BK polyomavirus in Kidney transplant recipients: screening, monitoring and clinical management

BK poliomavírus em receptores do transplante renal: rastreamento, monitoramento viral e manuseio clínico

Autores
Rafael Brandão Varella[1]
Jorge Reis Almeida[1]
Patrícia de Fátima Lopes[1]
Jorge Paulo Strogoff de Matos[1]
Paulo Menezes[1]
Jocemir Ronaldo Lugon[1]

[1] Fluminense Federal University (UFF).

Abstract

BK polyomavirus (BKPyV) is a causal agent of nephropathy, ureteral stenosis and hemorrhagic cystitis in kidney transplant recipients, and is considered an important emerging disease in transplantation. Regular screening for BKPyV reactivation mainly during the first 2 years posttransplant, with subsequent pre-emptive reduction of immunosuppression is considered the best option to avoid disease progression, since successful clearance or reduction of viremia is achieved in the vast majority of patients within 6 months. The use of drugs with antiviral properties for patients with persistent viremia has been attempted despite unclear benefits. Clinical manifestations of BKPyV nephropathy, current strategies for diagnosis and monitoring of BKPyV infection, management of immunosuppressive regimen after detection of BKPyV reactivation and the use of antiviral drugs are discussed in this review.

Keywords: infection control; kidney transplantation; monitoring; review.

Resumo

BK Poliomavírus (BKPyV) é um agente causal de nefropatia, estenose ureteral e cistite hemorrágica em receptores de transplante renal, sendo considerado uma importante doença emergente na transplantação. Rastreamento regular para reativação do BKPyV, principalmente nos dois primeiros anos pós-transplante, com subsequente redução preemptiva da imunossupressão é considerada a melhor conduta para evitar a progressão da doença, já que a eliminação ou redução da viremia é alcançada na grande maioria dos pacientes dentro de 6 meses. O uso de drogas com propriedades antivirais para os pacientes com viremia persistente tem sido tentado, embora sem benefícios claros. As manifestações clínicas da nefropatia por BKPyV, as estratégias para o diagnóstico e monitoramento da infecção por BKPyV, o manejo do regime de imunossupressão após a detecção da reativação do BKPyV e o uso de drogas antivirais são discutidas nesta revisão.

Palavras-chave: controle de infecções; monitoramento; revisão; transplante de rim.

Introduction

BK polyomavirus (BKPyV) belongs to the family *Polyomaviridae* (former *Papovaviridae*) and are small (45-50 nm), nonenveloped virus with an icosahedral capsid and a core of circular double-stranded DNA in association with histones.[1,2] The virus was first isolated in 1971 and named after the initials of a Sudanese transplant recipient with ureteral stenosis.[3]

BKPyV is subdivided into four subtypes/serotypes: I, II, III, and IV. The geographic distribution of the subtypes suggests a close relationship between BKPyV and migration of human populations, although without any apparent clinical significance.[4,5]

BKPyV is ubiquitous in human population.[6] Primary infection occurs in the first decade of life as evidenced by increases in BKPyV seroprevalence to 90% and more.[7] Natural BKPyV transmission is not clear, but likely occurs via the respiratory or oral route. Primary infection in healthy children is usually asymptomatic, but may manifest as a common cold.[8] After primary viremia, the

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Correspondência para:
Rafael Brandão Varella.
Laboratory of Virology.
Department of Microbiology and Parasitology - Universidade Federal Fluminense.
Rua Ernani Pires de Melo, nº 101.
Niteroi, RJ, Brasil. CEP: 24210-130.
E-mail: rvarella@id.uff.br
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virus establishes a latent phase, persisting indefinitely in different tissues, especially the urinary tract.[2,9]

In approximately 5% to 10% of healthy individuals, BKPyV reactivates with variations in immune status and gives asymptomatic low-level urinary shedding.[10] However, no histopathological changes are observed in the kidney parenchyma, and renal function is left unaffected.[1]

Clinical manifestations

Replication of BKPyV occurs during states of immune suppression. Viruria occurs in pregnancy, cancer, HIV infection, diabetes, and transplantation. However, viremia and BKPyV nephropathy (BKVN) are rare outside of kidney transplantation.[11] Apart from immune status, other variables such as older age, male gender, white ethnicity, diabetes, BKPyV seronegativity prior to transplantation, immunosuppressive drug regimen, ischemic lesion during transplantation and viral mutations, are considered risk factors for BK disease.[12]

BKPyV infections in immunosuppressed individuals can lead to distinctive pathological entities in different patient groups: in renal transplant recipients, it is associated with nephropathy and ureteral stenosis, whereas in hematopoietic stem cell transplant (HSCT) recipients with hemorrhagic cystitis.[2,8,12]

BKVN is the result of viral replication in renal tissue, and is characterized by a histologically manifest renal allograft infection with BKPyV and deteriorating graft function. The gold standard for BKVN is still a renal biopsy.[10] Since it has a patchy distribution affecting mostly the renal medulla,[13] two core biopsy samples including medulla should be obtained in order to confirm the BKPyV presence by *in situ* hybridization or immunohistochemistry for anti-SV40 or large T.[12] The histologic patterns of BKVN have been divided into three types, being characterized by the presence of nuclear inclusions (Type A), acute inflammation with little chronic fibrosis (Type B), and significant chronic fibrosis and atrophy (Type C).[14] In 25-40% of the patients experiencing high level viruria/decoy cell positivity will develop viremia, and in the absence of intervention, progression to BKVN may occur.[10] The prevalence of BKVN may vary from center to center, but generally ranges from 1% to 10% and the result is the graft loss in up to 80% of cases.[12,15] Its noteworthy that nephropathy can also be caused by another polyomavirus named JC in rare cases, which demands additional investigation in the event of nephropathy without BKPyV detection.[16]

Hemorrhagic cystitis (HC) is the most common BKPyV manifestation of genitourinary infection in HSCT recipients. The virally induced form of HC usually occurs after engraftment and is therefore referred to as late-onset hemorrhagic cystitis, which occurs in 6 to 29% of HSCT patients, generally within the first two months after transplantation. Patients present with hematuria, painful voiding, bladder cramps, and/or flank pain.[3]

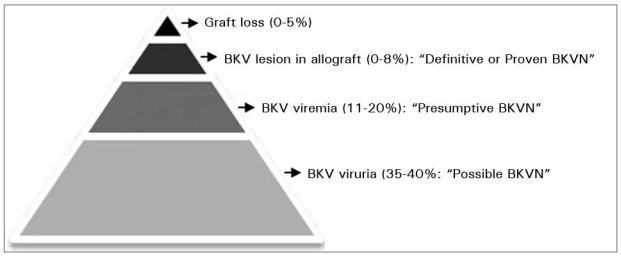
The ureteral stenosis occurs in approximately 3% (2-6% range) of renal transplant patients and generally develops several months after transplantation.[3] The virus may exert a direct cytopathic effect on the ureteral epithelium, resulting in ulceration and inflammation, which leads to obstructive uropathy.[17]

In addition, BKPyV is also possibly related to pneumonia, encephalitis and several types of cancer.[18] These non-urinary BKPyV-induced diseases are not surprising at all given the viral persistence in different human tissues and the oncogenic potential of polyomaviruses.[19,20]

Methods for BKPYV screening in urine and blood

The methods used to detect and quantify BKPyV are based on the pathogenesis of the infection.[11] Viral replication begins early after transplantation and progresses through detectable stages: viruria to viremia and then to nephropathy (Figure 1). The onset for each event is variable: viruria is usually reported ≥ 5 weeks after transplantation, followed by viremia after 4-5 weeks,[21,22] which in turn precedes BKVN in 8-12 weeks.[23,24]

Figure 1. BKPyV events following renal transplantation. * Adapted from reference 11.



In general, viruria-based methods are considered valuable tools for BKPyV screening (high negative predictive value, NPV) but weakly indicative of kidney or urinary tract diseases (low positive predictive value, PPV), since less than a half of all patients with viruria will progress to the viremia stage.[25] Three methods are available for BKPyV viruria screening: urine cytopathology ("decoy cells"), DNA detection/quantification, and electronic microscopy "Haufen" bodies.[26]

Decoy cells are epithelial cells with enlarged nuclei and large basophilic ground-glass intranuclear inclusions.[9] Although one decoy cell is sufficient to mark the activation of polyomaviruses, in clinical practice an arbitrary threshold level of more than 10 decoy cells per liquid-based cytology preparation has been set to distinguish 'decoy positive' from 'decoy negative' patients.[14] Decoy cell can be easily detected in standard Papanicolaou-stained cytology preparations and is considered a cost-saving technique without the cross-contamination risks of PCR-based methodologies.[22] Also the NPV of decoy cells approximates 100%.[26] On the other hand, the PPV of decoy cell analysis to predict BKVN is only 25 to 30%; cytology results are more susceptible to delays in processing and shipment of samples; and require a trained cytologist.[15] Nevertheless, due to its high cost-effectiveness, the use of decoy cell remains solid in several diagnostic centers.

Electronic microscopy methods are based on the detection of viral particles or "Haufen", defined as discrete, tightly clustered, cast-like aggregates of a minimum of six polyomaviruses with an unequivocal three-dimensional architecture.[27] Positive and negative predictive values of Haufen for BKVN are very high, reaching > 90%,[26] and may serve as a noninvasive means to diagnose BKVN in the urine.[28] However, the costs required to perform routine electronic microscopy is prohibitive for most diagnostic centers.

PCR-based methodologies for DNA detection/quantification in urine or blood have been considered the method of choice by current guidelines. Quantitative PCR (qPCR) is equivalent to decoy cytology to estimate BKPyV viruria and viral loads > 7 $\log_{10}$ copies/ml are considered significant.[26] The advantages of testing BKPyV viruria are similar to decoy: high NPV for BKVN; precedes viremia ≥ 4 weeks,[24] which works as a warning sign to viremia; and is a non-invasive technique. In addition, BKVN with detectable viruria without viremia has been reported.[23] Nonetheless, factors such as low PPV for BKVN, costs involved in qPCR, lack of standardization and natural fluctuation of BKPyV loads in urine, can be considerable disadvantages.[26]

BKPyV viremia, on the other hand, is universally considered the single most important parameter to predict BKVN,[10,23,26] reaching a PPV ≥ 90% and a sensitivity of 93% in persistently high BKV DNA loads (> 10^4 copies/ml). However, a viral load < 4 $\log_{10}$ copies/ml does not completely rule out BKVN, and deserves continuous monitoring.[28] The optimal threshold of BKPyV DNAnemia is not standardized, and values expressed in copies/ml > 500;[28] > 600;[22] > 750;[29] and > 1,000,[30] have been considered significant. Given its overall performance, BKPyV viremia testing without urine became the method of choice in many diagnostic centers and also recommended by the KDIGO Transplant Work Group in 2009,[31] although viruria screening prior to viremia quantitation is considered cost-saving.[22]

Current strategies for diagnosis and monitoring of BKPyV infection

BKVN is predominant (> 90%) in the first two years of transplantation, especially in the first trimester.[24] Screening efforts have mainly been focusing on the first 6-12 months. However, due to the precocity of BKPyV viremia in most cases, the tendency has been driven for condensed screening in the first months.

Current screening strategies relies on two basic principles: 1) viruria followed by viremia; 2) viremia only. Despite methodological variations, both strategies showed to be equally effective in detecting BKPyV infection, allowing for timely intervention.

Strategy 1: viruria followed by viremia

As previously mentioned, viruria can be assessed by electronic microscopy, decoy cytology and qPCR. However, performing these techniques simultaneously seems do not add useful clinical information.[30] Current strategies indicate that viruria testing should be performed biweekly during the first three months. After, it will be performed monthly until the sixth month. Then, every 2 or 3 months until 2 years post-transplant, and anytime during any allograft dysfunction.[11,22,26] Nevertheless, monthly or quarterly (less frequent) screening up to 2 years post-transplant is still employed for urine BKPyV

search.[10] Decoy cell cytology and qPCR are the most used procedures, although cost-effectiveness favors the former.[22] Despite the low clinical significance of isolated viruria, the maintenance of high BKPyV loads in urine (> 7 $\log_{10}$ copies/ml) or sustained decoy positivity (defined as ≥ 2 positive samples > 2 weeks apart) is a strong indicative of future viremia (75%) and BKVN. Quantitative measurement of viremia is not indicated in patients without viruria.[30] However, in case of positive detection of BKPyV in urine by the aforesaid procedures, viremia testing should be performed.

Strategy 2: viremia screening

The guidelines suggest reducing immunosuppressive medications when BKPyV plasma is persistently greater than 10,000 copies/ml,[30] and the diagnosis of "presumptive BKVAN" should be made.[12] Most of the current BKPyV screening procedures are focused on viremia only, without the support of viruria. In both cases immunosuppression reduction is recommended even in the absence of BKPyV in biopsy (see ref. 26 for details). The term "sustained" or "persistent" is defined as two or more consecutive positive plasma samples (over ≥ 2-3 weeks). However, different groups also recommend immunosuppression reduction after sustained[21,29] or a single low level (≈ 1,000 copies/ml) viremia.[24,28] Monthly testing in the first 6-12 months followed by three months intervals is being widely adopted.

Clinical management

Currently, reduction of immunossupression is the keystone of therapy for BKVN. Since late diagnosis of BKVN is usually associated with an irreversible decline of graft function[32,33] and most of patients with viremia will eventually develop BKVN, regular screening for BKPyV reactivation, mainly during the first 2 years posttransplant, with subsequent pre-emptive reduction of immunosuppression is the usual procedure adopted by transplant centers.[21-30] Successful clearance or reduction of viremia is achieved in more than 80% of patients after 4 to 6 months.[34,35] Viremia should be continuously monitored every 2 to 4 weeks along with the levels of serum creatinine after reducing immunossupression.[31]

When viremia is detected, a graft biopsy is usually indicated before reducing immunossupression, mainly in case of renal function deterioration, to distinct BKVN from rejection. Even if kidney function is unchanged, biopsy should be considered for those patients at a higher immunological risk in order to exclude a sub-clinical rejection episode.[26]

There is no clear evidence to support any specific modification of the immunosuppressive therapy. However, *in vitro* analyses suggest that reduction or withdrawn of calcineurin inhibitors should be the first step in immunossupression modification due to its effects on T cells.[36] Reduction or withdrawn of anti-proliferative drugs, mainly mycophenolate, is also an usual target for changing immunossupressive regimen.[34] On the other hand, *in vitro* analysis demonstrated a favorable action of mTOR inhibitors on BKVN progression.[37] Thus, despite the lack of controlled studies, it seems reasonable, at least for patients with a lower risk of rejection, the strategy of withdrawn or reducing tacrolimus and mycophenolate by approximately 25% to 50%,[26] meanwhile it might be considered to introduce mTOR inhibitors to the immunossupressive regimen. After reduction of immunossupression, renal function should be closely monitored due to the risk of rejection.

While reducing immunosuppression is a logical first line therapy, a second line option is not well defined. For these patients who fail to decrease viremia after reduction of immunossupression, the use of immunoglobulin, cidofovir and fluoroquinolone has been attempted despite unclear benefits. Among those options, the use of fluoroquinolones was more extensively studied. *In vitro* analyses have shown that fluoroquinolones could have antiviral properties by inhibiting BKV replication.[38] Retrospective studies suggested that fluoroquinolones, used as pneumocystis prophylaxis, were effective at preventing BKPyV viremia after HSCT and kidney transplant.[39,40] However, a recent randomized clinical trial failed to show any benefit of fluoroquinolones in kidney transplant recipients with BKPyV viremia.[35]

Cidofovir is a nucleotide analogue of cytosine which acts on viral DNA and is usually used in the treatment of CMV complications in HIV patients. Benefits of ciclofovir in patients with BKVN were described only in small non-controlled studies.[41,42] Due to its nephrotoxicity, ciclofovir should be considered for treatment of BKVN only when other options have failed.

Intravenous immunoglobulin administration for the treatment of BKVN is an attractive idea since BKPyV is ubiquitous in human population. Thus, it is expected that immunoglobulin contains antibodies against this virus. The use of immunoglobulin seems especially attracting when the diagnosis of allograft rejection cannot be ruled out. In this case, the use of massive dose of immunoglobulin could be useful for both rejection and BKVN. However, there is a paucity of studies addressing the use of immunoglobulin in the treatment BKVN[43-45] and randomized clinical trials are needed.

Repeat transplantation is a feasible option after graft loss due to BKVN. A study of 126 patients who underwent repeat kidney transplantation after graft loss due to BKVN showed a 3-year graft survival rate of 93.6%.[46] In another study, 11 out of 31 patients presented post-transplant BKPyV viremia but with only two of them experiencing BKVN. Viremia clearance after BKVN in the initial transplant was significantly associated with a lower risk of recurrence after repeat transplantation.[47] The post-transplant management should follow the screening and follow-up previously described but always having in mind the narrow limits between excessive immunossupression, with risk of reactivation of BKPyV viremia, and a loose immunossupressive regimen for a patient already sensitized by the previous transplant.

Conclusions

The advent of newer, more potent immunosuppressive agents may contribute to an apparently increasing incidence of BKVN in kidney transplant recipients. The optimal screening method and timing to detect BKPyV remains to be determined and cutoff values, especially for quantitative tests, need to be defined and standardized. Currently, early diagnosis and reduction of immunosupression therapy seems to be the most efficacious treatment for BKPyV infection.

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