REVIEW

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BK polyomavirus: A newly recognized threat to transplanted kidneys

ABSTRACT

Reactivation of latent infection with BK polyomavirus is now being recognized as a cause of failure of renal allografts. An increasing serum creatinine concentration in a kidney transplant recipient should prompt a referral for reevaluation by the transplant center.

KEY POINTS

Sixty percent to 90% of people have antibodies to the BK polyomavirus, reflecting latent infection.

Reactivation of the BK polyomavirus occurs in 10% to 60% of renal transplant recipients, and about 1% to 5% of recipients develop BK nephropathy. Half of allograft recipients who develop BK nephropathy lose their graft.

Risk factors for BK nephropathy are still poorly understood, but aggressive immunosuppression may be involved.

Quantitation of BK virus in the blood is emerging as the best noninvasive test for BK nephropathy, but biopsy evidence of tissue involvement in the renal transplant remains the definitive test.

Treatment of BK nephropathy is poorly defined as yet. Most often, immunosuppression is decreased, but this poses the increased risk of rejection.

AMONG THE MANY THREATS to the transplanted kidney for which physicians need to be alert, another is gaining recognition: reactivation of latent infection with BK polyomavirus.

Unfortunately, the signs of nephropathy due to BK polyomavirus infection (gradually declining renal transplant function, sometimes with microscopic hematuria, proteinuria, and obstruction) can be due to many other causes. When these findings arise, it is important that the patient be reevaluated by the transplant center. However, renal transplant recipients are so numerous (more than 200,000 transplantations have been performed since 1970—almost 14,000 a year currently) that general practitioners are bound to encounter them—and BK polyomavirus—in their practice.

Moreover, reactivation of this virus may occur not only in solid-organ transplant recipients, but also in patients with bone marrow transplants, hematopoietic neoplasms, HIV infection, chemotherapy for malignancy, pregnancy, and congenital immunodeficiency states.[1]

This paper reviews what we know about BK polyomavirus so far.

WHAT IS THE BK POLYOMAVIRUS?

The BK polyomavirus is a nonenveloped, double-stranded DNA virus first isolated in 1971 from the urine of a 39-year-old man (B.K.) who developed ureteral stenosis 4 months after receiving a renal transplant.[2] Although an important study appeared in 1980,[3] not until 1995 did a sustained series of clinical reports begin to document the importance of this virus in the fate of renal allografts.[4]

The other human polyomavirus, also dis-

covered in 1971, is found in patients with progressive multifocal leukoencephalopathy. Called the JC virus, it is named after the patient with Hodgkin lymphoma from whose brain it was cultured.

The polyomavirus family has 13 members, and they have narrow host ranges.[5] The BK and JC polyomaviruses occur in humans; their genomes show the closest homology to simian virus 40,[5] which occurs primarily in rhesus monkeys but has also been detected in humans.[6,7] The lymphocytotropic papovavirus infects African green monkeys. Another nine members of the family can be found in baboons, macaques, rabbits, and birds.

LATENT INFECTION IS COMMON

Worldwide, 60% to 90% of humans have antibodies to BK and JC polyomaviruses. Antibodies to either or both viruses independently develop typically in childhood or adolescence and remain elevated throughout life. The role of such antibodies, as well as cell-mediated immunity, remains unclear.[8]

Because neither the BK nor the JC virus is stable under conditions consistent with oral ingestion, inhalation of these viruses or a respiratory pathway is believed to be the most likely route of initial infection.[8]

REACTIVATION OF LATENT INFECTION

The BK virus typically remains latent in the kidneys and urinary tract. Sometimes, however, it can reactivate and begin replicating. In a transplant recipient the conversion from latent to active infection is influenced by:

- The host's antiviral immune function, which currently is not clearly defined for polyomaviruses[5,8]
- The amount of virus present[9]
- The microbiologic features of the specific virus[9]
- The individual or combined effects of various immunosuppressant agents (mycophenolate mofetil, tacrolimus, antilymphocyte globulin, and intravenous methylprednisolone currently being the most suspect)[10,11]
- Allogeneic stimulation from histoincompatibilities in the renal allograft itself, often with recurrent rejection.[9–12]

TABLE 1

Renourinary presentations of BK polyomavirus in renal transplant recipients

Declining or abnormal renal allograft function
Interstitial nephritis, interstitial fibrosis, chronic allograft nephropathy
Ureteral stenosis, obstruction
Acute tubular necrosis
Microscopic hematuria, hemorrhagic cystitis

Reactivation of the virus occurs in 10% to 60% of renal transplant recipients, and about 1% to 5% of renal transplant recipients develop BK nephropathy.[10,12,13] In a recent prospective study,[10] the median time after transplantation for the appearance of the disease was 16 weeks for shedding of decoy cells (uroepithelial cells with homogeneous "ground glass" intranuclear inclusion bodies), 23 weeks for BK viremia, and 28 weeks for BK nephropathy.[10]

Almost 50% of allografts affected with BK nephropathy are lost. Most of the graft loss is related to progressive BK nephropathy, while some graft loss and dysfunction may be due to progressive rejection when immunosuppression is drastically reduced.[9,13,14]

Almost 50% of allografts with BK nephropathy are lost

RENOURINARY PRESENTATIONS OF BK VIRUS

The presentation of BK viral infection in renal transplant recipients may be quite varied (TABLE 1).

Declining allograft function. It appears that most patients have no symptoms—just steadily increasing serum creatinine levels with progressive renal allograft dysfunction.[3,11–13]

Interstitial nephritis. Renal allograft dysfunction may be caused by BK polyomavirus-associated interstitial nephritis, which may be difficult to distinguish from acute cellular rejection.[4,14–19] The subsequent interstitial fibrotic changes associated with BK nephropa-

thy can also contribute to the entity known as chronic allograft nephropathy.[14]

Ureteral stenosis and obstruction may develop in some patients, and this is thought to be due to ascending progression of BK infection along the uroepithelium from the bladder to the kidney.[2,3,12,19]

Acute tubular necrosis can be due to viral involvement of the tubular epithelial cells.[12,19]

Microscopic hematuria and hemorrhagic cystitis as the initial signs of disease are most common in bone marrow transplant recipients, in whom higher peak levels of BK virus were found to be associated with hemorrhagic cystitis.[20]

Although initial reports suggested that BK nephropathy is more likely to occur in patients receiving the immunosuppressant drugs mycophenolate mofetil, tacrolimus, or both,[11,18] two recent studies did not support that relationship.[10,13] In fact, a key prospective study linked BK nephropathy to the use of intravenous methylprednisolone or antilymphocyte globulin for acute rejection and to a greater number of HLA mismatches.[10]

Some patients have successfully undergone removal and replacement of a renal allograft lost to BK infection

After losing a renal allograft to BK nephropathy, some patients have successfully received a second transplant kidney; the failed kidney was removed either before retransplantation[17] or at the same time.[21]

Unusual clinical expressions of BK infection. A case report described a patient with a systemic vasculopathy,[22] and another documented the involvement of the native kidneys in the recipient of a solitary pancreas transplant.[23] In a third report,[24] a patient with a simultaneous kidney and pancreas transplant developed carcinoma of the bladder with metastases, which was attributed to BK virus because of high-level expression of BK viral large T antigens in the primary and metastatic lesions and not in the non-neoplastic urothelium.

DIAGNOSTIC TESTS

A variety of methods have been used to diagnose BK polyomavirus infections in renal allograft recipients. These include detection of:

- Urinary decoy cells by cytology
- Virus-infected tubular epithelial cells in the urine by electron microscopy
- Viral DNA in the urine by polymerase chain reaction (PCR) with and without quantitation
- Viral DNA in the plasma by PCR with and without quantitation
- A variety of changes in the renal allograft tissue by biopsy[1–4,6,9–26]
- mRNA for the viral VP1 protein in the urine—recently reported to be a more specific way of identifying significant BK polyomavirus infection because VP1 protein is expressed only after viral DNA replication has begun (see below).[27]

Biopsy findings

Histopathologic abnormalities seen in renal allograft biopsy specimens include:

Intranuclear inclusions. Inclusion-bearing cells appear to be most abundant in the medulla. Four varieties of intranuclear inclusion bodies have been described:

- Amorphous, basophilic, ground-glass
- Eosinophilic granular with halo, resembling those seen in cytomegalovirus infection
- Finely granular without halo
- Vesicular variant.[15]

Focal tubular necrosis. Tubular epithelial cell necrosis with denudation of basement membranes is most common in distal tubular segments and collecting ducts. These findings are typical of BK infection, but are not pathognomonic.

A heterogeneous interstitial inflammatory reaction is also present and usually involves lymphocytes, macrophages, and occasional plasma cells.

Immunohistochemical studies. Nickeleit et al[15] argue that immunohistochemistry (using mouse monoclonal antibodies) and electron microscopy "serve only as ancillary techniques to confirm the diagnosis of BK nephropathy since intranuclear inclusion bodies are always found by light microscopy." In one patient BK virus-associated glomerular crescent formation was identified by light microscopy in two biopsies at 50 and 330 days after transplantation.[15,19]

The diagnosis of BK nephropathy has been made by immunostaining with either polyclonal or monoclonal antibody to simian

virus 40 T antigen that has cross-reactivity against the T antigen of the BK, and possibly the JC, virus. Because co-infection with simian virus 40 has been documented in renal allografts, however, diagnostic studies more specific than immunostaining with cross-reacting reagents are desirable.[6,7]

In situ hybridization and quantitation of viral DNA in transplant biopsies have also been used.[14,25]

Viral infection or acute rejection?

Although tubulitis (which implies acute rejection) is often not seen, more than half of biopsies performed during persistent BK nephropathy show cellular rejection as defined by the Banff criteria.[15] In cases of rejection, tubulitis and mononuclear cell infiltrates are most pronounced in areas without viral inclusions. However, it is often difficult to determine whether inflammatory interstitial infiltrates are due to viral infection or to acute rejection.

Two additional findings have been shown to be helpful in making that distinction.[15,16] First, in rejection but not in BK nephropathy, MHC-class II (HLA-DR) expression is up-regulated on tubular epithelial cells. Second, C4d, a complement degradation product of the activated C4 molecule, is typically detected along peritubular capillaries in the presence of acute rejection (usually antibody-mediated), but it has not been detected in BK nephropathy.[16] Immunofluorescence testing for C4d has become standard procedure in most transplant centers.

Presence of C4d along peritubular capillaries is a sign of acute rejection, rather than viral infection

URINARY VP1 mRNA: AN IMPORTANT NEW TEST

Detailed knowledge of the virus has been helpful in devising a noninvasive test with a high positive predictive value,[27] and may be critical to developing better therapy.

The virion structure of polyomavirus includes a capsid that contains three virus-encoated proteins (VP1, VP2, and VP3) that surround a single molecule of superhelical double-stranded DNA.[5] The DNA has about 5,000 base pairs that are replicated in the nucleus and complexed with cellular histones (H2A, H2B, H3, and H4) in the form of chromatin. The viral particle consists of 88% protein and 12% DNA.[5]

The polyomavirus genome is divided into "early" and "late" regions. Early regions are transcribed and expressed soon after the virus enters the cell, with continued expression late after infection. The small T and large T antigens are early genome components.

The late portion is expressed efficiently only after viral DNA replication begins, although low levels of late-region transcription occur early after infection as well. VP1, VP2, and VP3 are components of the late portion of the genome. The ability to detect mRNA for VP1 in the urine of renal transplant recipients with BK nephropathy will provide a powerful noninvasive diagnostic test.[27]

Polyomaviruses result in productive and nonproductive infection, as well as transformed cells.[5] Productive infection occurs in some cells when viral DNA replication occurs and is followed by progeny virions and cell death. This requires large T antigen plus interaction with host cell DNA in the S phase of permissive cells. Nonproductive infection occurs in some cells when viral DNA replication cannot occur, typically because of an inability to react with host cell DNA in nonpermissive cells. Transformed cells may arise if large T antigen expression continues in nonpermissive cells.

CLINICAL STUDIES

Several retrospective studies and two prospective studies of BK viral infections in renal transplant recipients are particularly notable.[3,10,12–14]

Nickeleit et al[12] performed a retrospective analysis of 9 renal allograft recipients with BK nephropathy, 41 renal allograft recipients without BK nephropathy (16 of whom had decoy cells in the urine), and 17 nontransplant patients with HIV.

BK viral DNA in plasma was detected by PCR in all 9 patients with BK nephropathy, 2 of the 41 subjects with no signs of BK nephropathy, and none of the HIV patients.[12] BK viral DNA was detected at the time of the initial histologic diagnosis an average of 46 ± 28 weeks after transplantation and, although initially undetectable, was found 16 to 33

weeks before the appearance of overt nephropathy confirmed by biopsy. BK viral DNA in the plasma became negative, and the nephropathy resolved after the doses of immunosuppressant drugs were decreased in 2 patients and after the removal of the renal allograft in 3 patients.

Randhawa et al[14] reported that the clinical course of biopsy-proven BK nephropathy with interstitial nephritis in 22 patients mimicked acute rejection in 19, chronic rejection with incidental diagnosis at nephrectomy in 2, and drug toxicity in 1.

Twelve of the patients received initial antirejection therapy, which was associated with clearance of the virus in 1 (8%), a partial therapeutic response in 3 (25%), and graft loss in 8 (67%). The other 8 cases that were treated by reduction of immunosuppression at the outset have retained graft function for up to 10 months from diagnosis, with a range of serum creatinine levels from 1.7 to 6.0 (median 2.4) mg/dL. Follow-up biopsy 1 month to 2 years after diagnosis showed chronic allograft nephropathy. Clearance of virus was documented in 3 of 6 cases.

Ramos et al,[13] in the largest retrospective study, compared 67 patients (5% of 1,315 renal transplants performed at one transplant center during the 4-year study period 1997–2001) with graft dysfunction and biopsy-proven BK nephropathy, and 162 case controls.[13] The diagnosis was made 12.8 ± 9.9 months after transplantation. Seventy-nine percent of the patients were men, and the mean age was 54 ± 14 years. Almost all (97%) of the patients received mycophenolate mofetil and prednisone, and 89% received tacrolimus.

After BK nephropathy was diagnosed, maintenance immunosuppression was decreased in 52 patients and left unchanged in 15. After approximately 1 year of additional follow-up, 8 (16%) of 52 in the reduction group and 3 (20%) of 15 in the sustained medication group had lost their grafts.

At the end of the observation period there was no significant difference in allograft function or in allograft survival between the group who had immunosuppression reduced and those with sustained medication. There was no significant increase in BK nephropathy among those receiving tacrolimus compared with those receiving cyclosporine. Only older age and male gender were significantly higher with BK nephropathy.

Six patients ages 51 to 76 years died, 5 due to cardiovascular disease and 1 due to sepsis.[13] After a reduction in immunosuppression the failure to achieve any significant reduction in allograft failure caused by BK nephropathy may have been due to the relatively late time of diagnosis and intervention.

Hirsch et al,[10] in the most recent prospective study of BK nephropathy, followed 78 renal transplant recipients by testing for urine decoy cells and qualitative and quantitative BK viral DNA in plasma at 3, 6, and 12 months after transplantation. Renal biopsy was performed whenever decoy cells were detected and allograft function deteriorated.

Of the 78 patients, 41 (53%) received mycophenolate mofetil, cyclosporine, and prednisone, 37 (48%) received tacrolimus, azathioprine, and prednisone, and 13 (17%) had induction with antilymphocyte globulin or anti-IL2 therapy.

Presumed graft rejection was treated with intravenous methylprednisolone until the diagnosis was confirmed by transplant biopsy, usually within 1 to 3 days. In 20 patients, transplant biopsies showed acute vascular rejection or acute interstitial rejection that was unresponsive to intravenous methylprednisolone and required additional treatment with antilymphocyte globulin. Patients were followed for a median of 85 weeks (range 43–130).

In one study, detection of decoy cells was 100% sensitive and 71% specific for BK nephropathy

At a median of 16 weeks after transplantation (range 2–69), 23 patients had decoy cells in their urine. Ten patients had BK viremia at a median of 23 weeks (range 4–73), and 5 had BK nephropathy at a median of 28 weeks (range 8–86). The probabilities of decoy-cell shedding, BK viremia, and BK nephropathy were 30%, 13%, and 8%, respectively.

The viral load in plasma was higher in patients with BK nephropathy than in those without it; all patients with BK nephropathy had at least 7,700 copies per mL. Detection of decoy cells was 100% sensitive and 71% specific for the diagnosis of BK nephropathy, and had a positive predictive value of 29% and a

negative predictive value of 100%. BK viremia had a 100% sensitivity, 88% specificity, 50% positive predictive value, and 100% negative predictive value.

BK nephropathy was established by histochemical staining for polyomavirus antigens and a rise in serum creatinine of 25% or more from baseline in the absence of other causes. Four of five patients with BK nephropathy had biopsy evidence of concurrent acute interstitial rejection.

At the end of the study, 75 (96%) of the 78 patients had functioning allografts, and there was no graft loss due to BK nephropathy. Treatment of acute rejection with intravenous methylprednisolone (and possibly antilymphocyte globulin) was significantly associated with the appearance of decoy cells in the urine, BK viremia, and BK nephropathy. There was also a trend toward a greater number of HLA mismatches between donor and recipient in patients with BK viremia and BK nephropathy. No associations were found with recipient BK seronegativity before transplantation, receipt of a cadaver organ, cold ischemic time, gender mismatch, use of tacrolimus or mycophenolate mofetil, or cytomegalovirus antigenemia.

It seems appropriate to screen renal transplant recipients for BK DNA by PCR at 4, 8, and 12 months

Additional risk factors for nephropathy

Several factors related to the BK virus have been[10,25,26] or could be[6,28] related to the development and acute severity of BK nephropathy.

- **High BK viral load** in plasma[10,26] and in renal allograft biopsies[25] has been associated with BK nephropathy.

However, although the current emphasis of BK infection is on BK nephropathy and on thresholds reported for BK virus in plasma and allograft tissue,[10,25,26] it seems possible that much lower levels of BK virus not currently considered pathogenic could, over years, contribute to changes in renal allografts variously labeled as chronic allograft dysfunction or chronic allograft nephropathy.

- **Co-infection** with simian virus 40[6] or JC polyomavirus[28] might also contribute to the severity of BK infection, a speculation with precedent in the increased severity of post-transplant cytomegalovirus infections when there is co-infection with human herpesvirus 6 or 7.[29,30]
- **No apparent association with BK genotype.** Baksh et al[28] reported that the frequency distribution of BK genotypes was the same in patients with BK nephropathy as that for normal individuals.

THERAPY

Treatment of BK nephropathy is still in the earliest stages.[9,12–14,31–35]

Cautious decrease of immunosuppression (possibly more important in those receiving both tacrolimus and mycophenolate mofetil), appears to be the most commonly accepted initial approach to treatment. However, concurrent rejection or the emergence of acute rejection after decreased immunosuppression needs to be carefully monitored and, if the situation permits, immunosuppression partially restored.

Leflunomide. The type of immunosuppression to be used under these circumstances is not currently defined, but in the future it might include leflunomide and related compounds that have both immunosuppressive and certain antiviral properties.[32,33] Promising preliminary results in six patients with BK nephropathy were obtained when leflunomide was substituted for mycophenolate mofetil.[34] All six patients responded with decreases in BK virus levels and with stable or improving renal function.

Cidofovir, an antiviral agent, is an option, but it has a long half-life, is renally excreted, and is quite nephrotoxic. Allograft failure has occurred with as few as one or two doses.[32] Two renal transplant recipients were treated with low-dose cidofovir after initial reduction of immunosuppression failed to prevent progressive deterioration of renal function; although viruria persisted, renal function improved and viremia cleared over 4 to 5 months.[32,35]

Intravenous immunoglobulin has been used but is still under evaluation without conclusive proof of effectiveness.[9,31,36]

Rimantadine was used in two patients with simultaneous kidney and pancreas transplants whose renal allografts failed because of BK nephropathy. The kidneys were later removed at the time of retransplantation; rimantadine was used during the progression

of BK nephropathy in the initial transplants without apparent benefit and was continued after retransplantation.[21]

Screening for BK DNA. Because more-potent immunosuppression protocols are being used nowadays and the tendency is to maximize them to prevent rejection, it would seem appropriate to screen renal transplant recipients at 4, 8, and 12 months after transplantation at least with urine cytology and ideally with quantitative plasma BK DNA PCR.

In patients with evidence of BK infection by quantitative plasma BK DNA PCR determinations, the next steps are to obtain a renal allograft biopsy to differentiate BK nephropathy from rejection, adjust immunosuppression downward as needed, and carefully evaluate the entire clinical picture to decide which antiviral therapy has the best risk-benefit profile for the individual patient.

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