Update on the Management of BK Virus Infection

Ahmed Saleh,[1,4,5] Mohamed Salah El Din Khedr,[1] Abeer Ezzat,[2] Anna Takou,[3] Ahmed Halawa[4,5]

Abstract

The BK polyomavirus was isolated in 1971; it has been a significant risk factor for both graft dysfunction and failure in renal transplant recipients. So far, no specific treatment option has been available for effective treatment or prophylaxis for BK virus infections. Although the use of heavy immunosuppression has been the main risk factor for BK virus infection, other risk factors are equally important, including elderly recipients, prior rejection episodes, male sex, human leukocyte antigen mismatching, prolonged cold ischemia time, pretransplant BK virus serostatus, and ureteral stenting. Regular follow-up for BK virus infections according to each institution's policy has been, so far, effective in detecting patients with BK virus viremia and consequently preventing allograft loss. The mainstay of management continues to be reduction of immunosuppression. However, newer options are providing new insights, such as cellular immunotherapy. In this review, we will address the diagnosis, screening, new diagnostic tools, and updated management of BK virus infections.

Key words: *Graft dysfunction, Immunosuppression, Polyomavirus, Renal failure*

Introduction

Polyomaviruses are small DNA viruses that can infect humans and animals like rabbits, rodents, and birds. BK polyomavirus (BKV) is considered one of the highly prevalent forms of polyomaviruses causing infection in humans, especially in immunocompromised patients. In renal transplant recipients, BKV can lead to tubulointerstitial nephritis and ureteral stenosis; it can also lead to hemorrhagic cystitis in bone marrow transplant patients.[1] The current consensus on management of BKV viremia is to decrease immunosuppression, to have regular follow-up of BKV polymerase chain reaction (PCR), and to have continuous monitoring of renal functions in an attempt to prevent allograft BKV nephropathy (BKVN), which could subsequently increase the risk of graft failure. The challenging part in the management of BKV infection is the balance between the fear of rejection due to reduction of immunosuppression and the maintenance of immunosuppression at the same level, which could cause more BKV viremia and consequently BKVN.[2]

BK virus is one of the most common infections in renal transplant recipients.[3-5] Every institution has its own local policy for screening BKV infection; however, most institutions tend to reduce immunosuppression to control BKV viremia, with few institutions following a preemptive immunosuppression reduction policy.[6-8] Reports have shown that BKVN management with reduction of immunosuppression has been effective in preserving allograft function.[9,10]

Virology

Properties

BK virus is a member of the family Polyomaviruses. This family is a double-stranded DNA virus with icosahedral symmetry. BK virus has been categorized serologically and genotypically into 4 groups (I to IV), with each one having a different virulence.[11]

Historical aspects

In 1971, a Sudanese renal transplant patient "whose initials were given for the virus" was diagnosed with BKV infection when he presented with ureteral

From the [1]Nephrology Department, Faculty of Medicine, Suez Canal University, Egypt; the [2]Microbiology Department, Faculty of Medicine, Suez Canal University, Egypt; the [3]Pathology Department and [4]Nephrology and Transplantation Department, Sheffield Teaching Hospitals, United Kingdom; and the [5]Institute of Medical Sciences, University of Liverpool, Liverpool, United Kingdom

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Corresponding author: *Ahmed Halawa, Consultant Transplant Surgeon, Sheffield Teaching Hospitals, Associate Professor, University of Liverpool, Liverpool, UK*
E-mail: *ahmed.halawa@liverpool.ac.uk*

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obstruction after renal transplant. When the ureters were examined under electron microscopy, viral particles were seen in the lining of the ureters. In addition, a high BKV antibody titer was detected in the patient's serum.[12]

Genome structure and transcription

Polyomaviruses are small (40-50 nm in diameter), uncovered, icosahedrals, with a double circular chain. Their genome is about 5000 base pairs, contained in the histones derived from host cells. When exposed to high temperature, their particles are stable, thus retaining their ability to infect. The external layer consists of structural proteins VP1, VP2, and VP3. VP1 is organized into 72 pentamers, each one associated with a unique copy of smaller structure proteins (VP2 or VP3). VP1 determines receptor specificity, whereas VP2 and VP3 are involved in viral particle stabilization outside the host cell and transport within it. The genomic structure encodes 6 chief proteins divided into 3 regions: early encoding region, late encoding region, and noncoding control region.[13]

Transmission mechanism

Primary BKV infection occurs in the first decade of life, on average at 4 to 5 years of age. Possible routes include the following: (1) airborne transmission through air droplets[14]; (2) a feco-oral transmission, as fecally eliminated polyomaviruses are detected in hospitalized children; (3) other mechanisms, including urinary-oral route or seroconversion after solid-organ transplant (such as renal transplantation)[15]; and (4) both through blood transfusion and vertical transmission; these have been considered routes for BKV transmission as BKV DNA has been found in the placenta, brain, and renal tissue of aborted fetuses.[16,17]

Primary polyomavirus infections usually occur during childhood through respiratory or oral routes.[18] Primary infections are often clinically insignificant; however, the virus stays in the renal epithelium, including in tubular, parietal, and transitional structures and in Bowman's capsule.[19] In the immunocompetent population, BKV replication is manifested by asymptomatic viruria, and the incidence of shedding is 20%. However, in immunocompromised individuals, the risk of shedding reaches 60% and the viruria is more common.[20,21] Patients with impaired cell-mediated immunity have a particularly greater risk of BKV infection; these patients include pregnant women where viral shedding usually disappears 2 weeks after delivery.[22] The mean prevalence of BKVN in renal transplant recipients is 5%, whereas the prevalence of ureteral stenosis is less.[23]

Risk factors and pathogenesis

The most important risk factor for developing BKV disease is the degree of immunosuppression rather than the type of immunosuppression used. Transplant physicians consider BKV infection as a marker of heavy immunosuppression.[24] Active BKV disease has been associated with various immunosuppression protocols, most commonly tacrolimus and mycophenolate mofetil based.[25,26] Other studies have suggested that BKV disease can occur with any immunosuppression medication.[27,28] In addition, immunosuppressive agents can affect T cells, which can lead to increased BKV replication. Tacrolimus specifically can increase BKV replication by a specific mechanism involving FK-binding protein (BP-12).[29] Other risk factors that could be involved, although not commonly, include diabetes mellitus, delayed graft function, treated episodes of acute rejection, ureteral trauma, use of antilymphocyte antibodies, coinfection with *Cytomegalovirus* (CMV), maintenance steroid immunosuppression, older age, white race/ethnicity, and presence of specific human leukocyte antigen (HLA) C loci.[30-32] Of note, the presence of BKV antibody titers in donors, which reflects recent BKV reactivation and replication, is another risk factor. The viruria in a potential donor can be considered as a predictor for posttransplant BKV infection.

Recent studies have demonstrated that BKV replication in a transplant recipient is usually due to transmitted infection from the donor.[30] Both HLA and ABO-incompatible transplants carry a higher risk of BKV nephropathy, possibly due to heavy immunosuppression (whether due to induction or maintenance immunosuppression or episodes of rejection). In 2004, Awadalla and associates demonstrated that renal transplant recipients who have HLA-incompatible transplant have increased incidence of rejection; this is especially shown in patients who were steroid resistant or treated with antilymphocyte treatment.[33] Similarly, ABO-incompatible recipients are at a higher risk of BKVN than HLA-mismatched recipients as they may have a higher rate of rejection and need more immunosuppression than HLA-incompatible patients. In a

study that compared 62 ABO-incompatible and 221 HLA-incompatible kidney transplant recipients, 17.7% versus 5.9% recipients developed BKVN, respectively.[32]

Clinical Picture of BK Virus Infection

About 90% of the population will become BKV seropositive during their life; this reactivates after solid-organ transplant, especially in bone marrow or kidney transplant recipients. In kidney transplant recipients, reactivation may lead to BKVN, which may end with graft dysfunction and failure by causing tubulointerstitial nephritis and/or ureteral obstruction. In bone marrow transplant recipients, BKV can lead to hemorrhagic cystitis. It is quite rare to have BKV reactivation in other immunocompromised patients, such as those with human immunodeficiency virus, systemic lupus, or other autoimmune diseases (Table 1).

Clinical manifestations are as follows: (1) asymptomatic, (2) slow and progressive increase of serum creatinine, and (3) an unsuspected finding of progressive renal damage (BKVN) on surveillance renal allograft biopsy.[34] Importantly, no signs and symptoms are identified with BKV infection. Usually, BKV infection occurs 10 to 13 months posttransplant. BK virus nephropathy may occur earlier at week 1 posttransplant or as late as 5 years posttransplant.[35]

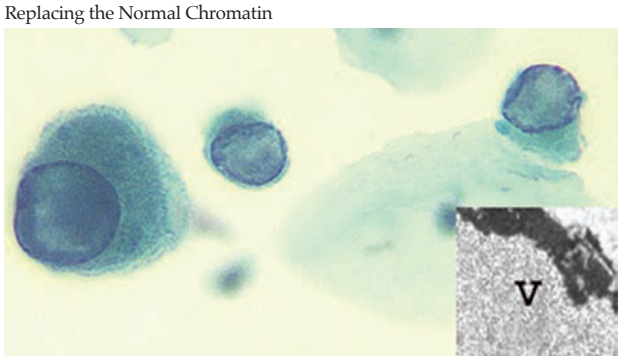
Laboratory findings in patients with BKV infection are as follows: (1) elevated serum creatinine and (2) urine analysis with pyuria, hematuria, and findings consistent with interstitial nephritis as cellular casts composed of renal tubular cells and inflammatory cells. However, these results could be normal.

Diagnosis Overview

A tissue (renal) biopsy is needed for a definitive diagnosis of BKVN; however, a diagnosis may be missed in the tissue obtained because viropathic lesions are patchy. In addition, for BKV, tropism is medulla, not the cortex, which may increase the risk of missing the viropathic lesions. Quantitative PCR is used to diagnose BKV viremia, which demonstrates BKV replication whether there is renal involvement or not. BK virus nephritis is suspected when the clinical diagnosis of tubulointerstitial nephritis is suspected; however, there are no clinical features of tubulointerstitial nephritis that are unique to BKVN. The presence of decoy cells in the urine analysis increases the suspicion of BKV nephritis, which should be followed by quantitative PCR of blood preferable to urine (Figure 1).

Different pathological patterns and associations with BKV infection are also shown in Figures 2 to 7.

Figure 1. Three Urine Decoy Cells With the Characteristic Large Viral Inclusion Replacing the Normal Chromatin



The nuclear inclusion is formed by dark, smudged material representing thousands of newly formed virions (V). Electron microscopy (inset) shows the contrast between the inclusion (V) and the darker surrounding chromatin. Courtesy of Cinthia Drachenberg, MD. Graphic 101386 Versions 1.0.

Definitive diagnosis of BK virus nephropathy

A definitive diagnosis of BKVN requires characteristic cytopathic changes on the renal biopsy plus positive immunohistochemistry (against BKV or against SV40 large T antigens), which has a specificity of 100%, and pathognomonic results for BKV infection (Figure 6).[36,37] A diagnosis of BKV in a renal biopsy could be missed in about 30% of cases because BKV has a focal tropism in the medulla rather than in the cortex, making an initial biopsy not enough to exclude

Table 1. Steps of BK Virus Infection in Renal Transplant Recipients[93]

1.	Primary infection	Initial infection of the host including viremic spread to susceptible tissues with mild or no clinical symptoms
2.	Latent infection	Asymptomatic inactive infection of susceptible cells after primary infection. Virus detection is perfomed only by molecular techniques.
3.	Serologic evidence of infection	Variation in antibody titers occurs in almost all healthy children and 60% - 90% of asymptomatic adults. No correlation with intrarenal latent viral load. Presents a weak correlation with viral disease.
4.	Viral activation	Evidence of replication can be detected by observing "decoy cells" or free urine virions. Viral detection by a polymerase chain reaction in urine, serum, or cerebrospinal fluid, can be considered to be a transient and asymptomatic event or as part of a viral disease.
5.	Viral disease	Histologic evidence of viral replication in organs (cytopathic signs and/or positive immunohistochemistry or in situ hybridization) and virus-induced tissue damage is often associated with clinical symptoms.

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the diagnosis of BKVN if highly suspicious.[38,39] In the absence of definitive criteria for BKVN diagnosis (Table 2), a presumptive diagnosis can be done if there is sustained (more than 2-week duration) urinary viral shedding and significant BKV replication (plasma DNA PCR load > 10 000 copies/mL), as detected using a specific assay with or without kidney dysfunction; these characteristics have been proposed to define presumptive BKVN.[36,38] Moreover, BKVN can be graded into 3 grades using Banff criteria according to the percentage of fibrosis and the amount of viral replication (Table 3).

In BKVN, light microscopy examinations would show the following: (1) basophilic intranuclear viral inclusions without a surrounding halo (Figure 7)[21,40]; (2) anisonucleosis, hyperchromasia, and chromatin clumping of infected cells[21,40]; (3) areas of tubular damage showing interstitial mononuclear or polymorphonuclear cell infiltrates (Figure 2)[21,40]; (4) tubular injury in the form of tubular cell apoptosis, desquamation, and flattened epithelial lining[21,40]; and (5) tubulitis with lymphocyte invasion to the basement membrane of the tubular epithelium. When extensive, it is difficult to differentiate between BKVN and allograft rejection (Figure 2).[21,40]

In BKVN, electron microscopy examinations would show the following: (1) viral inclusions with diameter size ranging from 30 to 50 nm and (2) tubular damage, including tubular cell necrosis, prominent lysosomal inclusions, and luminal protein and cellular casts.[40,41,49]

Table 2. Specific Histologic Findings of BK Virus Nephropathy[39,94]

Pattern	Characteristics
Pattern A	Cytopathic/cytolytic changes with absent or minimal inflammation (Figure 3)
Pattern B	Cytopathic/cytolytic changes associated with patchy or diffuse tubulointerstitial inflammation and atrophy
Pattern C	Graft sclerosis

BK virus nephropathy can be similar to cellular rejection; however, in situ hybridization or immunohistologic methods are used to differentiate between both. Usually BK virus infects epithelial cells; however, a severe case of BK virus infection can lead to vasculopathy (a feature of cellular rejection), which was confirmed later by immunohistologic methods.[95] Correlations between histologic findings (Table 2) and BK viremia is essential in patients who show ambiguous histologic features. Banff grading has been approved for BK virus nephropathy, which grades the degree of BK virus nephritis according to fibrosis and viral replication (Table 3).

Table 3. Banff Grading of BK Virus Nephritis

Grade	Percent Fibrosis and Viral Replication
Grade 1	Minimal viral replication in < 1% of biopsy with < 25% fibrosis
Grade 2	Any between grades 1 and 3
Grade 3	Marked virus replication in > 10% of cores with > 25% fibrosis

Figure 2. Marked Acute Tubular Necrosis With Significant Tubulitis Raises Concerns for Concurrent Rejection

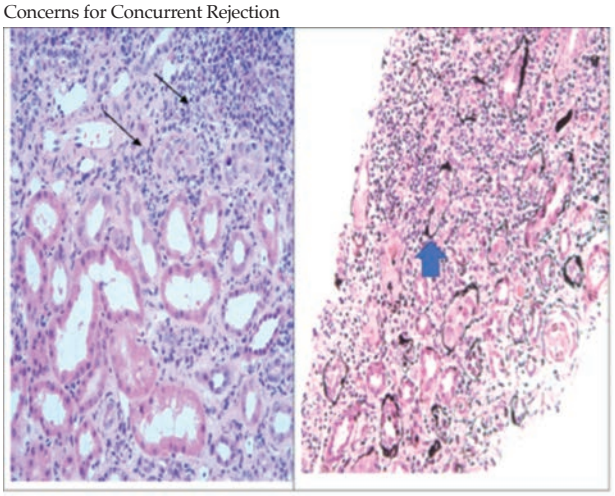
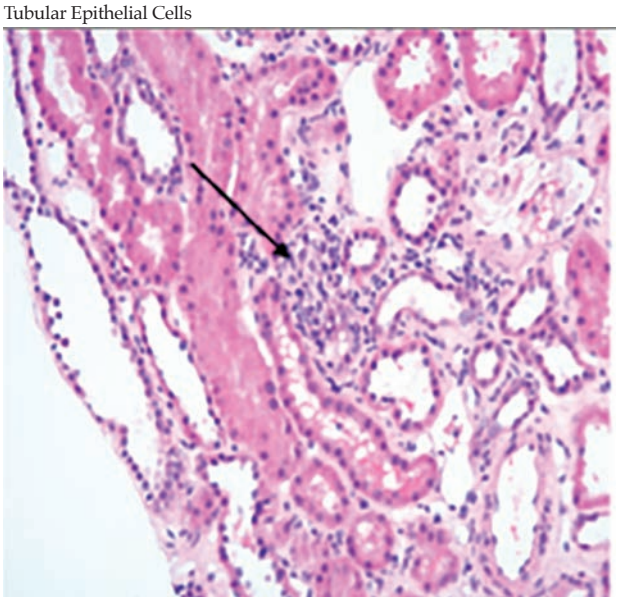


Figure 3. Early Stage With Minimal Inflammation, No Inclusions, and Normal Tubular Epithelial Cells



Differential diagnosis

BK virus infection can be similar to other types of viral infections (CMV, herpes simplex virus, adenovirus). Therefore, to confirm a diagnosis of BKVN, a blood quantitative PCR showing > 60 to 100 BKV copies plus characteristically pathologic morphology results are needed. Different pathological patterns and associations with BKV infection are shown in Figures 2 to 7.

Urine cytology findings for BK virus infections

Urine examinations may reveal BKV-infected cells. The most characteristic abnormality of infected cells is an enlarged nucleus with a single, large basophilic intranuclear inclusion (Figure 1).[34,42]

Figure 4. Focal Lesions Illustrate the Importance of Adequate Samples Including 2 Cores

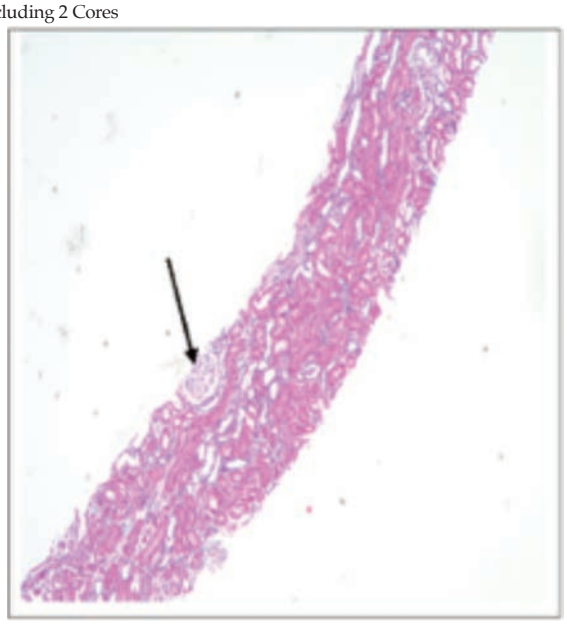


Figure 5. Significant Inflammatory Response (Hematoxylin and Eosin) With Evident Inflammatory Cells

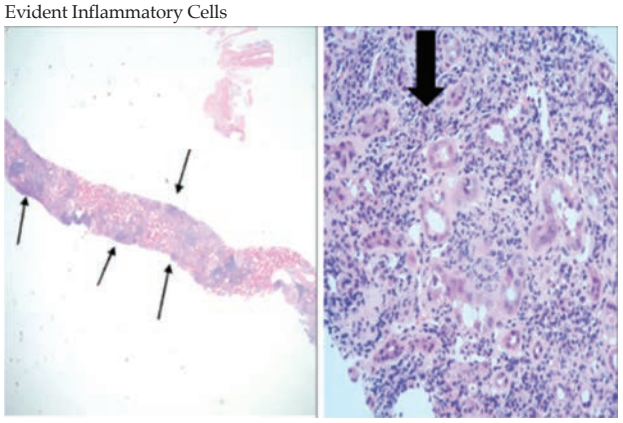
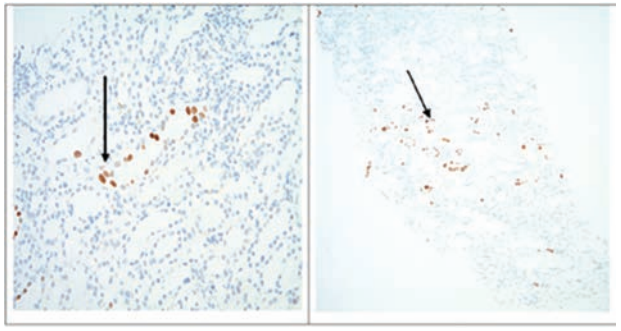


Figure 6. Immunohistochemistry Showing Positive SV40 Staining of BK Virus in Renal Tissue



The presence of characteristic cytopathologic changes in infected cells (which have been called decoy cells due to their similarity to renal carcinoma cells) is strongly suggestive of polyomavirus infections.[43,44] Viral replication in the urine is demonstrated by either decoy cells or BKV urine quantitative PCR.[36]

Cytological urine abnormalities (decoy cells) are suggestive but not specific, sensitive, or definitive for BKV infection because (1) decoy cells can be present in other renal viral infections (such as CMV or adenovirus[42]) and (2) decoy cells correlate poorly with biopsy-proven BKVN in renal transplant recipients.[44] Of note, their absence does not exclude the disease.[35]

Figure 7. Fine Granular Nuclear Features With Small Virions

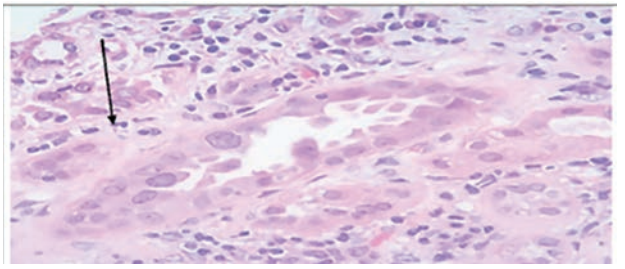
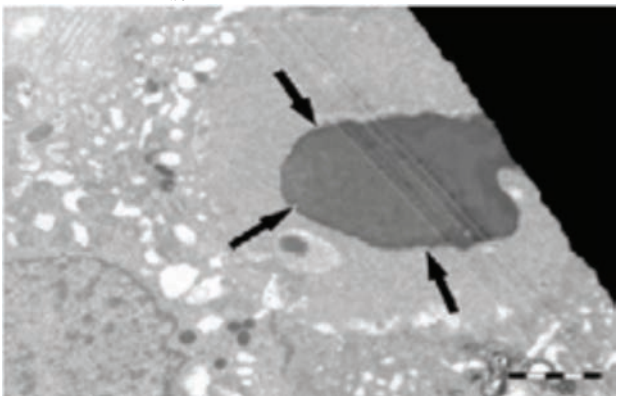


Figure 8. Intranuclear Spherical Viral Particles Seen in Tubular Epithelial Cells on Electron Microscopy (×10 000).[49]

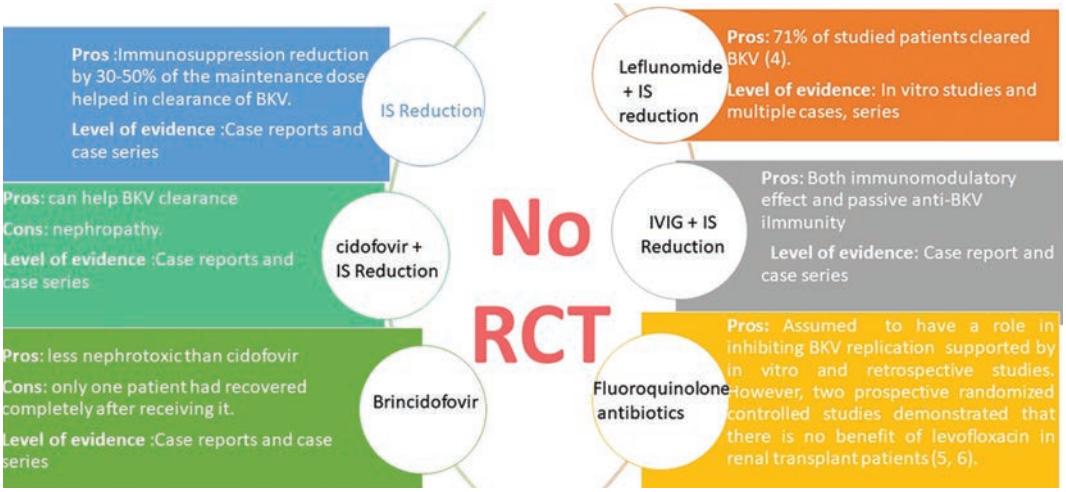


Courtesy of Simge Bardak.[49]

Quantitative polymerase chain reaction

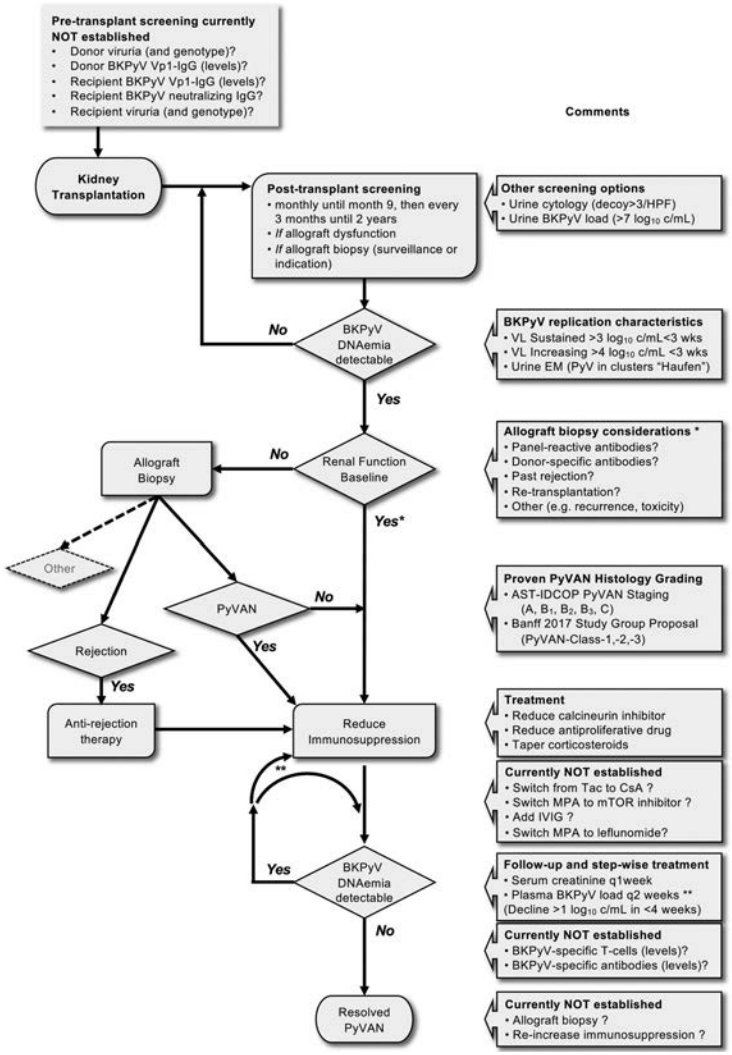
Sustained high viral DNA levels in the plasma of renal transplant recipients who have an appropriate clinical picture can suggest BKVN. In a study of 78 renal transplant patients, the sensitivity and specificity of quantitative PCR analyses in detecting BKV DNA were about 100% and 88%, respectively.[44] In another study, 9 of 9 transplant recipients with biopsy-proven BKVN had BKV DNA detected in plasma by PCR.[45] However, such DNA was found in only 2 of 41 transplant recipients without nephropathy and in 0 of 17 nontransplant patients with advanced human immunodeficiency virus-1 infection. Viral DNA disappeared with decreased immunosuppression.

Figure 9. Summary of Management of BK Virus Infection



Abbreviations: BKV, BK virus; IS, immunosuppression; IVIG, intravenous immunoglobulin; RCT, randomized controlled trial

Figure 10. Outlined Recommendations for BK Virus Screening, Diagnosis, and Management



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Renal transplant recipients can be monitored with quantitative or real-time PCR for BKV infections in either the plasma or urine.[46,47] Multiple retrospective and prospective studies have agreed that viruria precede viremia by 4 weeks.[46-48] Viral replication in the urine as detected by either analysis of urine cytology or demonstration of the virus by quantitative PCR has been shown to be present in 20% to 60% of renal transplant recipients, depending on the method of detection.[36] During the first 6 months, 10% to 30% of renal transplant recipients may show levels of BKV viremia; however, BKV viremia can decrease later to 5% to 10% of renal transplant recipients. One study showed that 2% to 10% of renal transplant recipients had no BKVN 12 weeks after BKV viruria.[36] Patients with a higher viruria level are highly prone to developing BKV viremia, and patients with high sustained viremia are susceptible to BKVN. In another study, although the risks of viremia and sustained viremia were 3- and 13-fold higher if the urine DNA level was > 9.5 log10 copies/mL, the sensitivity, specificity, positive predictive value, and negative predictive values of urine levels were 70%, 70%, 53%, and 83% for any viremia and 91%, 66%, 33%, and 98% for sustained viremia, respectively.[6] In addition, a strong correlation was shown between the negativity of urine BKV PCR and blood BKV PCR.[50] BK virus DNA levels can alter weekly by 1 to 2 log-folds depending on the commercially available PCR assay. It is recommended that medical decisions, especially those with regard to alterations of immunosuppression, be made on the basis of trends in quantitative DNA levels rather than on a single measurement.[20]

Serology

It is not helpful to examine serum for anti-BKV antibodies for a definitive diagnosis of BKV infection because positivity for these antibodies is quite common in the general population.[9,51] During BKV infection, there are high levels of BKV (immunoglobulin G [IgG]) titers during the first 6 weeks of infection or 2 years after primary infection.[51,52] The risk of developing higher levels of BKV IgG is directly correlated with donor anti-BKV antibody positivity.[52] Anti-BKV antibody does not seem to be protective; therefore, it can increase in both primary infections and reactivation of infections.[30] Previous BKV seropositivity in the recipient can affect progression of BKV infection, especially progression from viruria to viremia, which is considered a harbinger of BKVN.[53] In the laboratory, the intensity of infection can be classified according to the type of antibody response: IgG, IgM, or IgA.[53] The utility of assessing anti-BKV antibody levels before and after transplant is not clear. The utility of conducting BKV serology examinations before and after transplant is controversial because it is not entirely clear which antibodies are neutralizing.[54,55] The risk of developing a clinically significant BKV infection is high when transplant is performed between a positive BKV donor and a negative recipient.

Viral culture

Viral culture is rarely used as a method for BKV infection detection outside the research setting. Viral isolation from the clinical specimen can take weeks to months; therefore, this method is not clinically applicable.[56]

Urine electron microscopy

Urine examinations using negative-staining electron microscopy for patients with BKV infection will show cast-like 3-dimensional polyomavirus aggregates, which are called Haufen (Figure 8).[57] In a retrospective single-center study, Haufen presence was shown to be associated with 100% sensitivity and 99% specificity for biopsy-verified BKVN in kidney transplant recipients.[57] In addition, a relationship was reported among Haufen, high-level BKV viremia (median copy 1 206 325 copies/mL), and the occurrence of acute kidney injury and BKVN. However, urine analyses in patients with a low viremia (median of 26 959 copies/mL) did not show Haufen bodies. Thus, urinary Haufen bodies can act as a noninvasive method for BKVN diagnosis in renal transplant recipients. This diagnostic technique is of a great utility, especially in differentiating between BKVN and asymptomatic BKV infection. However, it remains to be determined whether this method can be used for diagnosis as it depends on a sophisticated analysis and it also requires a meticulous interpretation by pathologists. In addition, the study did not determine whether urine electron microscopy can discriminate between rejection and BKVN.[57] Despite these limitations, the presence of a high load of Haufen with equivocal biopsy would highly support the possibility of BKVN rather than rejection as a cause of allograft dysfunction, which could support medical decisions of reduction of

immunosuppression rather than augmentation as in cases of rejection.

Therapeutic Interventions

Few controlled studies are available to guide us through the management of BKV infection in renal transplantation.[58] Currently, there are no available antiviral medications against BKV. However, potential anti-BKV agents have been suggested by several reports. Concomitant administration of these agents with immunosuppression reduction was only documented in uncontrolled retrospective observational studies; therefore, it is difficult to make firm conclusions about their therapeutic efficacy. The usual approach in the management of BKV viremia or BKVN in renal transplant recipients is the reduction of immunosuppression and continuous monitoring of BKV viremia levels using quantitative PCR.[9,59] Various therapeutic interventions are discussed in the following sections.

Immunosuppression reduction

Despite the fact that reduction of immunosuppression has been the cornerstone in the management of BKV infection, it also carries a higher risk of rejection, making this decision challenging. Histologically, there is a similar feature between rejection and BKVN, which often shows severe interstitial inflammation in addition to the presence of viral inclusions and SV40 immunohistochemistry may become negative.[60] Moreover, modification of immunosuppression to treat BKV infection carries a higher incidence of long-term chronic rejection. One study suggested that patients with persistent sustained BKV viremia are prone to the development of de novo donor-specific anti-HLA antibodies.

Cidofovir

Multiple single-center studies and case series have described the benefits of adding cidofovir with immunosuppression reduction. However, no randomized controlled trials are available to support this approach.[61,62] One of the limitations of this approach is nephrotoxicity, thus making the decision to use cidofovir unlikely.

Brincidofovir (CMX001)

Because of the nephrotoxicity with cidofovir, scientists had developed brincidofovir, which is a prodrug of cidofovir that is administered orally. Phase 3 clinical trials have shown a lower incidence of nephrotoxicity with brincidofovir.[63] Successful outcomes in renal and hematopoietic transplant have been described in multiple case reports after treatment of BKVN with brincidofovir.[64,65] However, larger-scale clinical trials are needed to establish the safety and efficacy of brincidofovir in the management of BKVN patients.

Leflunomide

Leflunomide is an immunosuppressant agent that also has antiviral properties against BKV in vitro.[66] Several case series have utilized it as a replacement agent in lieu of mycophenolate.[67,68] These studies have shown a significant association between leflunomide and decrease in BKV viral load; however, this does not reflect the cause of BKV viral load (that is, whether it is a result of immunosuppression reduction or due to the antiviral properties of leflunomide). Side effects of leflunomide include thrombotic microangiopathy, hepatitis, and bone marrow suppression.[67] The active metabolite of leflunomide (known as teriflunomide or A771726) can be measured, which can be helpful in continuous monitoring of the level of leflunomide and avoid toxicity.[68] In a case series, achieving a level of 50 to 100 g/mL of teriflunomide or A771726 was associated with a reduction of BKV viral load, as shown in a follow-up of 22 renal transplant patients.[69] Further prospective controlled studies of leflunomide are needed to confirm the efficacy and safety of this drug against BKV infection[70]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) contains neutralizing antibodies against BKV, which makes it a good choice in the management of BKVN.[71] The evidence of using IVIG as adjunctive therapy for BKVN has been described in multiple case reports and case series[72,73]; however, no controlled studies have been reported. In patients with hypogammaglobulinemia, IVIG therapy was beneficial with regard to anti-BKV immunity; the immunomodulatory effects of IVIG may guard against allograft rejection in the context of reduced immunosuppression.[74]

Fluoroquinolone

In vitro studies have shown that fluoroquinolone antibiotics can inhibit replication of BKV or SV40 polyomavirus replication in vitro; therefore,

fluoroquinolone antibiotics have been considered as potential agents for controlling BKV infection in renal transplant recipients.[75,76] In vitro studies have revealed that fluoroquinolones appear to have an inhibitory effect through reduction of large T antigen expression and inhibition of large T antigen helicase activity.[75,76] In a retrospective study of fluoroquinolone given as prophylaxis against BKV infection in renal transplant recipients, fewer renal transplant recipients who received the fluoroquinolone developed BKV viremia, supporting the probability that fluoroquinolone may have a role in preventing BKV replication.[77,78] A single-center nonrandomized study demonstrated that coadministration of ciprofloxacin and leflunomide were successful in controlling BKV infections.[79] However, other prospective randomized trials showed no benefit from levofloxacin in renal transplant recipients to control BKV infection.[80-82] Overall, these data suggest that fluoroquinolones do not currently have a clinically significant role in the management of BKV-related diseases.[82]

Role of cellular immunotherapy in the management of BKV infection

BK virus infections usually occur during childhood; BKV then becomes dormant until it is reactivated after immunosuppression treatment as a result of failure of BKV-reactive T cells to control viral replication.[83] Therefore, the idea of this approach depends on the transfer of primed BKV-reactive T cells, which may help in controlling the BKV-associated disease. In the early 1990s, Riddell and associates were the first team to start cellular therapy using T cells to restore antiviral immunity in immunocompromised patients.[84] Since then, various research teams have refined new approaches for treating various chronic virus-associated diseases using the adoptive T-cell therapy approach.[85,86] Identifying viral immunogenic antigens is necessary for successful generation of virus-specific T cells. Herpesviruses immunodominant epitopes have been defined as researchers successfully used synthetic viral peptides or overlapping peptide pools to produce CMV- or Epstein-Barr-specific T cells.[87] Newer advanced techniques have been developed using interferon-capture technology or major histocompatibility complex multimers[88,89] to allow rapid selection and virus-specific T-cell enrichment.[90] Research on treating BKV-associated diseases using immunotherapeutic approaches is still in the early stages, and data on immunodominant BKV epitopes for T-cell priming are limited. Blyth and associates recently reported the use of overlapping peptide pools derived from all 5 BKV antigens to expand BKV-specific human T cells.[91] Functional characterization of the expanded T-cell population confirmed BKV reactivity, cytokine production, and in vitro cytotoxicity.[91] In a pilot study published in 2014, in vitro expansion of virus-reactive T cells was performed by use of overlapping peptide pools that included antigens from Epstein-Barr virus, CMV, adenovirus, BKV, and human herpesvirus 6.92 Generated cell products using this protocol were given to patients after hematopoietic stem cell transplant either prophylactically or in response to single or multiple viral infections. Few participants had active BKV infection, which improved after adoptive T-cell transfer.[92] This study has paved the way to the possibility of management of BKV infection using the adoptive transfer of BKV-reactive T cells.

Conclusions

BK virus is a member of human polyomaviruses, which are DNA viruses; BKV infections lead to tubulointerstitial nephritis and ureteral stenosis in the renal transplant population. The average incidence is about 10% of the renal transplant population.

There is a direct correlation between the incidence of BKV infection and the degree of immunosuppression, but not the drug itself. Other risk factors include diabetes mellitus, elderly patients, male patients, delayed graft function, acute rejection episodes, and previous CMV infections.

Clinical manifestations of BKV infection range from being asymptomatic to frank nephropathy with disturbed renal function and progressive increase of serum creatinine levels. Urine analysis may show hematuria, pyuria, and cellular casts. Urine microscopy shows decoy cells that are BKV-infected cells. A definitive diagnosis of BKVN is made by renal allograft biopsy using immunohistochemistry, which cross-react with the BKV, specifically SV40 large-T antigen part of the virus. BK virus nephropathy could be missed in about one-third of patients; therefore, 2 core biopsies are needed for confirmation, preferably including the medulla. Renal transplant recipients are usually monitored by serum and urine quantitative PCR for BKV DNA. Viral replication goes through stages, with

viruria preceding viremia by about 4 weeks and nephropathy by 12 weeks.

Acute rejection is the main differential diagnosis of BKVN. BK virus nephropathy could be differentiated with BKV inclusions and immunohistologic analyses. In addition, it is important to correlate histologic findings with PCR evidence of viremia.

There are no available antiviral medications for BKV infections, and there are few controlled studies available on management of BKV infection in renal transplant recipients. The concomitant administration of these agents with immunosuppression reduction has been reported in only uncontrolled retrospective observational studies; therefore, it is difficult to make firm conclusions about their therapeutic efficacy. The common approach for BKV infection management is active screening every 3 months after renal transplant; with any levels of BKV viremia, immunosuppression should be reduced and there should be continuous follow-up of BKV viremia levels using quantitative PCR and renal function tests. Newer options, including cellular immunotherapy, may carry potential hope for treatment of BKV infection.

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