BK Virus Nephropathy and Other Polyoma Virus Infections
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Polyomaviruses are mammalian (and a few avian) viruses, which appear to have coevolved with their hosts, leading to high prevalence, low morbidity, latent infections for the most part. The viruses generally have a restricted host range; 5 polyomaviruses are known to naturally infect humans (Table 1). Among them, BK virus is the most commonly encountered clinically, causing nephropathy, hemorrhagic cystitis, and ureteral stenosis in immunosuppressed hosts. A related rhesus macaque polyoma virus, SV40, is known to be oncogenic in experimental rodent animal and cell culture models. However, despite the inadvertent contamination with SV40 of certain lots of inactivated poliovirus vaccine (and early research lots of live-attenuated poliovirus vaccine) administered between 1951 and 1963, no disease in humans has been proven to result from SV40 infection.

HUMAN POLYOMA VIRUSES
Human polyomaviruses were initially named after the initials of the first patients with identified disease (BK and JC viruses, each described in 1971); the most recently described polyomaviruses are instead named for the institutions in which they were described (KI for Karolinska Institute and WU for Washington University in St. Louis) or the cell type in which they were discovered (Merkel cells). The polyomaviruses are small (40–45 nm), nonenveloped icosahedral viruses with a double-stranded DNA genome, which replicate in the nucleus of epithelial cells, oligodendrocytes, lymphocytes, and perhaps other cells. They likely enter target cells by attaching to glycoprotein receptors, inducing caveolae-mediated (BK) or clathrin-mediated (JC) endocytosis, and trafficking to the nucleus for replication. Both lytic and latent infection may occur.

Polyomaviruses BK and JC, and perhaps KI and WU also, appear to infect children early in life; it is uncertain whether the initial infection is asymptomatic or associated with minor upper respiratory tract infection. Transmission is thought to be by the respiratory route and perhaps also the fecal-oral route. By the age of 10 years, >90% of children are seropositive for BK virus infection (range in global prevalence studies, 60%–100%); seropositivity to JC virus is acquired more slowly, with about 75% positivity by the age of 25 years. In addition to reactivation of host BK virus infection during immunosuppression, direct transmission of donor infection to renal transplant recipients may result from latent BK virus in allograft epithelial cells. Factors associated with reactivation of BK include age >50 years, pregnancy, and immunosuppression, including after solid organ transplantation, hematopoietic stem cell transplantation, and HIV infection. JC virus also reactivates with severe immunosuppression, particularly HIV infection, but also after solid organ or hematopoietic stem cell transplantation, and recently, after the use of immunosuppressive monoclonal antibody therapy with natalizumab.

POLYOMAVIRUS CLINICAL SYNDROMES
Typical clinical syndromes associated with all 5 human polyomaviruses are summarized in Table 1. JC virus is the causative agent of progressive multifocal leukoencephalopathy (PML), a progressive demyelinating disease of the central nervous system described roughly 20 years before the discovery of the virus. PML is characterized by multifocal areas of white matter disease, with swollen oligodendroglial nuclei, giant astrocytes, lipid-laden macrophages, and loss of myelin in neuropathologic biopsy specimens. The diagnosis is suggested clinically in immunosuppressed patients, and generally confirmed by brain MRI scan and at times, CSF JC virus polymerase chain reaction (PCR) analysis, although brain biopsy is required for diagnostic certainty. PML was a rarely seen entity until the AIDS era, when it emerged as a common opportunistic infection in HIV-infected adults and older adolescents, albeit not in HIV-infected children. Its incidence has decreased somewhat less dramatically than that of other HIV-associated opportunistic infections as highly active combination antiretroviral therapy has become routine; however, a more substantial decrease in the mortality of PML has been seen. JC virus may be recovered in urine and other non-CNS tissues, but only very rarely causes polyomavirus-associated nephropathy. No specific treatment exists for PML, although in HIV-infected patients, combina-
The recently described KI and WU viruses have been associated with acute respiratory infection in both immunosuppressed and immunosuppressed children and adults, but the extent to which they cause disease (or simply are detected as reactivated viruses during infection with other pathogens) is unclear.

Similarly, the role of Merkel cell polyomavirus in causing Merkel cell cancer, a rare dermatologic cancer, is undergoing investigation; the presence of MC virus has been demonstrated in >75% of biopsies of Merkel cell cancer cells but not in control tissues, although the exact mechanism of pathogenesis is not yet known.

BK virus has been associated with 3 major clinical syndromes as follows: ureteral stenosis, hemorrhagic cystitis, and BK virus nephropathy (BKVN) (also known as polyomavirus-associated nephropathy, discussed further below). Although BK virus is thought of as a nephrotropic virus as opposed to the CNS-tropic JC virus, rare cases of BK pulmonary and CNS disease have been reported, just as rare cases of JC virus nephropathy have been reported. Ureteral stenosis associated with BK infection led to the virus’s discovery, but is now infrequently reported (<1%–3% of renal transplant recipients), perhaps because of improved surgical techniques and/or changes in immunosuppressive regimens (eg, use of calcineurin inhibitors) following renal transplantation.1,2

Hemorrhagic cystitis is particularly noteworthy in hematopoietic stem cell transplant recipients, with reported prevalence rates of 14% to 25% overall.1,2 BK virus without symptoms is much more common, found in 50% or more of stem cell transplant recipients, but only somewhat fewer than half of them will be persistently viremic or viremic, and subsequently develop hemorrhagic cystitis. Other causes of hemorrhagic cystitis, such as thrombocytopenia, and toxic effects of busulfan, cyclophosphamide, and ifosfamide, are likely more associated with relatively brief disease occurring soon after transplantation (<3 days after transplantation), whereas BK virus-associated cystitis occurs more commonly after posttransplantation day 10 and is longer lasting. BK virus is thought to cause the majority of this delayed posttransplant hemorrhagic cystitis, although the role of other viruses such as adenovirus is not well-defined.

**BK VIRUS NEPHROPATHY**

**Clinical Features**

Although BKVN was first recognized in 1978, its incidence appeared to increase in the mid-1990s, in association with the introduction of more potent immunosuppressive regimens (often including tacrolimus and mycophenolate mofetil) and perhaps also because of increased recognition by clinicians. A number of reviews have been published recently as interest in diagnosing, treating, and preventing BKVN has increased.1–7

Interestingly, BKVN occurs almost exclusively in transplanted kidneys, yet only rarely in the native kidneys of transplant recipients, or in patients with hematopoietic stem cell transplantation procedures, malignancy, or HIV/AIDS. Thus, immunosuppression in the context of BK virus infection appears to be a necessary but not sufficient cause in the development of BKVN; other factors, such as uroepithelial or renal tubular cell damage from ischemia or organ rejection also may play a role. Putative risk factors for BKVN include donor BK virus seropositivity with recipient seronegativity (especially in children), HLA mismatch, allograft injury, acute rejection, and to some extent, specific immunosuppressive medications (tacrolimus, mycophenolate mofetil, prednisone, and polyclonal antilymphocyte induction).1–3,7 Although BK virus seronegativity is a general risk factor for disease, the presence of BK-specific antibody does not appear to prevent or modify BKVN.7

BKVN affects 2% to 10% of adult renal transplant recipients, and over a few years time, grafts are lost in as many as 50% of those affected in the absence of therapy. Fewer prospective data have been collected in children, but estimated incidence and severity rates appear to be similar. In a retrospective, voluntary survey of the North American Pediatric Renal Trials and Collaborative Studies Registry participating clinical centers (N = 86 institutions and 1246 patients), BKVN was reported among 25 of 542 (4.6%) children from the 52 responding centers (60% survey response rate).8 The BKVN occurred at a median onset of 10.1 months after transplantation, at a median age of 11 years; during a mean of 2 years follow-up after BKVN diagnosis, the allograft loss rate was 24%.

There are no clearly associated systemic symptoms of fever, malaise, or allograft tenderness that accompany BKVN, despite viral replication and the conversion from latent to productive infection. BKVN classically presents as allograft dysfunction with an asymptomatic rise in serum creatinine, about 10 to 13 months (range, 6 days–5 years) posttransplant. The diagnosis of BKVN is made difficult by the lack of specific symptoms, by the relatively high frequency of BK virus reactivation after transplantation, and by the relatively common elevation of serum creatinine from a number of other causes including allograft rejection. However, children and adults with BKVN do have a progression of identifiable laboratory abnormalities, which have led to screening algorithms for diagnosis and therapy.1–7

**Diagnostic Tests**

Urinary shedding of “decoy cells,” tubuleepithelial cells with ground-glass intranuclear inclusions that are easily identified by staining of urinary sediment with the Papanicolaou stain, marks the onset of viral replication, and appears to precede the development of BK viremia by a median of 4 weeks and histologically proven BKVN by a median of 12 weeks.9,10 A number of research and commercial laboratories have now used real-time DNA PCR assays to quantitate viruria as a screening test for, and viremia as an adjunct to the diagnosis of, BKVN.11–13 All of these tests exhibit excellent sensitivity (100%), but are not highly specific (70%–90%) for BKVN, in that not all vuric or even viremic patients have biopsy-proven disease.11,11,12 Given that the prevalence of proven BKVN in prospective studies is <10%, even tests with 100% sensitivity and 90% specificity will have at most ~50% positive predictive value, making it difficult to “rule-out” BKVN with a positive PCR assay in the absence of a biopsy. However, the very high negative predictive value of 100% of assays for viruria and viremia do allow the clinician to “rule-out” BKVN with good confidence, given a negative test result.7,11,12 One caveat for the interpretation of polyomavirus PCR assays is that differences in PCR primers, probes, and viral control reagents have not been standardized, and substantial disagreement may be found among assays.14 Until reference materials and assays are better standardized, each laboratory needs to evaluate their own experience for validation.14

Despite laboratory assay variability, considering the performance characteristics

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**TABLE 1. Human Polyomaviruses**

<table>
<thead>
<tr>
<th>Polyomavirus</th>
<th>Notable Clinical Syndromes</th>
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<tbody>
<tr>
<td>BK virus</td>
<td>BK virus nephropathy (polyomavirus-associated nephropathy) Hemorrhagic cystitis Urinary stenosis</td>
</tr>
<tr>
<td>JC virus</td>
<td>Progressive multifocal leukoenephalopathy</td>
</tr>
<tr>
<td>KI virus</td>
<td>Respiratory infections? (under investigation)</td>
</tr>
<tr>
<td>WU virus</td>
<td>Respiratory infections? (under investigation)</td>
</tr>
<tr>
<td>MC (Merkel cell virus)</td>
<td>Merkel cell cancer? (under investigation)</td>
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of screening tests, the peak occurrence of disease in the first 2 years posttransplantation, and the invasiveness of renal biopsy (albeit its necessity for definitive diagnosis), an international, interdisciplinary group has suggested a consensus screening algorithm, which is similar to those put forth by a number of pediatric and adult nephrology experts (Fig. 1). The algorithm includes a heightened frequency of screening during the first 2 years after transplantation, with annual screening thereafter. Sustained positive tests suggest the need for renal graft biopsy (Fig. 1).

The histologic changes of BKVN are not pathognomonic, and can be mistaken for allograft rejection, ie, tubulointerstitial nephritis with varying degrees of inflammatory infiltrates, tubulitis and tubular atrophy, and fibrosis. The finding of intranuclear inclusion bodies is more specific, but may not be sensitive enough in a small core biopsy. The changes of BKVN may occur in a very focal distribution, including only the medulla; it is suggested to obtain at least 2 core biopsies, containing both cortex and medulla, for diagnosis. Most centers now use immunohistochemistry with polyoma virus antibody detection, and some use in situ hybridization or electron microscopy as adjuncts to light microscopy. A grading system has been proposed, which correlates biopsy findings with outcome and comorbidity.

Therapy

Nearly all experts believe that the principal treatment of BKVN is the reduction of immunosuppression, despite the risk of resultant allograft rejection. However, it is uncertain whether it is more effective (and less prone to graft rejection) to maintain all drugs in an immunosuppressive regimen at reduced doses, to switch some agents to others (eg, tacrolimus to cyclosporine A, tacrolimus or mycophenolate mofetil to sirolimus), or to discontinue one agent altogether (eg, change a 3-drug regimen to a 2-drug regimen). Suggested protocols for empirical reduction of immunosuppression in adult patients have been published, but controlled comparative clinical trials are not available for adults or children. Frequently cited protocols for adults include the reduction of calcineurin-inhibitor (eg, tacrolimus) dosing by 30%, antiproliferative drug dosing (eg, mycophenolate mofetil, azathioprine) by 50%, or to decrease prednisone dosing to <10 mg/d. Some authors also suggest the maintenance of blood trough levels <6 ng/mL for tacrolimus and sirolimus, <100 to 150 ng/mL for cyclosporine A, and dosing of <1 g/d for mycophenolate mofetil for adults (<600 mg/m2/d in children) or <100 mg/d for azathioprine in adults (<40 mg/m2/d in children).

Several adjunctive therapies for BKVN have been explored, including low-dose cidofovir, ciprofloxacin, IGIV, and the anti-inflammatory and immunomodulatory drug leflunomide. Each compound demonstrates in vitro activity (cell culture) against BK virus, although these assays are not standardized and drug cytotoxicity can mimic antiviral effect. Recent case series report some success with all of these agents, although in most cases the level of immunosuppression was also reduced, which might account for the observed remission of BKVN. The nephrotoxicity of cidofovir mandates that if used, it is given at a much lower dose than when used for cytomegalovirus infection: about 0.25 mg/kg by iv infusion every 2 to 3 weeks. It is uncertain how cidofovir inhibits BK virus, as unlike herpesviruses, BK virus does not produce a DNA polymerase.

The treatment of concurrent BKVN and allograft rejection (as demonstrated on renal biopsy) is problematic. Some experts will continue to reduce immunosuppression notwithstanding rejection; others may choose to provide a “pulse” of increased prednisone or other agents, followed by reduction of immunosuppression.

Retransplantation after graft loss from BKVN or rejection has been successful, and is not contraindicated. It is uncertain whether native and/or allograft nephrectomy is required, although it seems prudent if ongoing BK virus replication is occurring. BKVN may occur slightly more commonly after retransplantation (12%–15%).

REFERENCES


FIGURE 1. BKVN Screening, Monitoring, and Therapy.3–7,11

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