Polyomaviruses: An Overview

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Polyomavirus, a small nonenveloped DNA virus, has been known to cause severe hemorrhagic cystitis primarily in recipients of bone marrow transplantation and progressive multifocal leukodystrophy in patients with HIV infection. Recently, transplant nephropathy due to BKV, a member of the polyomavirus family, has been increasingly recognized as the cause for allograft failure. Polyomavirus has also been found to be associated with various neoplastic disorders and autoimmune conditions. At present, quantitation of polyomavirus DNA in the blood, cerebrospinal fluid, and urine; identification of virus-laden "decoy cells" in urine; and histopathologic demonstration of viral inclusions in the brain parenchyma and renal tubules are the few applicable diagnostics methods. Although various antiviral agents have been tried to treat polyomavirus-related infection, current management aims at the modification and/or improvement in the hosts' immune status. In this article, the authors provide an overview of polyomaviruses and briefly introduce the topics to be discussed in greater detail in later articles by experts in the field.

Introduction

Until recently, polyomaviruses and papillomaviruses were designated as the two subfamilies of the family *Papovaviridae*, but the term *papovavirus* has now been abandoned, and each subfamily is elevated to the status of a family. Viruses of the two families are unrelated immunologically and genetically, and they also have different biological characteristics. The polyomavirus family includes two human pathogens, JC virus (JCV) and BK virus (BKV), both of which were first isolated in 1971 from immunocompromised patients.[1] JCV was recovered from the brain of a patient (with the initials J. C.) who died of progressive multifocal leukoencephalopathy (PML), a demyelinating disorder of the central nervous system (CNS).[2] BKV was isolated from the urine of a Sudanese renal transplant patient (with the initials B. K.) who developed ureteral stenosis and was shedding inclusion-bearing epithelial cells in his urine.[3] In the late 1950s and early 1960s, millions of people were inadvertently exposed to a third polyomavirus, simian virus 40 (SV40) of rhesus macaques, due to administration of contaminated polio vaccines.[4]

Infections with both JCV and BKV are common in childhood and are largely asymptomatic. The viruses remain latent after primary infection and are reactivated in times of immune compromise, especially in conditions that bring about T cell deficiency. With few exceptions, the human illnesses associated with these viruses occur in immunocompromised hosts. Although the pathogenic effects of JCV are confined exclusively to the central nervous system, BKV-associated illnesses occur primarily in the urinary tract. Of great interest to the readers of this journal is the newly recognized syndrome of BKV nephropathy in renal transplant recipients. The contributions in this issue of *Graft* are therefore devoted primarily to the epidemiology, biology and pathogenesis, molecular mechanisms, and clinical implications of BKV infections.

Infectious Agent

Polyomaviruses are widely distributed in nature and have been described in humans and other animals (Table 1). They have probably coevolved with their hosts and are exquisitely adapted to grow in the species they infect. Each polyomavirus infects only one or a group of closely related species. In the immunocompetent host, primary infections occur in early life and are almost always completely unapparent.

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Table 1 | **Polyomaviruses and Their Natural Hosts**[a]

Host	Virus	Characteristics
Human	BK virus (BKV)	Early childhood infection; persists in renal epithelium and lymphocytes; causes nephropathy and ureteritis in immunocompromised hosts
	JC virus (JCV)	Late childhood infection; persists in renal epithelium, lymphocytes, and brain; causes progressive multifocal leukoencephalopathy (PML) in immunocompromised hosts
Monkey	Simian virus 40 (SV40)	Infects Asian macaques; persists in kidney; causes PML-like disease in immunocompromised animals
	Simian agent 12 (SA-12)	Infects African baboons
	Lymphotropic papovavirus (LPV)	Multiplies in B lymphoblasts of African green monkeys
	Cynomolgus polyomavirus (CPV)	Infects Cynomolgus monkeys; persists in renal epithelium and lymphocytes; causes nephropathy and ureteritis in immunocompromised hosts, similar to BKV nephropathy in humans
Cattle[b]	Bovine polyomavirus (BpyV)	Infects cattle; persists in kidney
Rabbit	Rabbit kidney vacuolating virus (RKV)	Infects cottontail rabbits
Hamster	Hamster papovavirus (HaPV)	Produces cutaneous tumors in hamsters
Mouse	Mouse polyomavirus	Natural infection of wild mice and may infect laboratory mouse colonies; persists in kidneys
	K virus	Infects pulmonary epithelium of mice
Athymic rat	Rat polyomavirus	Affects parotid gland
Parakeet	Budgerigar fledging disease virus (BFDV)	Produces acute fatal illness in fledgling budgerigars

a. Modified from reference 1.
b. A virus initially described as originating from stump-tailed macaques was subsequently identified as bovine polyomavirus.

Table 2 | **Properties of Polyomaviruses**

1. Species specific
2. 40–45 nm virion diameter
3. Naked icosahedral capsid
4. Superhelical double-strand circular DNA, 72 pentameric capsomeres
5. DNA genome: molecular weight 3.2×10^6, 5000 bp, constitutes 12% of virion mass
6. Share nucleotide sequences with other polyomaviruses
7. Nuclear site of multiplication

Polyomaviruses have the following properties: small size of the virion (diameter 40–45 nm), naked icosahedral capsid, superhelical double-strand circular DNA genome of molecular weight 3.2×10^6, shared nucleotide sequences with other polyomaviruses, and nuclear site of multiplication (see Table 2). The nonenveloped virion (Fig. 1) has icosahedral symmetry and 72 pentameric capsomers. The double-strand viral DNA genome constitutes about 12% of the virion mass and has about 5000 base pairs. BKV, JCV, and SV40 display a high degree of nucleotide sequence homology. Overall, the JCV genome shares 75% of the sequences with the BKV genome and 69% of the sequences with the SV40 genome.[1,5]

The virus-coded proteins of polyomaviruses are listed in Table 3. BKV and JCV have both species-specific and cross-reactive antigenic determinants. The viral genome is functionally divided into

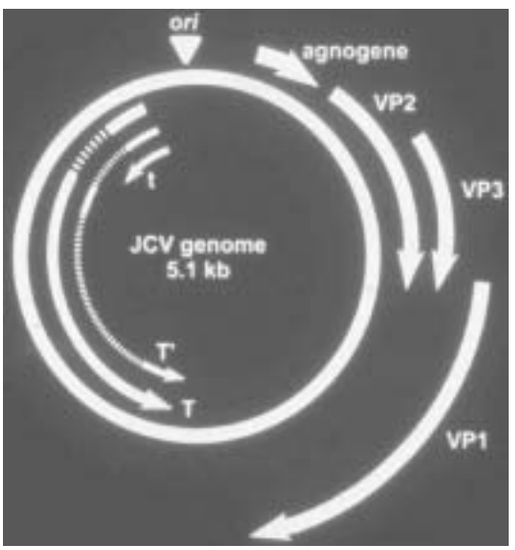

Figure 1. Polyomavirus: JCV structure and proteins.

1. an early region (2.4 kb), which codes for large and small T proteins;
2. a late region (2.3 kb), which codes for viral capsid proteins VP1, VP2, and VP3 and agnoprotein; and
3. a noncoding regulatory region (0.4 kb).

The early and late regions are transcribed from different strands of the DNA molecule. The regulatory region is located between the early and late regions and contains the large T antigen–binding sites, origin of DNA replication, and transcription control sequences. Viral DNA replication occurs bidirectionally, starting from the origin of replication. VP1 (molecular mass 39,600) is the major capsid protein and accounts for more than 70% of the virion protein mass. It mediates viral attachment to receptors on susceptible cells and contains epitopes for neutralization, hemagglutination inhibition, and other virus-specific and shared immunologic determinants. VP2 (37,300) and VP3 (25,700) are minor capsid proteins. BKV and JCV share a large number of amino acids, ranging from 83% (large T antigen) to 59% (agnoprotein). Compared to JCV and SV40, a greater homology exists between JCV and BKV.

BKV can be propagated in human epithelial cells and fibroblasts. For isolation of BKV, human embryonic kidney (HEK) cells, diploid lung fibroblasts, and urothelial cells are suitable.[6] The onset of viral cytopathic effect may take several weeks, whereas BKV-T antigen may be detected in infected cultures in 1 or 2 days.[7] In the case of JCV, primary human fetal glial (PHFG) cells are the most sensitive tissue culture system for isolation and propagation.[8] Human fetal Schwann cells[9] and astrocytes[10] also support JCV multiplication. Other cell types that allow isolation of JCV are urothelial, human amnion, adult brain, and HEK cells. Both BKV and JCV have been shown to produce plaque in HEK cells and can be assayed by scoring for cytopathic effect in end-point titrations in tissue culture tubes.

All polyomaviruses multiply in the nucleus, and during permissive infection, the viruses cause characteristic, often pathognomonic, nuclear changes and result in cell death. Urothelial cells infected with BKV or JCV, oligodendrocytes infected with JCV, and mouse pulmonary endothelial cells infected with BK virus display similar nuclear abnormalities and may result in ureteral obstruction and tubular injury, PML, and pneumonia, respectively. BKV and JCV also undergo nonpermissive infection and transform cells in tissue culture. In the case of BKV, transformed cells exhibit BKV-T antigen and contain multiple copies of BKV-DNA. BKV-DNA is integrated into the host cell genome in rodent cells, but in human cells, it may remain as free unintegrated copies.[11,12]

Pathogenesis and Pathology

BKV and JCV do not naturally infect any species other than humans. The host range and tissue specificity of polyomaviruses are determined by an interaction of cellular and viral factors. There are also significant differences between BKV and JCV with respect to their biological behavior and disease potential. When inoculated into a wide variety of laboratory animals, BKV and JCV produce serologic response and sometimes tumors but do not result in infections similar to that seen in humans. Although BKV and JCV are latent in the kidney and are reactivated in immunosuppressed states, only JCV infects the CNS and produces PML. In renal transplant recipients and in pregnant women, both BKV and JCV are reactivated frequently and

Table 3 | **POLYOMAVIRUS PROTEINS**[a]

Protein/Region	Molecular Weight	Number of Amino Acids JCV/BKV	Sequence Homology Shared with JCV[b] BKV	SV40	Function
Early coding					
Large T	79,305	688/695	83	72	Initiates viral replication; stimulates host DNA synthesis; modulates early and late transcription; establishes and maintains host transformation
Small T	20,236	172/172	78	67	Facilitates viral DNA replication
Late coding					
VP1	39,606	354/362	78	75	Major capsid protein; forms viral ichosahedron, enables entry, mediates hemagglutination
VP2	37,366	344/351	79	72	Minor capsid protein
VP3	25,743	225/232	75	66	Minor capsid protein; subset of VP2
Agnoprotein	8081	71/66	59	46	Facilitates capsid assembly

Molecular weight and number of amino acids of JCV proteins deduced from nucleotide data. In addition to large T and small T antigens, a middle T antigen is coded for by mouse polyomavirus and hamster papovavirus.
a. Modified from reference 1.
b. Percentage amino acids.

are excreted in the urine; however, in bone marrow transplant recipients, BKV reactivation is far more frequent than JCV reactivation.[1,13,14]

The pathogenesis of a polyomavirus infection involves the following sequence of events: entry of virus into the body, multiplication at the entry site, viremia with transport of virus to the target organs, and multiplication in the target organs. VP1 interacts with specific receptors present on susceptible cells and mediates virion entry into the cell by endocytosis; the virus is then transported to the nucleus, where it is uncoated.[15] After multiplication in the nucleus, the virus reaches the target organs by the hematogenous route. The viral determinants that affect host range and tissue specificity of BKV and JCV are located in the enhancer/promoter elements in the regulatory regions[16] and the early regions of these viruses.[17,18] With respect to BKV and JCV, the route of infection is not known. Although BKV is seldom recovered from the respiratory tract, the rapid acquisition of antibodies in the first few years of life is consistent with virus transmission by the respiratory route.[19] Primary infection may be accompanied by transient viruria and in the immunocompetent host; BKV and JCV persist indefinitely as latent infections. BKV and JCV also persist in the kidney and B lymphocytes for an indefinite period of time.[20,21] Reactivation of BKV and JCV in the urinary tract occurs under a wide variety of conditions, including kidney and bone marrow transplantation, primary immunodeficiency diseases, immunotherapy for malignancy and other disorders, pregnancy, chronic diseases (e.g., diabetes), infection with human immunodeficiency virus, and old age.

SV40-associated PML in a macaque colony and SV40-associated interstitial pneumonia and renal tubular necrosis in a rhesus macaque have been reported.[22,23] In the animal with renal disease, abundant numbers of SV40 particles and large intranuclear inclusions were seen in the renal tubular epithelial cells. The disease was similar to BKV-induced tubulointerstitial nephritis, described in a child with an inherited immunodeficiency disease.[24] SV40-associated PML occurred in immunosuppressed simian immunodeficiency virus (SIV)–infected rhesus macaques.

Gorder et al.[25] identified a new polyomavirus, cynomolgus polyoma virus (CPV), from renal tubules of cynomolgus monkeys (*Macaca fascicularis*) treated with cyclosporine and azathioprine. This virus has 84% DNA sequence homology to SV40. Twelve cynomolgus monkeys had polyomavirus interstitial nephritis in the native kidney

and/or the renal graft. Most of the animals that had polyomavirus infection developed lethargy and anorexia and had rising levels of creatinine. In the renal graft, the peak frequency of infection was from days 21 to 48 after transplant. In addition to interstitial nephritis, some of the graft had endarteritis and focal hemorrhage indicative of active cellular rejection. Several grafts had extensive rupture and destruction of collecting ducts. None of the animals with detectable virus in the allograft had infections of the native kidney. The donor ureter had detectable polyomavirus in 3 cases, showing acute ureteritis and apoptosis of the smooth muscle cells. All 3 developed acute cellular rejection in both the ureter and kidney and subsequently died. No particular association of polyomavirus with any of the immunosuppressive agents was evident. These studies identify a new polyoma infection in cynomolgus monkeys and provide insights into analogous infections in humans.

Clinical Features

Primary Infection

In healthy children, primary infection with BKV and JCV is a rarely associated clinical disease. In a prospective study, 11 out of 66 children with respiratory illness demonstrated BKV seroconversion; 7 of these children had mild respiratory disease and 4 were asymptomatic. BKV was isolated from the urine of 1 of the children showing seroconversion. Unintegrated BKV DNA was identified in the tonsillar tissue of 5 of 12 children with recurrent respiratory disease.[26] In immunocompromised children, primary BKV infection may cause cystitis or nephritis, and primary JCV infection may lead to PML. Primary BKV infection may also present with encephalitis. Following primary infection, viruses persist indefinitely as "latent" infections of the kidney.

Silent Viruria

BKV can be reactivated after many years, usually by states of acquired (cell-mediated) immunosuppression: pregnancy, HIV, neoplasm, systemic lupus erythematosus, nephrotic syndrome, bone marrow transplantation, and organ transplantation. Of immunocompetent patients, 20% are found to have JC viruria; in this situation, whether viral shedding represents reactivation or new infection remains unclear.[27]

Pregnancy

Approximately 3.2% of pregnant women during second (late) and third trimesters show cytologic evidence of BKV and JCV excretion in urine.[28] In tests of paired sera spanning pregnancy, a rise in antibody titers to BKV or JCV was found in 14% of the women.[29] The viral transcription may be induced by hormonal changes, and shedding continues intermittently throughout the pregnancy until the postpartum period. Although controversy exists about transplacental transmission to the fetus, viral excretion does not appear to be associated with any ill effect to the mother.[30]

Systemic Lupus Erythematosus (SLE)

The prevalence of BKV genome is significantly higher than JCV in the serum of patients with SLE. Using polymerase chain reaction (PCR), Sundsfjord et al.[31] have identified BKV genomic sequences in 16% of 44 patients with SLE. In another study, 65% (13/20) of SLE patients showed at least one urine positive for BKV. Viruria is independent of immunosuppressive therapy, suggesting that an unknown inherent immunologic defect in SLE patients may be the contributing factor. It has been suggested that BKV infection may contribute to the development of SLE, as supported by the findings that patients with BKV infection with expression of large T antigen develop anti-DNA antibodies, and anti-BKV antibodies have some cross-reactivity with DNA.[32]

Renal Transplant Recipients

Infections in renal transplant recipients have been studied by several investigators[33-35] and have been frequently reviewed.[29] In a multicenter serologic study of nearly 500 renal allograft recipients in the United States, BKV and JCV infections occurred in 22% and 11% of the patients, respectively.[33] Virus shedding in urine of renal transplant recipients has been monitored by a variety of techniques, including urinary cytology, immunoassay, electron microscopy, virus isolation, ELISA assays, nucleic acid hybridization, and PCR. In prospective studies,

25% to 44% of renal transplant patients excrete virus in their urine in the posttransplant period. The duration of excretion ranges widely, from transient viruria to excretion over several weeks or several months. The kidney of a seropositive donor may initiate infections in the recipient.[36] Infections may be either reactivations or primary infections affecting up to 5% of renal allograft recipients in about 40 weeks (range = 6–150) posttransplantation. More than 50% of the patients show serologic evidence of infection with the virus. Without treatment, progression to irreversible allograft failure has been reported in up to 45% of all cases.[37,38] The infections appear to be responsible for some cases of ureteral obstruction.[39,40] Risk factors may include treatment of rejection episodes and increasing viral replication under potent immunosuppressive drugs such as tacrolimus, sirolimus, or mycophenolate mofetil. BKV-related vasculopathy, a new tropism, has been described recently, in which a fatal case of disseminated BKV infection in a renal transplant recipient was associated with BKV multiplication in endothelial cells.[41]

HIV

Several studies have demonstrated that 20% to 30% of patients with HIV excrete BKV in the urine. The frequency of BK viruria increases with decreasing CD4 count, but viruria and absolute CD4 count are not strongly correlated. In patients with AIDS, BKV has been reported to cause fatal tubulointerstitial nephropathy and disseminated pulmonary and CNS infection.[42]

Bone Marrow Transplantation and Hemorrhagic Cystitis

Hemorrhagic cystitis (HC) is not an uncommon complication in recipients of bone marrow transplantation (BMT). Transient HC occurring in the first few days after transplantation usually represents drug toxicity. About one-half of the BMT patients excrete BKV in the posttransplant period, which is higher in recipients of allogeneic marrow (50%). Late-onset HC (2–12 weeks posttransplant) that lasts more than 7 days is associated with BK viruria.[43,44] In one study, HC occurred four times more frequently in BKV excreters than in non-BKV excreters, and in these patients, BK viruria was associated with 16 out of 18 cases of HC.[43] The onset and termination of BK viruria often coincided with the onset and termination of HC. BKV was recovered far more frequently in urine collected during the episodes of hemorrhagic cystitis (55%) than in urine collected in cystitis-free periods (8%–11%). In another study, BK viruria in BMT recipients was associated with gross or microscopic hematuria but without evidence of clinical cystitis.[45]

JCV-Related Disease: Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, subacute, demyelinating disease of the CNS primarily affecting individuals who have impaired immunity.[46-48] PML, previously a disease of the fifth and sixth decades of life, is now recognized in younger patients. PML is recognized in as many as 3.8% of patients with AIDS who have neurologic abnormalities.[49,50] The disease was reported more frequently in those who were exposed to HIV by blood transfusion than in those in all other exposure categories. In addition to AIDS, PML also occurs in patients with

1. lymphoproliferative disorders,
2. sarcoidosis and tuberculosis,
3. inherited primary immunodeficiency diseases, and
4. in those under prolonged immunosuppressive and chemotherapies.

In PML, JCV causes a cytocidal infection of oligodendrocytes, leading to demyelination. Neurons are unaffected, and morphologic changes in JCV-T antigen containing astrocytes probably represent nonpermissive infection.[46] The widespread and multifocal distribution of demyelination in PML suggests a hematogenous spread. JCV genome has also been isolated in B lymphocytes of individuals previously infected with JCV.[20] It has been proposed that during multiplication of JCV, infected B lymphocytes transport the virus to the CNS and initiate PML.[51] Alternatively, reactivation of JCV seeded in the brain during primary infection may also lead to PML, as seen in older patients.[52]

The onset of the disease is insidious and may occur at any time during the course of the underlying

condition. Early signs and symptoms point to multifocal, asymmetric lesions in the brain when patients present with impaired speech, vision, and mentation. As the disease progresses rapidly, paralysis, blindness, and sensory abnormalities develop. Death occurs within 3 to 6 months after onset of symptoms.

Macroscopically, the PML brain shows widespread demyelination of varying sizes (2–3 cm in diameter), distributed mainly in the subcortical white matter. In advanced cases, the lesions show central necrosis and cavitary changes. Histopathology demonstrates the loss of myelin and the presence of macrophages, reactive astrocytes, and enlarged oligodendrocytes containing basophilic or eosinophilic inclusion bodies. Greatly enlarged, bizarre, giant astrocytes with pleomorphic, hyperchromatic nuclei resembling the malignant astrocytes are additional findings.

Abundant amounts of JCV particles are often found in dense crystalline arrays in the altered oligodendrocyte nuclei. JCV in PML brains has been routinely identified by a variety of techniques, including

1. immune electron microscopy,
2. immunofluorescence or immunoperoxidase tests,
3. cultivation of virus, and
4. Southern blot, in situ hybridization, or PCR.

In PML brains, viral DNA is distributed more extensively than viral antigen and may be found in cytologically unaffected oligodendrocytes. In cases of PML, JCV is also found in the cerebrospinal fluid[53] and extraneural sites (e.g., kidney, liver, lung, lymph node, and spleen).[54] The amount of DNA in these tissues is significantly less than that in the brain.

Polyomaviruses and Human Malignancies

Polyomaviruses are oncogenic for laboratory animals and are capable of transforming human cells. Tumors or tumor-derived cells have been examined for viral particles, viral T antigen, and viral genomes; moreover, sera from cancer patients have been screened for the presence of antibodies to capsid and T antigens. Genomic sequences of BKV, JCV, and SV40 have been variably reported from a wide variety of human cancers, including mesothelioma, pediatric and adult brain tumors, osteosarcoma, and non-Hodgkin's lymphomas. The significance of these observations is unclear. The possibilities being examined include the following:

1. they are laboratory artifacts,
2. they represent passenger viruses, and
3. the infections contribute to the development of these cancers.

In this issue, Lee and Langhoff[55] have examined this topic in great detail.

Prevention and Control

BKV and JCV infections are extremely common and are essentially harmless except when the host is immunologically impaired. Infection with BKV occurs at an earlier age than that with JCV. In the United States, antibodies to BKV are acquired by 50% of children by ages 3 to 4 years, whereas antibodies to JCV are acquired by 50% of children by ages 10 to 14 years. The antibody prevalence to BKV reaches nearly 100% by ages 10 to 11 years and then declines to around 70% to 80% in the older age groups.[56] The antibody prevalence to JCV reaches a peak of about 75% by adult age.

Primary infections with BKV and JCV in healthy children are rarely associated with illness. BKV seroconversion is associated with mild respiratory illness.[18] Reactivations are brought about not only by significant immunosuppression, as in renal transplant recipients and HIV-infected individuals,[57] but also by more subtle factors, such as pregnancy, diabetes, and old age. There have been no attempts to devise strategies for the prevention and control of these infections.

Serial monitoring of the BKV load in plasma and performing urinary cytology for BK viruria are helpful in the early diagnosis of BKV nephropathy. At this time, due to the continued shortage of organs, discarding BKV-positive organs is an unacceptable proposal.

Diagnosis and Treatment

BKV

Cytomorphology of urinary epithelial cells is helpful as an indication of polyomavirus excretion

in urine.[58] Virus-infected epithelial cells are enlarged "decoy cells," and their nuclei contain a single, homogeneous, large, pale basophilic inclusion that may occupy the entire nuclear area. Polyomavirus-infected urinary cells should not be mistaken for cells infected with CMV, which are generally smaller, basophilic, or eosinophilic; are surrounded by a halo; and contain intracytoplasmic inclusions. The rough-textured nuclear chromatin of a malignant cell differs greatly from the structureless inclusion in a polyomavirus-infected cell. The cytologic findings by themselves are not definitive because they cannot distinguish between BKV and JCV infections, and virus excretion in urine may occur without marked cytologic abnormalities. The presence of virus in the urine can be demonstrated by a variety of techniques, including

1. tissue culture,
2. electron microscopic,
3. ELISA assays,
4. BKV and JCV DNA probes, and
5. polymerase chain reaction.

Although experience is limited, current management strategies aim at the judicious lowering, switching, and discontinuation of the dosage of the immunosuppressive therapy to allow clearance of BKV. Individual case reports support the view that early stages of BKV nephropathy might be more readily reversible.[59,60] In case of coexisting acute rejection, a two-step procedure of immediate antirejection treatment followed by reducing the maintenance immunosuppression might be indicated. In some situations, allograft and native nephrectomies were carried out to remove the source of infection, and then successful retransplantation was performed.[61] More, recently, antiviral treatment has been employed with variable results. Retinoic acid, DNA gyrase inhibitors, cidofovir, and 5′-bromo-2′-deoxyuridine inhibit polyoma virus replication in vitro. In clinical trials, cidofovir was effective when administered at 20% of the dosage recommended for treatment of CMV.[62] In clinical trials, 5′-bromo-2′-deoxyuridine has been ineffective, but vidarabine has reportedly produced dramatic remission in a patients with post-BMT HC.[63] Interferon has some activity against BKV in vitro but no effect on BK viruria in renal transplant patients.[64] Early results with two malonoitrilamide compounds, FK-778 and FK-779, and simian polyomavirus and murine polyomavirus showed that these agents demonstrated antipolyomavirus activity and were able to decrease free virus production.[65]

JCV

Signs and symptoms of asymmetric multifocal brain disease without signs of increased intracranial pressure in an immunocompromised person would suggest the diagnosis of PML. Computed tomographic scan or magnetic resonance imaging of the brain is effective in establishing the diagnosis, but stereotactic biopsies may be needed to distinguish PML from other conditions.[66] Serologic studies are not helpful as JCV antibodies levels tend not to increase in the course of the disease. Viral antibodies are not detected in the cerebrospinal fluid. The unique histopathologic features of PML can be identified by light microscopy and can be confirmed by demonstration of JCV particles, antigen, or DNA in the brain. JCV DNA can be amplified from the cerebrospinal fluid of PML patients.

Attempts to treat PML have not been generally successful, although some remissions have been reported.[46] The general strategy has been to discontinue, if possible, immunosuppressive drugs and treatments and to attempt to inhibit viral multiplication by chemotherapy. The drugs most frequently tried are nucleic acid base analogues, adenine arabinoside, cytosine arabinoside, and alpha-interferon. Patients most likely to benefit by therapy are those whose basic defense mechanisms are relatively intact (e.g., renal allograft recipients) and in whom it would be possible to eliminate or reduce iatrogenic immunosuppression. Patients with inflammatory response in the PML lesions appear to survive longer than patients without such response.[67] Unfortunately, early detection of PML and aggressive symptomatic treatment do not seem to extend the survival time of PML patients.

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