transplant recipients with BKVN manifest with renal dysfunction.^{4,7,8,15,16} Occasionally, subjects can also present with ureteric obstruction and hydronephrosis, and cases of cystitis have been reported.¹⁷ In recent years, routine post-transplant protocol biopsy has also detected BKVN in the absence of serum creatinine elevation.^{18,19} Progressive renal failure has been reported in approximately 30–60% of cases.^{7,8,20} Rare fatal disseminated BK virus infection after cadaveric transplantation has also been reported.²¹

Diagnosis

The diagnosis of BKV infection is based on the documentation of viral cytopathic effects (urinary decoy cells), the virus itself (in blood, urine, and/or renal tissue), immunity to virus

(BKV-specific antibody), and renal histological findings of nephritis. Each diagnostic modality and its limitations are shown in Table 1. Urinary decoy cells are a good diagnostic screening test, but the positive predictive value is around 20%. Thus, demonstration of urinary decoy cells suggests the presence of BKV in urothelium, but does not confirm BKVN.

Circulating BKV DNA in plasma has been seen in approximately 10–40% of renal transplant recipients.^{22,23} However, not all viremic subjects have clinical nephritis. Demonstration of viremia by blood polymerase chain reaction (PCR) is a reliable test for nephritis, as it is seen in nearly 100% of the cases with BKVN. However, the positive predictive value for nephritis is only 60%. Viruria is seen in 30–40% of renal transplant recipients and the quantity is 100-fold over that of blood.^{6,12,24} Similar to blood BKV DNA, the utility of urinary BKV DNA has an excellent negative predictive value, but a poor positive predictive value; an alternative approach is to amplify viral VP1 messenger ribonucleic acid (mRNA) in urine, as it may represent active BKV replication.²⁵ From this single study, positive and negative predictive values for mRNA in urine are above 90%; however, this must be confirmed in further studies. The levels of circulating plasma BKV DNA correlating with BKVN remain controversial; Hirsch *et al.*¹² reported copies greater than 7000 with acute BKVN. However, BKVN can occur even with copies as low as 1000 copies (personal observation) and better correlation has been noted with persistent viremia.

The diagnosis of BKVN is usually made by the demonstration of viral cytopathic effect in renal histology with inflammatory response. Renal involvement can be focal in earlier stages and could have predominant fibrotic changes with minimal inflammatory changes in the later stages of the disease.²⁶ Nonetheless, histological findings remain the gold standard diagnostic test (Figure 1) and typical findings are focal interstitial mononuclear inflammatory cell infiltrates, presence of plasma cells, necrotic tubular epithelium, and

Table 1 | Diagnosis of BK virus nephritis

Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40–60% of transplant recipients, good screening test, positive predictive value around 20%
Viremia (plasma BKV DNA)	Copies > 7000 per ml of plasma	Seen in 10–20% of transplant recipients, good screening test, positive predictive value around 60%
Viruria (urinary BKV DNA)	Copies 100-fold higher than plasma values	Seen in 30–40% of transplant recipients, good screening test, positive predictive value around 40%
Urinary BKV mRNA (active viral replication)	Copies diagnostic of BKVN	To be confirmed in other studies, research tool
BKV DNA in renal tissue	Detection of BKV DNA in renal biopsy tissue	Negative predictive value 100%, positive predictive value around 70%
Renal histology	Inflammatory changes with viral cytopathic effects, positive immunoperoxidase reaction with SV40 stain, predominant CD20-positive lymphocytic infiltrates	Gold standard, invasive procedure, focal lesions, chronic state with minimal viral cytopathic effects, mimics acute rejection
Serum BKV-specific antibodies	Diagnostic levels of IgM and IgG?	Seen in 80–90% of general population
BKV-specific antibodies and BKV DNA	Diagnostic levels of BKV-specific antibodies IgM, IgG and BKV DNA?	Research tool
T-cell immunity	Diagnostic measurement?	Research tool

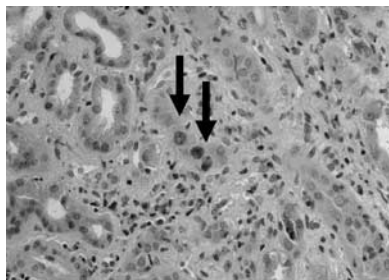


Figure 1 | Renal histological findings of interstitial infiltrates and viral cytopathic effects in a case with BKVN.

presence of homogenous intranuclear inclusion bodies. Renal interstitial inflammation with BKVN cannot always be differentiated from acute rejection. Immunohistochemistry with SV40 staining has been used as an indirect method to document the presence of BKV in renal tissue. Demonstration of predominant CD20-positive lymphocytes (B cells) in renal histology is suggestive of BKV infection.⁷ The degree of acuity and chronicity can be differentiated by the degree of inflammatory response and fibrosis.²⁶

Prior exposure to this virus can be demonstrated by the presence of BKV-specific immunoglobulin (IgG) antibody in the circulation. The high prevalence of this infection in the general population rules out BKV-specific antibody as a diagnostic test for BKVN.²⁷ The detection of Immunoglobulin-M(IgM) and degree of rise of IgM levels remain to be proven as a diagnostic method for acute BKVN. Recently, we have evaluated the role of BKV-specific antibody along with BKV DNA in cases of clinical BKVN.²⁸ Individuals with BKVN generally have a very high BKV DNA and low BKV-specific IgG levels. The subjects who recover from BKVN have undetectable viral copies in circulation with elevated BKV-specific IgG levels. Combinations of BKV-specific antibody and BKV DNA are a novel approach to diagnose as well as manage subjects with BKVN. Deficient humoral immunity in subjects with viremia and those with BKVN may be an important factor in the pathogenesis of this disease. Prompt increase in BKV-specific IgG antibody, with clearance of viremia and stabilization of renal function, was noted with reduction in immunosuppression in our series.²⁸

The natural history of BKVN varies from case to case, as illustrated in Figure 2. Our ability to diagnose BKVN was delayed owing to misdiagnosis of acute rejection, lack of knowledge about this disease in the mid-1990s, and unavailability of diagnostic tools such as BKV DNA and BKV-specific antibodies. Rapid progression of renal disease was common, with aggressive treatment for presumptive acute rejection, as shown by the evaluation of renal failure as 100/serum creatinine (Figure 2a). However, recent cases have been detected early using appropriate tools such as BKV DNA and BKV-specific antibodies. Prompt treatment with reduction in immunosuppression perhaps prevented further renal injury and arrested progressive renal failure in a case as shown in Figure 2b.

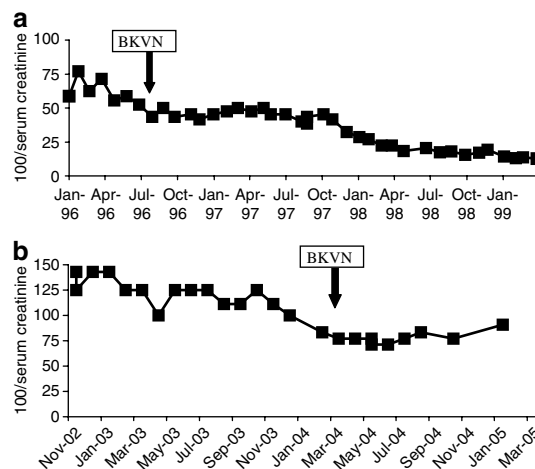


Figure 2 | (a) Evolution of renal function using 100/serum creatinine, illustrating progressive renal failure in a case with BKVN. (b) Evolution of renal function using 100/serum creatinine, illustrating stabilization of renal function in a case with BKVN.

Risk factors

Investigators have explored various risk factors associated with the occurrence of BKVN. However, no specific donor, recipient and transplant variables have been implicated in the occurrence of this disease. Seronegative subjects who receive kidneys from seropositive donors appear to have a higher chance of nephritis in a small pediatric study.²⁹ Deficient humoral and/or cellular immunity in subjects with BKVN may lead to a poorer outcome. In our recent analysis, individual immunosuppressive medications, cold ischemia time, plasma renin activity (PRA), organ source (living vs deceased), and human lymphocyte antigen (HLA) mismatches did not appear to point out single or multiple risk factors.³⁰ The level of renal dysfunction, defined as serum creatinine >2.2 mg/dl at the time of diagnosis of BKVN, correlated with poorer long-term graft survival.³⁰ In a recently published series, renal histological features of moderate to severe fibrosis have been shown to have poorer outcome.²⁶

Outcome

Approximately 40–60% of renal grafts with BKVN develop progressive graft loss. We observed lower graft survival in recipients with BKVN in 2001.⁷ In 2002, rapid graft failure was noted when intense treatment with antilymphocyte agent was implemented as a result of misdiagnosis as acute rejection.⁸ Investigators from the University of Maryland have reported a similar experience.²⁰ As of March 2005, we have diagnosed a total of 48 cases of BKVN out of 1139 transplants performed from January 1996 to December 2004. The actuarial renal graft survival of these 48 cases is lower than the rest of the transplant population, as shown in Figure 3. Graft failure occurred in 19 of 48 (39%) cases. In recent years, however, there is a trend toward lower graft loss, due to the combination of better diagnostic tools, prompt

diagnosis, and prompt reduction in immunosuppressive therapy.

TREATMENT OF BKVN

The management of BKV infection has been aimed at eliminating the virus, avoiding acute rejection, and preserving renal function. Potential therapeutic options and limitations are shown in Table 2. These include reducing immunosuppression alone and reducing immunosuppression as well as antiviral therapy such as cidofovir or leflunomide.^{31–33} Decreasing the level of immunosuppression in individuals with BKVN can lead to acute graft rejection. Thus, prevention of BKVN remains an optimal therapeutic approach.

Prevention of BKVN by monitoring BK viral loads in renal transplant patients is an important option, as BKV infection is diagnosed prior to or at an early stage of nephritis. This research is in its early stage, as what constitutes a normal, abnormal, and pathologic elevation in viral load is still being defined. In a recent analysis, using quantitative real-time PCR, we have measured the BK viral loads in kidney transplant patients and have seen that patients who are PCR-positive in the peripheral blood present with a wide range of viral loads.²³ Pre-emptive reduction of immunosuppression alone as a preventive therapy for BKVN appears

to be a safe and attractive option.^{22,23} In a recent large prospective study by Brennan *et al.*,²² pre-emptive reduction of immunosuppression was successfully performed in response to BK viremia and BKVN was prevented. Thus, prevention of nephritis by regular monitoring for viremia/viruria seems to be a good approach.

Leflunomide is an immunosuppressive agent, yet its metabolite A77 1726 has antiviral activity *in vitro* and in animals. In a recent report, leflunomide was used in 17 subjects with BKVN.³³ MMF was discontinued and Tac dose was decreased with loading dose of leflunomide at 100 mg/day for 5 days, followed by 20–60 mg daily, with a target trough blood level of 50–100 µg/ml. Marked reduction in viremia and viruria occurred in subjects who tolerated leflunomide, with a target level above 40 µg/ml. However, this reduction in viremia and viruria may be secondary to discontinuation of MMF and dose reduction of Tac. Cidofovir has been used in the treatment of BKVN in an uncontrolled fashion.^{31,32} However, as it is nephrotoxic, it is primarily excreted by the kidneys and adequate hydration is required. The use of other antiviral agents such as amantidine has been attempted unsuccessfully.³⁴ Vidarabine has been used in bone marrow recipients with cystitis³⁵ and gammaglobulin has been attempted to augment the immune response.

Our recent analysis of 25 cases with BKVN shows successful stabilization of renal function with reduction in immunosuppression alone.³⁰ Quantification of this evolution showed a loss of creatinine clearance of 4.8 ml/min/month for a period of 4 months prior to the diagnosis of BKVN, and a loss of 0.7 ml/min/month during subsequent follow-up. Reducing immunosuppression alone was successful and appears to be a safe and noncontroversial approach in 16 out of 25 cases, as documented by stabilization of renal function and clearance of viremia.³⁰

Modifying immunosuppression for subjects with BKVN, avoiding further renal injury, and delaying the progression of

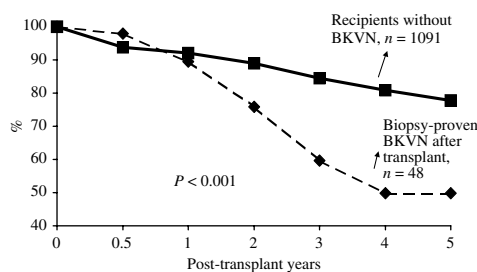


Figure 3 | Lower actuarial graft survival rates in patients with BKVN – results from the Medical College of Wisconsin 1996–2004.

Table 2 | Treatment of BKV nephritis

	Mode of action	Comments
Amantidine	Antiviral	Poor efficacy?
Vidarabine	Antiviral	Used in cystitis, efficacy in nephritis unknown
Cidofovir	Antiviral	Nephrotoxicity, potential benefit with reduction in immunosuppression, however, needs evaluation
Leflunomide	Antiviral	Potential clinical efficacy with therapeutic trough level (50–100 µg/ml) with reduction in immunosuppression
FK 778	Antiviral	Shorter-acting leflunomide, investigational agent, and efficacy unknown
Gammaglobulin	Augments immunity	Efficacy unknown
Reduction, discontinuation, and/or change in immunosuppressive agents (MMF, Tac, CSA, sirolimus, prednisone)	Decreasing immunosuppression	Safe and appears effective, risk of acute rejection in selected recipients
Prevention: monitoring viral disease (urinary decoy cells, viremia, viruria, and surveillance biopsy) and altering immunosuppression	Diagnosis of preclinical, subclinical, or early nephritis	Safe and effective with proper monitoring, risk of acute rejection with immunosuppressive alterations

renal failure remain the main focus of therapy. Measuring circulating virological and immune markers such as BKV DNA copies and levels of BKV-specific IgG antibodies should be used as a tool in managing BKVN. Measuring time to disappearance of BKV DNA from circulation, documentation of increase in BKV-specific IgG antibody level, and stabilization of renal function with the appropriate therapy should be used for defining treatment of BKVN.²⁸

Repeat transplantation has been successfully performed on subjects with graft failure due to BKVN.³⁶ A pooled analysis from five US transplant centers revealed that successful transplantation can be performed without recurrence in nine out of 10 cases, with a mean follow-up of over 2 years.³⁶ These subjects were virologically quiescent prior to their second transplant and their immunosuppression varied from center to center and from case to case. Thus, the risk of recurrent BKVN after second transplantation is low but real and should not be ignored.

PATHOGENESIS OF BKV NEPHRITIS

The exact pathogenesis of BKV infection leading to BKVN remains unclear. The hypothetical mechanisms involved are shown in Figure 4 and are as follows: source of BKV; immunological aspects such as host humoral and cellular immunity, alloimmune activation and immunosuppression medications; renal specificity such as tropism and ischemic injury; and viral virulence.

Source

There are two competing hypotheses regarding the source of BKV infection. The first hypothesis is that transmission occurs through the donor kidney.²⁷ In such a case, the transmission may occur directly through the transplanted organ in recipients who have never been exposed to BKV. In a recent pediatric transplant study with BKVN, the source of infection was thought to be derived from the donor, as many recipients were never exposed to this infection prior to transplantation.²⁹ However, the majority of adult renal transplant recipients have been exposed to this infection

prior to transplantation. The second hypothesis is that latent BKV infection is reactivated in the renal epithelium after transplantation. Since BKV resides in the renal epithelium, its reactivation may be due to defective immune surveillance in the immunosuppressed recipient and manifests as nephritis.^{3,5,24,37} Occurrence of BKVN has also been noted in recipients who have had pre-transplant bilateral native nephrectomy (personal observation). Thus, it is possible that the viral latency may be located in ureteral and bladder mucosa and not renal *per se*, and may reactivate after transplantation.

In a recent retrospective analysis, pretransplant donor and recipient BKV-specific antibody correlated to the occurrence of post-transplant infection.³⁸ Donor antibody titer correlated inversely to the onset of post-transplant viruria ($P=0.001$) and directly proportional to duration of viruria ($P=0.014$) and peak urine viral titers ($P=0.005$). Thus, the source of infection from the donor may explain the early onset of infection; however, reactivation of virus in the recipient's urothelium is still a potential pathogenetic mechanism involved in this infection. Uncovering the modes of BKV infection, that is, exogenous vs reactivation, is of significance in understanding the disease process.

Immunology

To date, the intensity of immunosuppression has been implicated in causing BKVN with minimal attention to the host immunity. From other viral infections, it is clear that natural killer cells of the immune system offer antiviral cytotoxic activity. Adaptive immune responses follow with CD8-positive cytotoxic T cells. CD4-positive T cells boost antibody production with macrophage and augment viral clearance. Thus, host humoral and cellular immunity may play a major role in the pathogenesis of BKVN.

Humoral immunity

A fatal case of BKV infection with hyper-IgM immunodeficiency may suggest a mechanism for humoral antibody protection against BKV.¹³ Lack of development of BKV-specific IgG may be the key feature in the manifestation of this disease. IgG class switching is impaired in hyper-IgM immunodeficiency by lack of function of the CD40 ligand. Similar class switching may be defective in renal transplant recipients due to immunomodulatory drugs. Humoral antibody testing was carried out in renal transplant recipients in the early 1980s when this disease was not clinically significant,²⁷ as well as recently in a small pediatric study.²⁹

Recipients with prior immunity to BKV and circulating viral copies may not develop nephritis, as opposed to those with deficient humoral immunity. Thus, a patient with an elevated viral load with a robust level of humoral antibody may not require any intervention at all, whereas a patient with a small elevation in viral load and no detectable anti-BKV immunity may be in grave danger. At the Medical College of Wisconsin, we have evaluated 20 renal transplant recipients at various stages of BKVN.²⁸ The mean BKV-specific IgG

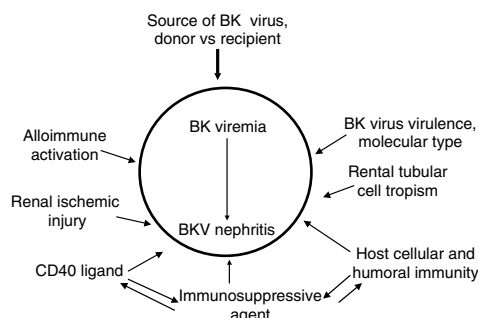


Figure 4 | Potential pathogenetic mechanisms involved in the occurrence of BKVN from BK viremia. These include sources of BKV infection, molecular viral type, renal tropism, host immunity, and renal transplant ischemic injury prior to engraftment, alloimmune activation, immunosuppression type, and defect in CD40 ligand.

levels in patients at the time of diagnosis of BKVN and those with stabilizing BKVN after reduction of immunosuppression were 64 and 39 enzyme immune assay (EIA) units, and they were significantly lower than the levels of 138 EIA units seen in patients with resolved BKVN, $P=0.007$ and 0.008 .²⁸ The mean BKV-specific IgM level in patients with stabilizing BKVN was 130 EIA units, which was higher than the levels of 51 EIA units detected in patients with resolved BKVN; $P=0.006$. The means and ranges of plasma BKV loads for subjects at the time of diagnosis, during stabilization, and those who had resolved BKVN were 955 925 (21 153–2 999 632), 5642 (593–14 636), and 42 (0–243) copies/ml of plasma, respectively. From our series, after a complete resolution of nephritis with stabilization of renal function, BKV-specific IgG antibody increased in all subjects from their baseline BKV-specific IgG antibody level. From our study, we also observed that there was a trend toward rapid clearance of viremia in subjects with BKV IgG > 50 EIA units compared to those who had IgG < 50 EIA units.²⁸ Thus, humoral immunity may play an important role in the pathogenesis of BKVN. Deficient humoral immunity at the time of transplant and BKV infection may determine the occurrence of BKVN and its subsequent outcome.

Cellular immunity

Subjects with elevated BKV-specific IgG can still develop BKVN, suggesting the possible role of defective cellular immunity. The effector function of T lymphocytes is critical to viral immunity. It is conceivable that a lack of cellular immune response to a rising viral load determines the occurrence of BKVN. Investigators from Italy have identified defective cellular immunity using Enzyme-Linked Immuno SPOT (ELISPOT) signal in subjects with BKVN.³⁹ The absence of ELISPOT signal was noted at the time of diagnosis of BKVN in two cases, and this reversed with reduction in immunosuppressive therapy. Establishing a relationship between defective T-cell response and BKV infection may be of great clinical significance and needs further investigation.

Alloimmune activation

Occurrence of BKVN in renal transplant recipients, as opposed to heart and liver transplant subjects, unveils the role of alloimmune activation with BKV activation and subsequent frank nephritis. Investigators from Emory University have explored the role of immune activation in a mouse transplant model, and have documented that viral nephritis occurs only in the presence of alloimmune activation.⁴⁰ Thus, subclinical alloimmune activation in renal graft may trigger BKV replication and nephritis. This also explains why this infection occurs in renal grafts only, as opposed to other solid organ transplant recipients. However, alloimmune activation is usually a result of suboptimal immunosuppression that contradicts BKVN therapy, which is a reduction in immunosuppressive therapy.

Immunosuppressive medications

Immunosuppressive combination therapies have been implicated in the occurrence of BKVN. Prior to 1995, BKVN was rarely identified as a problem in renal transplant recipients. Around this period, MMF and Tac were introduced as immunosuppressive agents for clinical transplantation. Prompt reduction in acute rejection rates with potent immunosuppressive agents has been accompanied by an increasing incidence of BKVN. However, BKVN has also been seen occasionally in recipients receiving cyclosporine (CsA) and sirolimus.⁴¹ Hence, the occurrence of BKVN is not due to specific immunosuppressive agents, but may be related to the overall degree of immunosuppression. Brennan *et al.*²² prospectively evaluated the differences between viremia and viruria with three immunosuppressive combination therapies. Viruria was the highest with Tac-MMF combination (46%) compared to CsA-MMF (13%) therapy, and choice of calcineurin inhibitor or adjuvant immunosuppression did not influence viremia or nephritis. The role of induction antibody and steroid avoidance therapies in influencing BK viremia and nephritis requires further clarification.

Renal specificity

BKV, which infects renal tubular cells, is most commonly seen in renal transplant recipients, as opposed to other immunosuppressed individuals and other solid organ transplant recipients.

Renal tubular cells

The precise sites of activation of BKV and mechanisms through which BKV infects renal tubular epithelial cells in transplant recipients are unknown. In animal models, viral replication during the acute phase of infection is seen in pulmonary, systemic vascular endothelial cells, and in splenic lymphoid cells. However, viral nucleic acids are seen in renal tubular epithelial cells at 2 months and the virus itself after 6 months, which remains the major site of viral persistence.⁴² Thus, BKV has tropism to renal tubular epithelial cells and replication occurs in these cells. The receptor site at the cellular level remains to be identified.

Renal ischemic injury

BKV can be detected in the urine of renal transplant recipients; however, it can be present in other renal diseases as well as in the urine of normal healthy individuals.⁴³ Approximately 40% of renal transplant patients shed virus in the urine.¹² It is still unclear why this infection occurs predominantly in renal transplants and not in immunosuppressed heart and liver transplant recipients. It is conceivable that renal ischemic injury during organ retrieval and implantation occurs only in kidney transplant compared to heart or liver transplant. Thus, ischemic injury at the time of transplantation may play a role in creating an environment for viral replication leading to nephritis. However, there is no correlation between cold ischemia time and organ source

(deceased vs living) and the occurrence of BKVN. In addition, occurrence of nephritis around a year after transplantation challenges the role of ischemic injury as an important causative factor in nephritis.

BKV virulence

BKV genomic heterogeneity has been described in systemic lupus erythematosus and bone marrow transplant recipients, as well as in healthy donors.^{44,45} The reported rates of mutation differ in these reports and may be correlated with changes in disease status.^{44,46} It is plausible that specific BKV types may have altered virulence, or changing genomic sequence may be associated with the occurrence of nephritis or a more severe form of the disease. The NCCR shows a high degree of sequence variability. In the report, Rhandawa *et al.* sequenced the NCCR in 26 paraffin-embedded biopsies from 15 patients with BKV nephritis and compared them to the archetype WW strain.⁴⁷ Their results demonstrated that there is an extensive natural variation in the viral sequence between patients. However, an analysis on NCCR sequence variations did not reveal any rearrangement pattern in five subjects with nephritis.⁴⁸ Thus, the role of molecular characterization at the DNA sequence level still needs to be explored.

Thus, the pathogenesis of BKVN is complex, as the virus may be introduced into the recipient through the donor, or reactivation in the recipient, or both. Tropism of this virus for renal tubular cells lays the foundation for the infection, which may be modified by host humoral and cellular immunity, as well as recipients' alloimmune activation in the graft, with concomitant immunosuppressive therapy leading to nephritis.

CONCLUSION

BKVN is an important problem after renal transplantation that has limited improvements in graft survival. Increasing awareness of this condition, utility of BKV DNA estimation in blood and urine, careful renal histological evaluation, and avoiding further aggressive immunosuppression after the diagnosis of BKVN are changing the outcome of this disease. Screening for BKV in blood and urine, along with preemptive reduction in immunosuppression, has been a useful strategy to prevent BKVN. The role of BKV-specific antibody and host cellular immunity in the pathogenesis of BKVN is evolving. Alloimmune activation, as a potential factor influencing the occurrence of BKVN, remains strong in renal transplant recipients; however, our ability to measure alloimmune activation remains a challenge. Virological variance such as molecular type of virus and changing virulence by altering DNA sequence needs further studies. Reducing immunosuppression appears to be the best approach for the treatment of BKVN until a safe antiviral agent becomes available to treat this condition.

ACKNOWLEDGMENTS

I thank Eric P Cohen, MD, Christopher P Johnson, MD, and Brahm Vasudev, MD for their valuable input.

REFERENCES

- Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. *Lancet* 1971; **19**: 1253-1257.
- Purighalla R, Shapiro R, McCauley J, Randhawa P. BK virus infection in a kidney allograft diagnosed by needle biopsy. *Am J Kidney Dis* 1995; **26**: 671-673.
- Mathur VS, Olson JL, Darragh TM, Yen TS. Polyomavirus-induced interstitial nephritis in two renal transplant recipients: case reports and review of the literature. *Am J Kidney Dis* 1997; **29**: 754-758.
- Randhawa PS, Finkelstein S, Scantlebury V *et al.* Human polyoma virus-associated interstitial nephritis in the allograft kidney. *Transplantation* 1999; **67**: 103-109.
- Binet I, Nicleleit V, Hirsch HH *et al.* Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. *Transplantation* 1999; **67**: 918-922.
- Hirsch HH. Polyomavirus BK nephropathy: a (re-)emerging complication in renal transplantation. *Am J Transplant* 2002; **2**: 25-30.
- Ahuja M, Cohen EP, Dayer AM *et al.* Polyoma virus infection after renal transplantation. Use of immunostaining as a guide to diagnosis. *Transplantation* 2001; **71**: 896-899.
- Hussain S, Bresnahan BA, Cohen EP, Hariharan S. Rapid kidney allograft failure in patients with polyoma virus nephritis with prior treatment with antilymphocyte agents. *Clin Transplant* 2002; **16**: 43-47.
- Stolt A, Sasnauskas K, Koskela P *et al.* Seroepidemiology of the human polyomaviruses. *J Gen Virol* 2003; **84**: 1499-1504.
- Flaegstad T, Ronne K, Filipe AR, Traavik T. Prevalence of anti BK virus antibody in Portugal and Norway. *Scand J Infect Dis* 1989; **21**: 145-157.
- Shah KV, Daniel RW, Kelly Jr TJ. Immunological relatedness of papovaviruses of the simian virus 40-polyoma subgroup. *Infect Immun* 1977; **18**: 558-560.
- 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**: 488-496.
- Rosen S, Harmon W, Krensky AM *et al.* Tubulo-interstitial nephritis associated with polyomavirus (BK type) infection. *N Engl J Med* 1983; **308**: 1192-1196.
- Smith RD, Galla JH, Skahan K *et al.* Tubulointerstitial nephritis due to a mutant polyomavirus BK virus strain, BKV(Cin), causing end-stage renal disease. *J Clin Microbiol* 1998; **36**: 1660-1665.
- Pappo O, Demetris AJ, Raikow RB, Randhawa PS. Human polyoma virus infection of renal allografts: histopathologic diagnosis, clinical significance, and literature review. *Mod Pathol* 1996; **9**: 105-109.
- Drachenberg CB, Beskow CO, Cangro CB *et al.* Human polyoma virus in renal allograft biopsies: morphological findings and correlation with urine cytology. *Hum Pathol* 1999; **30**: 970-977.
- Gupta M, Miller F, Nord EP, Wadhwa NK. Delayed renal allograft dysfunction and cystitis associated with human polyomavirus (BK) infection in a renal transplant recipient: a case report and review of literature. *Clin Nephrol* 2003; **60**: 405-414.
- Gloor JM, Cohen AJ, Lager DJ *et al.* Subclinical rejection in tacrolimus-treated renal transplant recipients. *Transplantation* 2002; **73**: 1965-1968.
- Buehrig CK, Lager DJ, Stegall MD *et al.* Influence of surveillance renal allograft biopsy on diagnosis and prognosis of polyomavirus-associated nephropathy. *Kidney Int* 2003; **64**: 665-673.
- Ramos E, Drachenberg CB, Papadimitriou JC *et al.* Clinical course of polyoma virus nephropathy in 67 renal transplant patients. *J Am Soc Nephrol* 2002; **13**: 2145-2151.
- Petrogiannis-Halios T, Sakoulas G, Kirby J *et al.* BK-related polyomavirus vasculopathy in a renal-transplant recipient. *New Engl J Med* 2001; **345**: 1250-1255.
- Brennan DC, Agha I, Bohl DL *et al.* Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005; **5**: 582-594.
- Hussain S, Orentas R, Walczak J *et al.* Prevention of BKV nephritis by monitoring BK viremia in renal transplant recipients: a prospective study. *Graft* 2004; **7**: 28-30.
- Nicleleit 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.
- Ding R, Medeiros M, Dadhania D *et al.* Noninvasive diagnosis of BK virus nephritis by measurement of messenger RNA for BK virus VP1 in urine. *Transplantation* 2002; **74**: 987-994.
- Drachenberg CB, Papadimitriou JC, Hirsch HH *et al.* Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. *Am J Transplant* 2004; **4**: 2082-2092.

27. Andrews CA, Shah KV, Daniel RW *et al.* A serological investigation of BK virus and JC virus infections in recipients of renal allografts. *J Infect Dis* 1988; **158**: 176–181.
28. Hariharan S, Cohen EP, Vasudev B *et al.* BKV specific antibodies and BKV DNA in renal transplant recipients with BKV nephritis. *Am J Transplant* 2005; **5**: 2719–2724.
29. Smith JM, McDonald RA, Finn LS *et al.* Polyomavirus nephropathy in pediatric kidney transplant recipients. *Am J Transplant* 2004; **4**: 2109–2117.
30. Vasudev B, Hariharan S, Hussain SA *et al.* BK virus nephritis: risk factors, timing and outcomes in renal transplant recipients. *Kidney Int* 2005; **68**: 1834–1839.
31. Vats A, Shapiro R, Singh Randhawa P *et al.* Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. *Transplantation* 2003; **75**: 105–112.
32. Kadambi PV, Josephson MA, Williams J *et al.* Treatment of refractory BK virus-associated nephropathy with cidofovir. *Am J Transplant* 2003; **3**: 186–191.
33. Williams JW, Javaid B, Kadambi PV *et al.* Leflunomide for polyomavirus type BK nephropathy. *N Engl J Med* 2005; **352**: 1157–1158.
34. Al-Jedai AH, Honaker MR, Trofe J *et al.* Renal allograft loss as the result of polyomavirus interstitial nephritis after simultaneous kidney–pancreas transplantation: results with kidney retransplantation. *Transplantation* 2003; **75**: 490–494.
35. Chapman C, Flower AJ, Durrant ST. The use of vidarabine in the treatment of human polyomavirus associated acute haemorrhagic cystitis. *Bone Marrow Transplant* 1991; **7**: 481–483.
36. Ramos E, Vincenti F, Lu WX *et al.* Retransplantation in patients with graft loss caused by polyoma virus nephropathy. *Transplantation* 2004; **77**: 131–133.
37. Rubino MJ, Walker D. Immunosuppression and murine polyomavirus infection. *Virus Res* 1988; **9**: 1–10.
38. Bohl DL, Storch GA, Ryschkewitsch C *et al.* Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. *Am J Transplant* 2005; **5**: 2213–2221.
39. Comoli P, Azzi A, Maccario R *et al.* Polyomavirus BK-specific immunity after kidney transplantation. *Transplantation* 2004; **78**: 1229–1232.
40. Lee EH, Wang J, Dong Y *et al.* Inability to clear polyoma virus in MHC disparate murine kidney transplant model results in accelerated rejection. *Am J Transplant* 2004; **4**: 599.
41. Lipshutz GS, Flechner SM, Govani MV, Vincenti F. BK nephropathy in kidney transplant recipients treated with a calcineurin inhibitor-free immunosuppression regimen. *Am J Transplant* 2004; **4**: 2132–2134.
42. Greenlee JE, Clawson SH, Pheleps RC, Stroop WG. Distribution of K-papovavirus in infected newborn mice. *J Comp Pathol* 1994; **111**: 259–268.
43. Major EO. *Field's Virology*, 4th edn., vol. 2. Lippincot Williams and Wilkins: Philadelphia, 2001; pp 2175–2196 (Chapter 64).
44. Sundsfjord A, Osei A, Rosenqvist H *et al.* BK and JC viruses in patients with systemic lupus erythematosus: prevalent and persistent BK viremia, sequence stability of the viral regulatory regions, and nondetectable viremia. *J Infect Dis* 1999; **180**: 1–9.
45. Negrini M, Sabbioni S, Arthur RR *et al.* Prevalence of the archetypal regulatory region and sequence polymorphisms in nonpassaged BK virus variants. *J Virol* 1991; **65**: 5092–5095.
46. Stoner GL, Alappan R, Jobes DV *et al.* BK vs regulatory region rearrangements in brain and cerebrospinal fluid from a leukemia patient with tubulointerstitial nephritis and meningoencephalitis. *Am J Kidney Dis* 2002; **39**: 1102–1112.
47. Randhawa P, Zygmunt D, Shapiro R *et al.* Viral regulatory region sequence variations in kidney tissue obtained from patients with BK virus nephropathy. *Kidney Int* 2003; **64**: 743–747.
48. Boldoroni R, Veggiani C, Turelle E *et al.* Are sequence variation in the BK virus control region essential for the development of polyomavirus nephropathy. *Anatomic Path* 2005; **124**: 303–312.