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Graft 2002; 5; 445

DOI: 10.1177/1522162802238649

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BK Virus: A Pathogen of 21st-Century Transplant Medicine

Jina Bae, George Sakoulas, Nina Tolloff-Rubin, Nelson Goes, Francis Delmonico, Winfred Williams, A. Benedict Cosimi, and Manuel Pascual

Polyomavirus BK has recently surfaced in clinical medicine as a rare but important pathogen causing significant morbidity and mortality, especially among immunosuppressed individuals. In renal transplant recipients, it can cause significant allograft dysfunction and often leads to allograft failure. The diagnosis is currently made by the histologic examination of renal tissue, combined with immunohistochemistry and/or electron microscopy. The use of polymerase chain reaction to detect the presence of BK virus in plasma may become an important tool both to diagnose and to follow the clinical course. The treatment for BK virus nephropathy remains careful adjustment of immunosuppression, but new antiviral approaches are currently being evaluated. Because early recognition and intervention may lead to an improved outcome, clinicians should have a heightened awareness about the possibility of BK virus nephropathy in any renal transplant recipient with allograft dysfunction in the modern era of immunosuppression.

ABBREVIATIONS:

BKV	BK virus
IVIg	Intravenous immunoglobulin
PCR	Polymerase chain reaction
CMV	Cytomegalovirus

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Introduction

The significant advances in medical science of the 20th century that are being carried into the new millennium bring with them unexpected challenges by presenting clinicians with new syndromes or diseases. In the field of transplantation, one newly recognized infectious agent is the polyomavirus BK. Although we have known about it for more 30 years,¹ only during the past decade has this virus been recognized as a pathogen. More potent immunosuppressives that have come into use in recent times may have allowed BK virus (BKV) infection to become an emerging problem.²

The Polyomavirus Family

Thirteen distinct members of the polyomavirus family have been found in nature. Their virion size is approximately 40 to 45 nm (Table 1). They have an icosahedral capsid structure and a superhelical double-strand circular DNA genome of 5.2 kb.^{3,4}

Polyomavirinae belongs to the *Papovaviridae* family, whose name is derived from the combination of the names of three of its members: rabbit papillo-

ma virus (pa), mouse polyoma virus (po), and simian virus 40 (SV40).³

Three strains of polyomavirus have clinical significance in humans: BKV, which is implicated as an important cause of kidney allograft dysfunction and failure, and JC virus (JCV), which is the causative agent in progressive multifocal leukoencephalopathy (PML). They were named after the initials of the patients from whom they were first isolated in 1971.^{4,5} BK virus was isolated from the urine of a renal transplant patient,¹ and JCV was isolated from the brain of a patient with PML.⁶

SV40 is another member of the polyomavirus family. The contribution of SV40 to oncogenesis has been well documented, as its DNA has been found in human tumors such as ependymomas, choroid plexus tumors, pleural mesotheliomas, and osteosarcomas.⁷⁻¹⁰ A significant amount of our current knowledge of cellular transformation, and thus our understanding of neoplasia, has its origins in the study of SV40-transformed murine cells. For example, the p53¹¹ and retinoblastoma¹² tumor suppressor genes were initially discovered as part of

Table 1 | THE KNOWN POLYOMAVIRUSES

Virus	Host
BK	Human
JC	Human
Simian virus 40	Rhesus monkey
Lymphotropic	African green monkey
Cynomolgus	Cynomolgus monkey
Bovine	Cattle
Hamster	Hamster
Mouse	Mouse
Kirstein virus	Mouse
Rabbit	Rabbit
Rat	Rat
Simian agent 12	Baboon
Budgerigar fledgling disease virus	Parakeet

the myriad of host cell proteins bound to SV40 viral proteins. In addition, partial and complete BKV DNA sequences have been demonstrated by southern hybridization in some human tumors, such as rhabdomyosarcomas, brain tumors, and lung, kidney, and liver carcinomas.^{13,14}

Cynomolgus polyoma virus (CPV) is a novel virus that has recently been described by van Gorder et al.¹⁵ After 3 to 11 weeks of immunosuppression of cynomolgus monkeys, renal dysfunction with tubulointerstitial nephritis developed in 12 of 57 monkeys. The clinical picture was quite similar to the one seen in humans with BKV infection and thus may provide a useful and relevant experimental model.

Virology and Epidemiology of BKV

The BKV genome shares 75% of DNA sequence homology with JCV and 70% of DNA sequence homology with SV40. It is divided into 3 regions. The early region is transcribed and expressed early after the virus enters the cell and continuously expressed later in the viral replication cycle. It encodes large T and small t “tumor” antigens that function in cellular transformation, viral replication, and overall gene regulation. The late region encodes viral capsid proteins VP1, VP2, VP3, and the agnoprotein. The noncoding regulatory region, which lies between the early and late genes, includes the origin of replication, viral promoters, and enhancers.^{3,4,16}

BKVs and JCVs are ubiquitous and cause disease states mainly in immunosuppressed hosts. Primary infection with BKV occurs at an earlier age than that with JCV. In the United States, antibodies to BKV are acquired in 50% of children by ages 3 to 4, whereas antibodies to JCV are acquired in 50% of children by ages 10 to 14. The antibody prevalence to BKV reaches nearly 100% by ages 10 to 11 and then declines to 70% to 80% in older individuals.⁴ Studies performed in different countries show seropositivity in early childhood to vary between 60% and 100%.¹⁷⁻²⁰

Little is known about the mode of transmission, but it is believed to occur via the oral or upper respiratory route. The detection of BK viremia in about 3% of pregnant women suggests the possible role of viral reactivation during pregnancy, with possible vertical transmission.^{4,21}

Interaction with Other Viruses

Coinfection of cells by BKV and other viruses may occur, resulting in viral interactions. As an example, the interaction of cytomegalovirus (CMV) and BKV has been investigated in vitro, as both viruses may be reactivated by immunosuppression or other states of host-virus imbalance. Interestingly, CMV has been shown to induce SV40 DNA replication.²² BKV T antigen is able to enhance the expression of immediate early (IE) and early (E) CMV genes.²³ Although not studied in a controlled manner, many reports of BKV infection in the lit-

Table 2 | CLINICAL SYNDROMES DUE TO BK VIRUS

SYNDROME	MOST COMMON SETTING
Common	
Asymptomatic viremia	Normal hosts, pregnancy, defective cell-mediated immunity (AIDS, transplant, systemic lupus erythematosus, malignancy)
Hemorrhagic cystitis	Bone marrow transplant
Ureteral stenosis	Renal transplant
Interstitial nephritis	Renal transplant
Rare	
Meningoencephalitis	AIDS, bone marrow transplant
Pneumonitis	AIDS, bone marrow transplant
Retinitis	AIDS

erature demonstrate concomitant CMV infection. Whether this is coincidental awaits further study. In addition, HIV genome transcription was shown to be induced by polyoma virus middle T antigen *in vitro*.²⁴ These observations suggest that interaction between BK and other viruses directly or indirectly may be able to influence the clinical course of BKV infection.

Clinical Disease Manifestations of BKV Infection

Primary infection with BKV occurs in childhood. It is usually asymptomatic or accompanies mild upper respiratory tract symptoms in immunocompetent hosts. In this setting, BKV DNA can be isolated in the tonsils.⁴ However, a very rare case of primary BKV infection was reported in a 34-year-old immunocompetent patient manifesting as encephalitis.²⁵

Following primary infection, BKV persists indefinitely in the kidney and can be reactivated by immunosuppression.^{4,14} BKV may also undergo periods of intermittent reactivation even in immunocompetent hosts, as a small percentage of healthy people excrete BKV in the urine. The prevalence of BK viremia ranges from 0% to 17.6% in immunocompetent individuals.^{5,26-29} Moreover, cytologic evidence of polyoma viremia as evidenced by the presence of decoy cells in the urine was found in 3.2% of 1235 pregnant women, and both JCV and BKV were isolated.^{4,21} BK viremia occurred mostly in the third trimester and ceased after delivery. In this report, there was no evidence of adverse consequences of BK viremia to the

mother or of transmission of BKV infection to the fetus.⁴

Sundsford et al.³⁰ investigated the prevalence of BK viremia in 44 patients with systemic lupus erythematosus using PCR. Sixteen percent of the patients demonstrated BKV in urine compared to 0% in the control group. The prevalence of asymptomatic BK viremia in HIV-seropositive individuals as demonstrated by PCR analyses is about 20% to 30%.²⁷⁻²⁹ The severity of HIV-related immunosuppression may correlate with a higher frequency of BK viremia.^{27,28} BKV is capable of causing severe disseminated infection in immunocompromised hosts. Several cases of disseminated BKV infection have been reported in HIV-seropositive patients. Fatal BKV infection in this population was reported to include meningoencephalitis, atypical retinitis, interstitial desquamative pneumonitis, and tubulointerstitial nephritis.³¹⁻³³

Silent BK viremia, as measured by PCR analyses, may occur in approximately 51% to 55% of bone marrow transplantation recipients.^{5,34} BK viremia is most often observed within 2 months after transplantation and is seen only in those who were seropositive before transplantation, suggesting reactivation rather than primary infection. In this patient population, the association seems to exist between BK viremia and the development of hemorrhagic cystitis, suggesting a possible pathogenic role of BKV in inducing urothelial damage, resulting in hemorrhagic cystitis or renal dysfunction.^{34,35} As in the case with HIV-related immunodeficiency, BKV is able to induce fatal infection in bone marrow transplant recipients.³⁶

BKV Infection after Renal Transplantation

The most recognized and clinically significant BKV-mediated disease that has emerged in recent years is renal allograft interstitial nephritis, which may lead to allograft dysfunction and failure. As with other groups of patients mentioned above, asymptomatic viral shedding is relatively common in the renal transplant recipients, without inducing apparent allograft dysfunction. Earlier studies have demonstrated the prevalence of BK viruria in renal transplant recipients to be 7% to 30% by PCR analyses or the combination of urine cytology and serology.^{5,37-40} However, the high prevalence of BK viruria demonstrated by urine cytology and serology in earlier studies was fraught with the problem of a lack of specificity. In recent years, however, several case series have been published based on single-center clinical experiences, which are the basis of our current knowledge of BKV nephropathy.

BKV nephropathy, that is, the clinical syndrome of significant BKV infection of the renal allograft, occurs infrequently. The reported prevalence ranges from 1.5% to 5.0%.⁴¹⁻⁴⁵ It is most common in the first year after transplantation, when immunosuppression is most intense. BKV nephropathy is usually associated with ureteral obstruction, lymphocele, bacterial urinary tract infection, hematuria, and systemic CMV infection.^{2,42}

Use of the newer and more potent immunosuppressive agents (e.g., mycophenolate mofetil, tacrolimus, sirolimus) has been associated with an increased risk of BKV nephropathy in renal transplant patients compared to traditional regimens that include cyclosporine, prednisone, and/or azathioprine. This is supported by the fact that BKV has emerged as an important pathogen in the past several years.^{2,42,46}

Once the diagnosis has been made, the clinical course of BKV nephropathy is variable, but the prognosis tends to be poor, reflecting the lack of an effective therapy. In a retrospective analysis by Howell et al.,⁴² 7 patients with BKV nephropathy presented with allograft dysfunction. Renal function stabilized or improved in 4 out of 6 patients in whom immunosuppression was decreased, and the remaining 2 patients progressed to end-stage renal disease. In another retrospective cohort study,² 4

out of 5 patients lost allograft function in a few months after the diagnosis of BKV nephropathy was made. They received induction therapy with an antilymphocyte preparation and experienced recurrent rejection episodes requiring rescue therapy with tacrolimus before clinical BKV nephropathy became apparent. However, a better clinical outcome was subsequently reported at the same institution, citing only 45% allograft loss (5 out of 11 patients).⁴⁴ In another retrospective review of 22 patients, allograft loss was reported to be 36%.⁴⁷ In most patients with prominent tubulitis on kidney biopsy, where it was difficult to exclude concurrent rejection, steroid therapy failed to yield a favorable response. These patients with refractory renal dysfunction were then treated with a 25% to 50% reduction of tacrolimus or cyclosporine. In 2 patients, intravenous immunoglobulin (IVIg) was administered. However, despite the IVIg treatment, one patient required transplant nephrectomy and the other patient progressed to allograft failure.⁴⁷

Recently, a unique case of BKV infection with tropism to endothelial cells was described by Petrogiannis-Haliotis et al.⁴⁸ A recipient of a cadaveric renal transplant developed disseminated BKV infection 7 months after transplantation. He died several days later, with massive capillary leak syndrome and myocardial infarction. Autopsy revealed the viral infection to be mainly located in the small vessels of the myocardium and skeletal muscle.⁴⁸

Diagnosis and Histology of BKV Nephropathy

The gold standard test for diagnosing BKV nephropathy remains the histology. The hallmark of BKV nephropathy on light microscopic examination is an interstitial nephritis largely composed of mononuclear lymphocytes, tubulitis, and atypical enlarged tubular nuclei with viral inclusions. The infected cells may become necrotic, detached from the basement membrane, and form a cellular cast.⁴⁴ However, this finding is not diagnostic for BKV nephropathy, since it can resemble other viral infections such as CMV, Epstein-Barr virus, or herpes simplex virus, or even certain lymphoid malignancies.⁴

One important diagnostic dilemma is to distinguish BKV nephropathy from acute cellular rejection, as both are marked by interstitial inflamma-

tion and tubulitis. This distinction is critical, as the therapy to treat acute rejection may worsen the interstitial nephritis caused by BKV. There are some subtle features suggestive of one and not the other. Areas marked by tubulitis and interstitial inflammation without viral inclusions are more typical of acute rejection than BKV nephropathy. Interstitial inflammation seen in BKV nephropathy tends to comprise lymphocytes, macrophages, and plasma cells. The plasma cell infiltration can be prominent in viral infections such as BKV or CMV. Viral inclusions are present in tubular epithelial cells. Interestingly, there is tubular upregulation of HLA-DR and intercellular adhesion molecule 1 (ICAM-1) in biopsies showing acute rejection, but not in biopsies of BKV nephropathy.⁴⁴ In many cases, however, concurrent acute cellular rejection and BKV nephropathy cannot be distinguished with certainty, which may pose a significant therapeutic challenge.

Electron microscopic examination reveals affected nuclei packed with typical crystalloid arrays of virion particles of 35 to 45 nm in diameter.⁴⁹ However, due to lack of specificity, the suggestive findings of BKV nephropathy on light and electron microscopic examination must be combined with a confirmatory test. Immunohistochemical staining using antibodies against the large T antigen of SV40 can confirm the diagnosis of BKV/polyomavirus infection by demonstrating a typical nuclear staining pattern.

BKV-induced changes in urinary tract epithelial cells may be detected using cytologic evaluation of the urine. "Decoy cells," which are of renal tubular or ureteral epithelial origin and are sloughed off and excreted in urine, display an enlarged nucleus with basophilic intranuclear inclusions and altered chromatin patterns.^{4,44} These cells are seen in Papanicolaou stained urine and can easily be detected by phase-contrast microscopy.⁵⁰ Due to its noninvasive nature, the test can be used to prospectively screen patients to identify those at risk of developing symptomatic BKV infection. Drachenberg et al.⁵¹ recently studied the correlation between the detection of urinary decoy cells and biopsy-proven BKV nephropathy by studying 571 concurrent urine and biopsy samples from 413 patients. They

found that demonstrating urinary decoy cells had 97% sensitivity and specificity, 90% positive predictive value, and 99% negative predictive value. In addition, immunohistochemistry or electron microscopy may confirm the presence of polyomavirus in decoy cells in urinary sediments.

The use of PCR to detect BKV in plasma may be helpful to diagnose BKV nephropathy. Nicleleit et al.⁵² performed a retrospective analysis of BKV PCR from plasma in 9 renal transplant recipients with allograft dysfunction who had histologically confirmed BKV nephropathy, as well as 41 renal transplant recipients without nephropathy and 17 patients with HIV infection. BKV DNA was detected in the plasma of all 9 patients with BKV nephropathy, in 2 of 41 renal transplant recipients without nephropathy, and in none of the HIV-positive individuals. Thus, the PCR demonstrated 100% sensitivity and 95% specificity in detecting BKV-mediated renal allograft dysfunction.

Similar findings were observed by Limaye et al.⁵³ in a retrospective investigation. BKV DNA in serum was detected by quantitative PCR at a median of 32 weeks before a histological diagnosis of BKV nephropathy. Moreover, the BK viral load measured by quantitative PCR decreased with reduction in immunosuppression and resolution of BKV nephropathy.

Finally, because the majority of healthy adults have antibodies to BKV, serological blood tests have little clinical use other than to confirm that a patient has been exposed to the virus. Moreover, viral culture is rarely used in the clinical setting because of the prolonged incubation required, typically 14 to 28 days. To circumvent the need for the prolonged incubation of viral culture, investigators at the Mayo Clinic published methods on a urine shell vial assay.⁵⁴

In summary, to make a diagnosis of BKV nephropathy, histologic examination with immunohistochemistry and electron microscopy of the biopsy specimens is essential. Detection of BKV by plasma PCR has a potential both to diagnose the viral nephropathy and to follow the clinical infection. However, until it becomes widely available, an allograft biopsy is critical, and patients should ideally be followed by serial allograft biopsies. Screening

for decoy cells in the urine is a simple test, but more studies are needed to confirm its clinical utility.

Therapy of BKV Infection

Once BKV nephropathy is established, the treatment is careful lowering of immunosuppression. The main dilemma often encountered is the frequent features of concurrent acute cellular rejection. As a result, the decision to lower immunosuppression is often a difficult one, since the risk of acute rejection must be weighed carefully against the risk of persistence of BKV infection. As noted previously, high-dose steroid therapy administered to 12 out of 22 patients for the treatment of tubulitis associated with possible concurrent acute cellular rejection did not improve renal function in 67% of patients. Even after immunosuppression was carefully decreased, the prognosis was unfavorable, resulting in allograft failure in 36% of patients.⁴⁷

In vitro, cidofovir demonstrates activity against polyomavirus, with 50% inhibitory concentration of 4 to 7 $\mu\text{g/mL}$. Other acyclic nucleoside phosphonates also show some activity against BKV. Acyclovir, ganciclovir, ribavirin, foscarnet, and cytarabine do not demonstrate activity against polyomavirus in vitro.⁵⁵ Because of nephrotoxicity, cidofovir in patients with renal failure should be used with extreme caution. Although it is difficult to translate these in vitro data to clinical settings, cidofovir has been used anecdotally to treat BKV infections in humans. For example, 3 doses of cidofovir at 5 mg/kg were administered to a 54-year-old man with hemorrhagic cystitis associated with a high level of BK viruria and concomitant CMV reactivation following allogeneic bone marrow transplant, with clinical and virological response to both infections.⁵⁶

Treatment of hemorrhagic cystitis due to BKV with other antivirals has also been discussed in the literature at the case report level. One report discussed treatment with vidarabine at 10 mg/kg for 5 days in a 23-year-old patient who developed hemorrhagic cystitis 47 days after a bone marrow transplant. Hematuria resolved completely in 7 days, with a subsequent clearance of BKV from the urine.⁵⁷ Currently, however, there are no antiviral agents with proven clinical efficacy in BKV infections.

The Massachusetts General Hospital Experience (1998–2002)

In this section, we briefly review our single-center experience over the past 4 years and report the outcome of 3 treated cases. We examined all renal allograft biopsies or transplant nephrectomies performed at the Massachusetts General Hospital (MGH) between January 1998 and December 2001. During this period, the standard of care was cyclosporine, steroids, and mycophenolate mofetil, but tacrolimus and sirolimus have also been used in specific protocols.⁵⁸ Of 233 renal transplant biopsies and 3 transplant nephrectomies from 165 patients, a total of 7 biopsies from 3 patients were identified as having BKV nephropathy, thus representing a 2.9% prevalence of BKV nephropathy in the biopsies performed, or a 1.8% prevalence in recipients who underwent renal transplant biopsies during this period.

Patient 1

SN was a 15-year-old boy with Noonan's syndrome with end-stage renal disease secondary to focal segmental glomerulosclerosis. He underwent cadaveric renal transplantation in January 1999. His postoperative course was complicated by delayed graft function, and he received a 7-day course of rabbit thymoglobulin (total dose: 675 mg) in addition to steroids and mycophenolate mofetil. On day 8, he was started on cyclosporine. His allograft function subsequently improved, with serum creatinine nadir at 1.9 mg/dL. The serum creatinine increased to 2.9 mg/dL 2 months after transplantation. He underwent an allograft biopsy, which revealed arteriosclerosis of donor origin. Pending the biopsy result, two 500 mg boluses of solumedrol were administered. He also developed systemic CMV infection, which was treated with intravenous ganciclovir.

He required a second allograft biopsy 2 months later when his serum creatinine was further elevated to 3.9 mg/dL. The biopsy showed an interstitial infiltrate suggestive of acute cellular rejection. However, the immunostaining for BKV using the antibody to SV40 large T antigen subsequently returned positive.

The patient's serum creatinine progressively rose to 5.6 mg/dL 1 month later. At this time, he un-

derwent a third allograft biopsy, which showed persistence of the interstitial infiltrate with BKV nephropathy as well as thrombotic microangiopathy. Due to the difficulty in excluding concomitant acute cellular rejection in the background of BKV interstitial nephritis, he was treated with 3 boluses of 500 mg solumedrol. Cyclosporine was changed to tacrolimus, and mycophenolate was changed to azathioprine; however, in the ensuing weeks, his allograft progressively failed.

Patient 2

AM was a 66-year-old man with IgA nephropathy who successfully underwent cadaveric renal transplantation in July 1999. Good allograft function was achieved initially, but a lymphocele developed postoperatively, requiring surgical drainage. His immunosuppression consisted of cyclosporine, prednisone, and mycophenolate mofetil.

Four months after transplantation, his serum creatinine was elevated to 1.5 mg/dL from a baseline of 1.0 mg/dL. Because he declined an allograft biopsy, he was empirically treated with 2 doses of 500 mg solumedrol, and his serum creatinine returned to baseline. He also developed systemic CMV infection 3 months later and was treated with intravenous ganciclovir.

Eight months after transplantation, his serum creatinine progressively rose to 2.3 mg/dL. He underwent an allograft biopsy that showed mononuclear cell interstitial nephritis, which was interpreted as acute cellular rejection. He received 2 boluses of 500 mg solumedrol. However, the immunostaining for BKV using the antibody to SV40 large T antigen subsequently became positive.

The patient's serum creatinine continued to rise to 3.5 mg/dL 1 month later. He underwent a second allograft biopsy, which revealed persistent BKV interstitial nephritis with possible acute cellular rejection. Urine cytologies revealed the presence of decoy cells. His tacrolimus and mycophenolate mofetil regimen was discontinued, and he was maintained on monotherapy with prednisone 7.5 mg daily. However, his serum creatinine continued to rise. Because of the possibility of concomitant acute cellular rejection and the progressive deterioration of his allograft function, he was treated with 5 consecutive daily doses of 100 mg of thymoglob-

ulin without improvement, and his allograft progressively failed.

Patient 3

HG was a 17-year-old boy who developed end-stage renal disease due to Alport's syndrome. He underwent living-related renal transplantation from his father in May 2000 followed by excellent initial allograft function. His immunosuppressive regimen consisted of tacrolimus, prednisone, and mycophenolate mofetil.

Two months after transplantation, his serum creatinine rose to 2.0 mg/dL from a baseline of 1.4 mg/dL. He underwent an allograft biopsy that revealed interstitial nephritis with plasma cells and atypical tubular nuclei with basophilic inclusions, consistent with BKV nephropathy. Mycophenolate mofetil was discontinued, and the dose of prednisone was decreased from 10 mg to 5 mg daily. Tacrolimus was also decreased and eventually changed to cyclosporine. The diagnosis of BKV nephropathy was further supported by 2 urine cytology examinations, which were positive for decoy cells and confirmed by positive immunostaining with the antibody to SV40 large T antigen. He was also treated with polyclonal IVIg over 4 days.

Despite these changes in his medical regimen, his serum creatinine further increased to 3.5 mg/dL 3 months after transplantation. He underwent a second allograft biopsy, which revealed persistent BKV nephropathy. Because of the progressive allograft function deterioration with an intense interstitial infiltrate on histologic examination, it was decided to administer local irradiation to the allograft (total 600cGy over 4 days). With this therapy, his allograft function subsequently improved steadily, and the last follow-up creatinine 1 year later was 2.5 mg/dL.

Summary of Cases

In summary, at the MGH 3 cases of BKV nephropathy have been encountered in the past 4 years in renal allograft recipients. As shown in many other reports, once the diagnosis of BKV nephropathy has been established, the prognosis of renal allograft is poor. In our limited experience, there were 2 graft losses and 1 improvement of allograft function. The 2 earlier cases with allograft

failure illustrate well the extreme difficulty in differentiating BKV nephropathy from acute cellular rejection. In the third patient, after immunosuppression was lowered, a new treatment approach was attempted (i.e., IVIg followed by local irradiation of the graft). So far, there have been no published reports of either one having efficacy in the treatment of BKV nephropathy. Both the local irradiation therapy and IVIg may decrease the inflammation associated with the interstitial nephritis due to BKV nephropathy. In the past, the MGH transplant unit has successfully used local irradiation of allograft in cases of refractory renal allograft rejection.⁵⁹ Because the widespread interstitial nephritis is often a predominant feature of BKV nephropathy, it is conceivable that this therapeutic strategy may be beneficial. Additionally, IVIg may provide some passive immunity against BKV, as the majority of adults are seropositive to BKV. More prospective studies with larger groups of patients need to be performed to determine whether local graft irradiation (or IVIg) may have a role in the treatment of BKV nephropathy after renal transplantation.

Conclusions

In recent years, syndromes due to polyomaviruses such as BKV have surfaced in the clinical arena as a direct consequence of the increase in the population of immunosuppressed hosts. This increase is partly due to transplantation medicine, with its associated immunosuppressive agents, and to the HIV pandemic. As the field of transplantation continues to expand, and novel, more potent immunosuppressive agents are introduced, the currently recognized clinical syndromes attributed to these viruses may become more frequently recognized. Based on the fact that the evolution of renal transplant patient management is incorporating more potent immunosuppressive medications, one might predict that the prevalence of BKV-mediated diseases will continue to increase among renal transplant patients in the near future. As a result, careful use of immunosuppressive medications as well as heightened awareness of BKV nephropathy should be emphasized among clinicians. Alternatively, the "minimization strategies" (avoidance of calcineurin inhibitors or steroids) currently under

investigation may decrease the risk of BKV nephropathy.⁶⁰

Finally, with the possible future clinical development of xenotransplantation, known (Table 1) or unknown polyomaviruses that infect other species may become clinically relevant in human disease.

Acknowledgments

This work was supported by the Helen and George Burr Endowed Research and Educational Fund in support of transplantation and by the Yates Fund for Transplant Technology.

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