BK virus nephritis after renal transplantation

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

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VIROLOGY

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

HISTORY OF BKV NEPHRITIS

The terminology of BK virus originated from a renal transplant patient, initial BK, in whom it was first detected as a clinical disease in 1971.[1] There were no reported cases of this disease for the next 24 years, until Purighalla and co-workers observed their first case in early 1995.[2] Subsequently, there has been a surge of BKV nephritis (BKVN) cases from many transplant centers across US, including ours.[3–8] The key factor associated with this increasing incidence remains unclear. Introduction of immunosuppressive agents such as mycophenolate mofetil (MMF) and Tacrolimus (Tac) has been thought to play a causative role in BKVN. However, this infection is also seen in patients who have never received the above combinations of immunosuppressive agents, as well as those receiving sirolimus, and those with steroid avoidance protocols. Thus, in recent years, the incidence of this infection has increased in renal transplant recipients and now poses a threat to improving graft survival.[6,7]

PREVALENCE OF BKV INFECTION

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

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

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

CLINICAL FEATURES, DIAGNOSIS, RISK FACTORS, AND OUTCOME

Clinical features

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

Diagnosis

The diagnosis of BKV infection is based on the documentation of viral cytopathic effects (urinary decoy cells), the virus itself (in blood, urine, and/or renal tissue), immunity to virus (BKV-specific antibody), and renal histological findings of nephritis. Each diagnostic modality and its limitations are shown in Table 1. Urinary decoy cells are a good diagnostic screening test, but the positive predictive value is around 20%. Thus, demonstration of urinary decoy cells suggests the presence of BKV in urothelium, but does not confirm BKVN.

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

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

Table 1 | Diagnosis of BK virus nephritis

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