BK virus-induced renal allograft nephropathy

Karel Krejci[a], Tomas Tichy[b], Jana Bednarikova[c], Kamil Zamboch[a], Josef Zadrazil[a]

BK virus nephropathy (BKVN) is a serious opportunistic infection threatening renal function especially during the first year after transplantation. Its incidence is now on the rise and is closely related to the level of the recipient's immune system inhibition. This is more intensive with current trends in transplantation medicine, where more potent immunosuppressive protocols are used and more aggressive antirejection therapy is applied. In the absence of BK virus (BKV) specific therapy and limited treatment options for advanced BKVN, active screening of BKV replication and subsequent preemptive adjustment of immunosuppression are essential measures to prevent BKVN. However, it remains unclear how to modify immunosuppressive protocols as well as how to address initial stages of BKV replication. This comprehensive review summarizes the currently applied and not completely uniform procedures for the detection, prophylaxis and therapy of BKV replication and BKVN. The pitfalls brought by reduced immunosuppression, as a typical response to a significant viral replication or a developed BKVN, are also mentioned, particularly in the form of graft rejection. The paper also outlines the authors' experiences, and lists currently ongoing studies on the subject. The perspectives of new, especially immune-based, procedures in the treatment of complications associated with BKV infections are highlighted. Different views on the management of patients indicated for kidney re-transplantation whose previous graft failed because of BKVN are also discussed.

Key words: kidney transplantation, immunosuppressive therapy, BK virus immunotherapy, BK graft nephropathy, kidney biopsy, preemptive therapy

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[a]Department of Internal Medicine III - Nephrology, Rheumatology and Endocrinology, University Hospital Olomouc, I. P. Pavlova 6, 779 00 Olomouc, Czech Republic
[b]Institute of Molecular and Translational Medicine, University Hospital Olomouc, I. P. Pavlova 6, 779 00 Olomouc, Czech Republic
[c]Department of Clinical Biochemistry, University Hospital Olomouc, I. P. Pavlova 6, 779 00 Olomouc, Czech Republic
Corresponding author: Karel Krejci, e-mail: karel.krejci@fnol.cz

INTRODUCTION

As the number of prognostically risky renal transplantations increase, especially retransplantations performed in patients with previous repeated or severe rejections, more intensive immunosuppressive protocols must be chosen. Subsequently, profound attenuation of the recipient's immune system increases the risk of various infectious complications including BK virus (BKV). BKV can cause kidney allograft damage with the development of BKV nephropathy (BKVN), and can significantly impact renal allograft survival and prognosis[1,2]. Recent observational posttransplantation protocols therefore recommend routine BKV monitoring in an attempt to preemptively intervene in case of detection of BKV replication in order to prevent the development of graft-threatening BKVN. Treatment of already developed BKVN is currently difficult. There is no specific antiviral therapy and the basis of treatment of ongoing viral replication or developed nephropathy is to minimize immunosuppression with potential risks to the graft. At present, intensive attention is paid to the search for new, especially immune-based options in the treatment of complications associated with BKV infection[3].

EPIDEMIOLOGY AND PATHOGENESIS OF BKVN

BKV belongs to polyomaviruses, small (30-45 nm), ubiquitous DNA viruses that can infect humans, but also a number of other animals. In humans, polyomaviruses, in particular BKV and JC virus (JCV), have a wide range of seroprevalence[1], where BKV is clinically significant. It was first identified as the cause of graft dysfunction in 1995, when it was isolated from a tissue sample, obtained by biopsy of the transplanted kidney[4].

BKV consists of the capsid and double helix DNA, but lacks the lipid envelope. It has 4 serological groups and genotypes that have different virulence. Its genome is divided into three major genetic regions: the early coding region, the late coding region, and the non-coding NCCR control region that regulates the expression of small T-antigen, large T-antigen, VP1, VP2, VP3 capsid proteins and agnoprotein. The large T-antigen is important for BKV replication, recognition by the cellular immunity components and virus oncogenicity. Within the NCCR section of DNA, we distinguish four main genotypes of BKV – I, II, III, IV, which differ in the variable VP1 sequence. The predominant genotype I and its subgroup I/b-2 are most commonly found in the European and American populations, whereas the subgroup I/c-2 is more common in Asians[5].

The clinical and immunological consequences of infections with the different BKV genotypes are still unclear[3]. In the general population, BKV usually causes banal childhood infections. Studies show that 70% of children are infected with BKV by the age of 10 and more than 90% of adults are seropositive by the end of their twenty-third year[1]. However, the route of transmission is not very clear. Most likely are the tonsils and the upper respiratory tract, including Waldeyer's ring, but other pathways are possible – faecal-oral via waste water, blood transfusion containing leukocytes and the transplacental transmission[6].

BKV induces a latent infection of the renal epithelium (transient epithelium, renal tubular epithelium, parietal epithelium of Bowman's capsule) and lymphoid cells, usually without a significant clinical impact. As for this long-term persistence in the host's body, it is not entirely clear whether the virus remains in the latent phase permanently or shows a low level of gene expression with a persistent infection[3]. In immunocompetent adults, recurrent and transient BKV excretion in the urine was found at a low level in 5-27% of individuals. In immunocompromised persons, BKV viruria was found in 10-60% of patients[7]. Insufficient immune system surveillance in these subjects allows BKV replicates in distal tubule cells, causing necrosis, inflammation and local tissue damage. The virus is then detected in the urine. The tubular basal membrane is also exposed and damaged, allowing the virus to penetrate into the intertubular space and peritubular capillaries. Subsequently, the virus spreads to adjacent cells, causing further inflammation and renal tissue damage[8].

The transition from the latent phase of infection to clinically apparent disease thus usually occurs only in immunocompromised patients. Individuals with altered cell-mediated immunity are particularly at risk, especially patients after kidney transplantation. In these cases, BKV replication with subsequent urinary excretion occurs in up to 30% of patients. Up to 10% of these patients then develop graft damage in the form of BKVN, or more rarely as a ureteral stenosis[2,9,10]. Renal graft failure occurs in 50-80% of recipients who developed BKVN within 24 months of virus detection[11]. The risk of viral reactivation is highest in the first year after transplantation, when immunosuppression is at the highest level. With regard to JCV, it causes nephropathy rarely (≤ percent) and is associated with a milder progression of the disease. According to one study, JCV infection provides even some protection against BKV reactivation and reduces the risk of BKV viruria[12].

IMMUNE RESPONSE TO BKV

Innate immune response

The role of innate immune mechanisms in the control of BKV infection in recipients of transplanted kidneys is only partially explored[3]. Some studies have documented the activation of dendritic cells that are likely to play a role in the protective immune response against BKV. However, the mechanism of their activation is unclear. The situation is similar in the case of natural killers (NK) (ref.[3]), which may also be useful in the control of BKV infection. The absence of a human leukocyte antigen (HLA) C7 in the donor or recipient increases the risk of BKV viruria and viraemia after transplantation; the mechanism may be associated with lower expression of the immunoglobulin-like receptor on the NK surface with a possible negative impact on defence against BKV (ref.[13]). In addition, BKV may inhibit the ability of NK to recognize BKV and thus avoid the immune response. The role of defensins, which may have antimicrobial effects against a wide range of viruses, bacteria and fungi has also been described. Specifically, defensin 5 has been shown to inhibit binding of BKV to the host cell. Nevertheless, innate defense mechanisms can also contribute to the graft damage in developed BKVN, involving a number of proinflammatory mediators expressed in biopsy specimens, upregulation of some proinflammatory genes and profibrogenic agents[14].

Adaptive immune response

Antibody response

The BKV specific antibody response follows an initial childhood exposure and plays an important role in neutralizing the circulating virus. However, the presence of antibodies does not affect latent infection and does not prevent BKV reactivation and associated diseases. In addition, neutralizing antibodies do not affect certain BKV genotypes due to the variability of viral surface antibody-binding receptors[15].

T cell response

T cells, especially BKV specific T cells, play an important role in the control of BKV infection and their reconstitution in renal transplant recipients can lead to faster resolution of viruria and viraemia[15]. The immune response depends on both CD4 and CD8 T cells and correlates with the frequency of multi-functional BKV-specific T cells. The intensity of the BKV-specific 9mer CD8 T cell response has been shown to correlate with the clearance of BKV viraemia at 6 and 12 months after transplantation. Monitoring of 9mer reactivity could thus serve as a novel marker for the restitution of CD8 T cell function and would be complementary to plasma BKV load assessment via polymerase chain reaction (PCR) (ref.[16]). Even in the absence of CD8, BKV reactivation can be controlled by CD4 T cells[17]. The occurrence of CD4 helpers increases significantly before and after the clearance phase, while cytolytic CD4 cells grow during this phase.

The presence of BKV specific cells was also investigated in the renal tissue of individuals with histological confirmation of BKVN. In addition to the increased population of virus-specific T-cells, an increased presence of T cell clones, associated with alloreactive immune response, involved in tissue damage was found[17].

An important role in the development of BKVN may also play the pre-transplant T-cell phenotype. Low blood CD4 and an increased number of effector CD8 cells were found in patients with BKV viraemia occurring after kidney transplantation, where this phenotype is characteristic of immune system weakening[18].

RISK FACTORS OF BKVN DEVELOPMENT

BKVN is primarily a disease of transplanted kidneys, which implies, in addition to the immune alteration induced by immunosuppressants, an additional insult that predisposes the graft to the damage by this virus. An important moment for the development of BKVN may be an ischaemic-reperfusion injury to the tubular cells, toxic effect of applied drugs and immunological insult. Replicating tubular epithelial cells (in response to their previous damage) can also increase BKV replication and thus its virulence[19].

Excessive immunosuppression

The recipient of the kidney typically receives initial induction and subsequent maintenance immunosuppressive therapy. Application of antithymocyte globulin in the induction is associated with a longer duration of BKV viraemia as well as with a higher incidence of BKVN compared to patients who received a less aggressive anti-CD25 monoclonal antibody. This is consistent with the view that the leading factor of BKV reactivation is the intensity of immunosuppression, as lymphocyte depletion therapy using antithymocyte globulin is significantly more immunosuppressive than CD25 blockade. A similar correlation with the intensity of induction therapy was seen in a large 3C study that demonstrated a significantly higher BKV viraemia rate in the first 6 months after transplantation in recipients randomized to alemtuzumab (anti-CD52 monoclonal antibody) versus CD25 blockade by basiliximab[20]. However, a higher cumulative dose of another CD25 blocker, daclizumab, has been described as an independent risk factor for the development of BKVN (ref.[21]). The application of induction immunosuppression in various forms thus appears to be associated with a higher risk of BKVN development. However, the initial pulse of methylprednisolone administered without further induction was also documented as a potential risk factor for BKVN (ref.[2]).

Maintenance immunosuppression in most recipients of the transplanted kidney consists of three immunosuppressants: a calcineurin inhibitors (CI) tacrolimus or ciclosporin, an antiproliferative agent mycophenolate or azathioprine, and corticoids. It is documented that high levels of CI suppress virus-specific anti-BKV T-lymphocytes in response to the large T-antigen. Some, but not all studies, demonstrated a higher risk of BKV viruria and viraemia in patients treated with tacrolimus versus ciclosporin[22-24]. The incidence of BKV viraemia at 6 months post-transplant was 16.3% for tacrolimus compared to 10.6% for ciclosporin. This association between tacrolimus and higher incidence of BKV viraemia could be explained by the fact that tacrolimus, in addition to the T-cell immunosuppressive effect, promotes BKV replication through a mechanism involving the FK-binding protein (BP-12), while ciclosporin inhibits BKV replication in vitro[25]. A positive correlation was also documented between greater exposure to corticosteroids in maintenance immunosuppressive therapy and BKV viraemia. Combination therapy of mycophenolate with calcineurin inhibitors has also been shown to carry a higher risk of BKV viraemia compared to calcineurin inhibitor monotherapy. In one study, mycophenolate combined with ciclosporin showed the highest incidence of viruria, while a mycophenolate-free ciclosporin regimen was associated with the lowest level of BKV replication and faster viral elimination[24]. BKV viraemia and BKVN were less common in patients receiving mammalian target of rapamycin inhibitor (mTORi) sirolimus or everolimus, immunosuppressants that are considered less potent than CI with an inhibitory effect on BKV replication[25,26]. However, everolimus in combination therapy with mycophenolate was associated with a higher incidence of BKV viruria versus the combination of mycophenolate and ciclosporin[24]. Thus, it should be noted that BKVN can also be found in patients receiving ciclosporin, azathioprine and mTORi as well as protocols without CI. The available data point to the fact that the risk of BKV reactivation is associated rather with the overall level of immunosuppression, but the specific effect of a particular immunosuppressant on BKV replication cannot be ruled out altogether.

Not only the intensity of total immunosuppression, but also the variability of immunosuppressive levels may predispose to the development of BKVN. Higher variability in mean tacrolimus levels has been associated with BKVN development as well as more frequent acute rejections[27]. Important data about the risk-benefit profile of individual immunosuppressive protocols in terms of BKVN development could be provided by the completed conversion randomized study by the University of Giessen comparing three immunosuppressive protocols, ciclosporin and mycophenolate, tacrolimus and mycophenolate and tacrolimus and everolimus (ClinicalTrials.gov, identifier: NCT00160966).

Donor and recipient BKV serostatus and virus replication

An important role in the development of BKVN is also played by BKV serostatus of the donor and recipient at the time of transplantation. BKV donor seropositivity and seronegativity of the recipient have been shown to significantly increase the risk of BKV viraemia and graft BKVN compared to both donor and recipient seronegativity[28]. Higher risk of BKVN is found in children under the age of six, who are more likely to have no BKV-specific antibodies at the time of transplantation. Not only seronegativity, but also different BKV specific antibody titres, which may reflect current BKV replication, affect the risk of BKV viraemia and viruria in renal transplant recipients[28]. Higher titre of anti-BKV IgG in the donor and their lower titre in the recipient increase the risk of early BKV viraemia, where the donor serum reactivity level is associated with the amount of persistent virus in the donor kidney[28,29].

Testing donor and recipient for the presence of BKV viruria or viraemia may also be associated with the risk of BKVN in the post-transplant period. Studies show that the probable source of BKV is, in most cases, the donor rather than reactivation of the latent BKV infection in the recipient, and that donor pre-transplant viruria is an

independent risk factor for post-transplant BKV infection. However, kidney transplant recipients with isolated pre-transplant viruria without viraemia are not at a significantly higher risk of developing post-transplant viraemia or BKVN (ref.[30]). Alternatively, if BKV viraemia is present in the recipient at the time of transplantation, it often persists after transplantation and is associated with a high risk of BKVN. Therefore routine screening of the recipient for BKV vireamia at the time of transplantation is recommended[31].

HLA and ABO blood group incompatibility

A specific category of risk factors for BKVN development is the level of HLA compatibility between the donor and recipient. Donor-recipient matching in HLA-A2, HLA-B44 and HLA-DR15 has been associated with a reduced risk of BKV viraemia in kidney transplant patients[32]. Alternatively, with an increase in the number of HLA mismatches, the risk of BKVN rises and is even more pronounced in HLA and ABO incompatible transplants due to more frequent rejections and more intense immunosuppression in these patients[32-34]. Compared to HLA incompatible transplants, ABO incompatible procedures are almost three times more likely to cause BKVN, and ABO incompatibility is a significant independent predictor of BKVN development[34].

Other factors contributing to BKVN development

Not only immunosuppression and donor and recipient incompatibilities but also other factors are associated with an increased risk of BKVN. The most common ones are white ethnicity, older or younger age, male gender, diabetes mellitus, prolonged cold ischaemia time, ureteral trauma, delayed onset of renal transplant function, cytomegalovirus (CMV) infection and treatment of acute rejection[9,35]. This increases the risk of BKV reactivation due to a higher exposure to immunosuppressants in antirejection therapy, especially in patients receiving an antithymocyte depleting antibody. Mechanical traumatization of the ureter of the transplanted kidney due to stenting in time of surgery is considered by some authors to be a risk factor for the development of BKV viraemia[36]. For this reason, there is a tendency for earlier stent removal after 2-3 weeks versus the current practice of 4-6 weeks after transplantation. However, there are no prospective studies to confirm the benefit of this procedure.

BKV viraemia and BKVN may also occur in patients who have undergone other than renal transplantation[37]. For example, in the case of bone marrow transplantation, BKVN is rather rare and replication usually manifests as haemorrhagic cystitis. This is probably related to the use of different regimens of immunosuppression, doses and duration of immunosuppressive therapy. But cases of BKVN in native kidneys have been reported in adults and pediatric patients after heart transplanation, where renal failure developed, or as a complication of immunosuppressive therapy reduction, cardiac allograft rejection occurred[38]. BKV viraemia was also reported in patients after liver and lung transplantation[39,40]. Thus, BKV reactivation is always bound to the administration of immunosuppressive therapy or to otherwise immunocompromised individuals, as in the case of BKVN captured in a patient with tuberculosis or diabetes mellitus[40].

The prevalence of BKVN in kidney transplants indicates an important role of primary damage to the renal graft, which facilitates the subsequent development of BKVN and contrasts with the relatively rare occurrence of BKVN in non-renal solid organ transplants. However, even in these patients, it is currently advisable to perform BKV screening in the first year after transplantation in the case of deterioration of native kidney function[41]. Similar recommendations for early screening of BKV viraemia also apply to paediatric heart recipients[38].

DIAGNOSIS

Clinical manifestation

The dominant morphological manifestation of BKVN is tubulointerstitial nephritis, but can also rarely present as ureteral stenosis with urinary tract obstruction. Unfortunately, there are no specific clinical signs of tubulointerstitial damage in BKV infection that would facilitate its detection. These patients usually have only an asymptomatic acute or gradual increase in serum creatinine and haematuria may be present. From a time point of view, the disease most often manifests on average 10 to 13 months after the transplantation; however we can detect it within a wide range of 6 days to 5 years after surgery[42].

A rarer manifestation of BKV infection is also non-haemorrhagic cystitis, which occurs, similar to its haemorrhagic form, mainly in bone marrow transplant patients[43]. Other, unusual presentations include vasculopathy, retinitis, hepatitis, systemic lupus erythematosus, Guillain-Barré syndrome, meningoencephalitis, interstitial pneumonitis[44] and various types of tumours, especially urothelial[45]. In addition to bladder carcinoma, a direct correlation between previous BKV infection and development of urothelial carcinoma limited to the transplanted kidney was also documented, which occurred 5 years after clinically successful BKVN therapy. Tumour tissue was positive for simian virus 40 (SV40) large T antigen. The case demonstrates the possible association of persistent subclinical BKV infection in the graft with the development of malignant transformation of epithelial cells, despite the disappearance of BKV viraemia[46]. Although there is an increasing amount of data demonstrating a possible relationship between BKV infection and the development of malignancy, the carcinogenic potential of BKV remains unclear.

The influence of BKV infection on the de novo formation of donor specific antibodies (DSA) and antibody-mediated rejection also remains to be elucidated. Limited data point to a significantly higher early DSA formation in African Americans occurring in the first 24 months after kidney transplantation in recipients with BKV viraemia[47]. In another patients population, a relationship between persistent BKV viraemia (≥140 days) and a sig-

nificant de novo class II DSA formation was observed. However, after a median follow-up of 3 years, the survival of kidney grafts and patients with persistent viraemia and without viraemia did not significantly differ, despite the DSA formation[48].

Case reports also mention other rare post-transplant complications that may possibly be associated with BKV infection. Bioptically proven BKVN associated with proteinuria and graft dysfunction was reported one year after transplantation in a pediatric patient following living related kidney transplantation. After immunosuppressive therapy reduction, BKV viraemia decreased within two months but remained detectable. Graft dysfunction recurred, and repeat biopsy showed collapsing glomerulopathy in the setting of resolving BKVN (ref.[49]). Another case reported coincidental BKVN and CMV glomerulitis within the first weeks following kidney transplantation[50].

Laboratory examination

If BKVN has already developed, we usually find a deterioration of the kidney graft function. In the urine, haematuria, white blood cells and cellular cylinders containing renal tubular cells and inflammatory elements may occur. Such a urinary finding corresponds to the presence of interstitial nephritis, however, urine testing may also be normal. From the point of view of diagnostics, emphasis is currently placed on prospective screening of BKV reactivation in asymptomatic patients in order to prevent graft dysfunction. Most transplant centres today use basic urine screening procedures with urine cytology, or quantitative PCR-BKV analysis of urine or peripheral blood[51].

Urine cytology

Infected epithelial cells desquamate into tubule lumen, get into the urine and can be detected in a cytological examination as Decoy cells (DC). The presence of these cells, which have enlarged nuclei with one large basophilic intranuclear inclusion, should lead to a strong suspicion of polyomavirus infection[2]. Viral replication detected by DC was found to predict the development of BKV viraemia by an average of 4 weeks[9]. However, even asymptomatic individuals can excrete DC, and their capture does not necessarily mean an active viral replication[19]. Thus, DC are not sufficiently sensitive and specific for BKV infection. They may also occur in other viral diseases, mainly adenoviruses or CMV, although in the case of CMV this generally leads to cytoplasmic rather than intranuclear inclusions. The finding of DC may support a suspicion of BKVN, however, other methods of analysis, in particular quantitative PCR, are 2-4 times more sensitive in detecting BKV replication[52].

PCR

PCR of urine and blood currently plays a dominant role in the detection of BKV replication after kidney transplantation.

BKV viruria

BKV viruria usually precedes viraemia by a median of 4 weeks and BKVN with renal graft dysfunction by a median of 8 weeks[9]. BKV viruria can be considered the most sensitive marker of BKV reactivation that occurs in 23-73% of transplanted kidney recipients, depending on the method of detection by urinary cytology or PCR and the sensitivity of the methods used. According to some authors, the presence of the viruria does not correlate with the occurrence of BKVN, since most patients with viruria will never develop BKVN. One of the reasons for this is that more than 95% of urinary viral load originates from BKV replication in uroepithelium and only less than 5% from tubular cells[53].

However, BKV viruria has been lately given a certain clinical significance. At the minimum, high levels of PCR-BKV viruria ($\geq 2.5 \times 10^7$ copies/mL) may be an early marker of BKV viraemia or BKVN (ref.[54]). If BKV viruria develops in early post-transplant period, risk for BKVN development is higher compared to later occurrence. In our pilot group of 165 repeated protocol renal biopsies carried out in the first year after transplantation, significantly higher incidence of PCR-BKV viruria with frequent transition to BKV viraemia were seen in the case of persistent histological manifestation of CI nephrotoxicity, compared to patients with normal histological findings (prepared for publication).

Frequent BKV viruria screening is therefore wellusable in preventing BKVN development due to good sensitivity and early detection of replication, even before positive BKV viraemia[55]. It is of highest importance in the first year or two after transplantation. However, some authors recommend routine monitoring of viruria in longer period after transplantation, even more than 5 years[56].

BKV viraemia

As for the blood samples testing, it is recommended to carry out PCR-BKV analysis from plasma as up to one third of the tested whole blood samples were negative, despite the histologically verified BKVN (ref.[57]). BKV viraemia affects 8-62% of transplanted kidney recipients with a maximum incidence between 3-6 months after transplantation[22,23]. BKVN incidence in the first year after transplantation is stated in a broad range of 1-10% (ref.[20,58]). This variability of BKVN incidence observed in large patient populations may be due to differences in individual transplantation centres in immunosuppressive protocols, different frequency of monitoring and different sensitivity of the methodologies used. Due to these reasons, the World Health Organization's Expert Committee on Biological Standardization has published international standards for BKV PCR-based assays, which should lead to harmonization in the determination of BKV loads between different laboratories[59].

Plasma PCR-BKV has a sensitivity of 100% and a specificity of 88% (ref.[2]) in the diagnosis of BKVN, but not every BKV viraemia necessarily signifies renal impairment. In the case of histologically verified BKVN, these individuals have up to 100% positive plasma PCR. However, there are rare references of BKVN without the simultaneous capture of viraemia. For example, a case with BKVN detection was presented in a 2-year protocol biopsy, without simultaneous graft dysfunction and with

PCR negative urine and blood for both BKV and JCV. However, DC were detected in the urine[60].

Plasma viraemia more than 10^4 copies/mL has a stronger positive predictive value for BKVN than viruria[61], making the BKV plasma detection the preferred virus reactivation test. Kidney Disease Improving Global Outcomes suggests that a biopsy test should be considered at this level of viral load to exclude BKVN. However, this cut-off can lead to underdiagnosis, with up to 35% of BKVN patients showing less than 10^4/mL BKV plasma copies[62].

Alternative methods of BKV replication detection

Besides urine and blood testing, PCR methods were used to detect BKV in other biological fluids, gingival crevicular fluid, saliva and mouthwash. By comparing the findings in patients with chronic kidney disease and after kidney transplantation with healthy controls, these oral fluids were found to have similar efficacy in detecting BKV and JCV, as in blood and urine analysis[63].

However, other methods of viral DNA testing than PCR are also investigated in the detection of active virus replication. One of these is the assesment of BKV urinary mRNA levels. Using a cut-off limit of 6.5×10^5 BKV VP1 mRNAs/ng RNA in urinary cells, high sensitivity and specificity (more than 90%) were detected in case of viral replication[64]. Further studies are needed to verify, whether this method can accurately identify patients at increased risk of developing BKVN.

Electron microscopic urine testing

Another possibility to demonstrate the presence of BKV viruria is electron microscopic examination of urine. Singh et al. first documented the detection of cylinder-like three-dimensional aggregates of polyomaviruses, Haufen bodies (HB). In renal transplant patients, the detection of these HB was associated with a large BKV viraemia and provided 100% sensitivity and 99% specificity in the detection of bioptically verified BKVN. HB was not found in urine in patients with low BKV viraemia or in patients with haemorrhagic cystitis. In the later work, an excellent correlation was found between the quantitative determination of HB and the presence of BKVN (ref.[65]). Moreover, the number of HB correlated strongly with 1 to 3 BKVN histological stages. These findings suggest that HB capture in urine could be a sufficiently sensitive and specific non-invasive method of detecting BKVN in renal transplantations[66]. At present, the greatest benefit of this method seems to lie in the distinction between BKVN and asymptomatic BKV replication. Yet, the importance of this technique must be confirmed by further studies. A project on urinary HB detection as a possible diagnostic biomarker in patients with bioptically verified BKVN is currently ongoing at the University of North Carolina, Chapel Hill (ClinicalTrials.gov, identifier: NCT01094691).

In addition to the HB, the electron microscopic examination of urine can also play a significant role in the differential diagnosis of other viral graft disorders, where the individual viral particles differ not only by their localization, but also by their size; in the case of BKV, the size of these particles is typically 30-50 nm[67].

Serological examination

A serological examination aimed at the detection of BKV antibodies is not useful in the BKVN confirmation. These antibodies occur frequently in the population and are thus regularly detected in patients indicated for kidney transplantation. In primoinfection after transplantation, their apparent increase in the IgG class develops no sooner than 6 weeks after the contact with the virus, sometimes even 2 years after infection, which further limits their clinical utility. Antibodies do not seem to have a protective effect, however, they can reduce the severity of the disease, restrict virus replication and transformation of the viruria to persistent viraemia[68].

Histological examination

BKVN confirmation requires kidney graft biopsy. Histological, immunohistochemical, ultrastructural or molecular genetic examinations can be used to detect the virus in biopsy tissue. Biopsy should be performed whenever graft function is compromised with BKV viruria or viraemia present, especially if BKV viraemia repeatedly exceeds 10^4 copies/mL (ref.[3]). However, the histological finding may be falsely negative, as lesions are naturally focal, in particular for early BKVN. In addition, BKV affects primarily medulla rather than cortical tubules, where the medulla portion is usually not found in biopsy specimen[69]. It is therefore advisable to always collect two biopsy samples and try to get tissue also from the medulla. However, the diagnosis may not be determined in up to one third of cases, and repeated biopsy should be considered in such a situation.

The study of the immunohistochemical characteristics of BKVN revealed that lesions of proximal tubular cells appeared at the advanced stages of BKVN after the initial affection of the collecting canals. Although tubules are predominantly affected in BKVN, significant glomerular changes, in particular viral cytopathic changes in the epithelial cells of the parietal Bowman's capsular epithelium have been reported, occasionally with crescents and glomerulitis. A case of fatal BKV-bound vasculopathy is also documented, where BKV immunoreactivity was present in endothelial, but not epithelial cells[70].

An important benefit of biopsy is also the fact that it allows the elimination of other causes of renal dysfunction, such as drug toxicity and recurrence of the original kidney disease. Distinguishing from an acute rejection may be more difficult. In basic histological staining with haematoxylin-eosin, both BKVN and acute rejection can manifest as typical mixed interstitial inflammation, focal tubular damage and tubulitis. Particularly in the case of extensive tubulitis with lymphocytic infiltration of the tubular basal membrane, the BKVN differentiation from rejection is problematic[10] and the situation may be further complicated, if a BKVN resolution is already ongoing, with some less clear cytopathic viral changes[71]. In such a

case, it is necessary to look for other attributes of cellular or antibody-mediated rejection, especially after endarteritis, fibrinoid vascular necrosis, glomerulitis and C4d deposition. The absence of these changes should support the considered diagnosis of BKVN. However, both cellular and antibody-mediated rejection may occur concurrently with BKVN, which makes the choice of the right therapeutic procedure more difficult.

Characteristic viral cytopathic changes have been defined based on standard morphological evaluation, which, together with interstitial impairment, allow us to classify BKVN as type A, B or C (ref.[69]). Cytopathic changes consist of the presence of abnormally enlarged nuclei of adjacent cells with crescent-shaped basophilic intranuclear viral inclusions surrounded by a halo. Depending on the degree of tubulo-interstitial inflammatory infiltrate and fibrosis, we obtain the following classification scheme of BKVN (ref.[72]):

Degree A: cytopathic/cytolytic changes with or without minimal inflammation; the tissue contains only intranuclear inclusions of the virus. Changes affect only the medulla.

Degree B: cytopathic/cytolytic changes associated with acute focal or diffuse tubulointerstitial inflammation, only a small degree of chronic interstitial fibrosis and tubular atrophy. There is infiltration of polynuclears, monocytes and plasma cells. Changes affect the medulla and the cortex. Subclassification to B1-B3 is based exclusively on the degree of inflammation, which is an independent indicator of the prognosis of the graft.

Degree C: graft sclerosis, signs of chronic interstitial fibrosis and tubular atrophy, scarring and the presence of calcifications.

Determining the degree of graft impairment according to this classification scheme enables us to estimate the prognosis of the disease in the particular individual. Banff classification indicates that the presence of inflammation (stage B) and fibrosis (stage C) are significant negative prognostic factors, whereas the earlier stage of tubular damage (stage A) and the viral load in tissue itself do not affect graft survival. According to the American Society for Transplantation Transplant Infectious Diseases group classification, the graft function loss is described for 13% grafts of type A, 55% grafts of type B, and 100% grafts of type C (ref.[69]). In the case of persistent BKVN, this leads to parenchymal scarring, progressive tubular atrophy[73] with unavoidable cessation of graft function.

However, the above cytopathic viral changes can also be observed in infections caused by other viruses, e.g. CMV, adenovirus and human herpes simplex virus (HHSV), and thus many of these findings are not pathognomic. In the case of CMV, cytoplasmic localization of viral inclusions is found; in the case of HHSV, both intranuclear and cytoplasmic inclusions can be detected. Nonspecific changes also include anisonucleosis, hyperchromasia and chromatin clusters of infected cells. Interstitial mononuclear or polynuclear infiltrates, apoptosis and tubular cell segregation and flat epithelial lining may occur as a part of tubular damage[10]. Electron microscopic examination of histological samples can also be performed in case of diagnostic doubts and vague morphological changes. Electron microscopy can detect intranuclear viral inclusions of 30-50 nm in diameter, necrotic tubular cells, prominent lysosomal inclusions, and luminal protein and cellular cylinders[10].

Currently, the presence of BKV in the renal tissue is immunohistochemically tested using a BKV-targeted or cross-reacting antibody with the large antigen of SV40 common for BKV, JCV and SV40 virus[74]. The positivity of this staining is a diagnostic confirmation of BKVN, because it is associated with nearly 100% specificity. This examination allows for reliable differentiation of interstitial inflammatory changes associated with BKVN from acute cellular rejection and is pathognomic for BKV replication in the kidney.

However, definitive diagnosis of BKVN may be difficult in some cases. This is particularly so in the absence of a clear biopsy finding. In this situation, BKVN diagnosis appears to be likely if urinary DC excretion persists with simultaneous detection of significant BKV replication in plasma (DNA PCR-BKV $>10^4$ copies/mL) even in the absence of graft dysfunction. The confirmation of the diagnosis of BKVN cannot be expected even from a direct PCR testing of a kidney tissue sample, because PCR analysis also captures latent colonization of tissues with non-replicating virus in otherwise asymptomatic individuals[75].

BKVN SCREENING AND PROPHYLAXIS

Screening for BKV activation in the post-transplantation period plays an important role in the prevention of BKVN development as BKV infection and subsequently graft dysfunction occur in a stepwise fashion. During periods of asymptomatic viruria and viraemia, there is an opportunity for preemptive immunosuppressive dose reduction to prevent progression to BKVN (ref.[76]). The effectiveness of this preemptive strategy has been evaluated in only a few studies[9,23,69]. In one such study of 200 patients with BKV viraemia, antimetabolite discontinuation resulted in the resolution of BKV viraemia in 95% of patients and no cases of BKVN were observed. This protocol was not associated with a significantly higher risk of acute rejection or graft loss, and patient and graft survival were 91% and 84% respectively in the subsequent five-year period[23]. The rationality of the preemptive strategy is also supported by a study showing that even BKV viraemia without clinically apparent BKVN can be associated with worse long-term allograft function, highlighting the importance of early intervention to limit BKV viral replication[77].

As with isolated BKV viraemia, there are few controlled studies of the efficacy of preemptive strategies in the management of presumptive (positive PCR-BKV viraemia and graft dysfunction) or proven (bioptically verified) BKVN. Unfortunately, there is currently no specific antiviral therapy targeting BKV. As a result, therapeutic recom-

mendations on how to proceed in the case of presumed or proven BKVN are similar to isolated BKV viraemia and predominantly rely on enhancing the immune defense of the organism by reducing immunosuppressive therapy[9]. The goal of reducing immunosuppression is to prevent viral replication without inducing the development of rejection, although the optimal procedure for the stepwise reduction in immunosuppressive therapies remains unclear. No study has compared different strategies and the approach to immunosuppression reduction depends to a large extent on the experience of the individual centres. Initially, a dose reduction of antimetabolite (mycophenolate or azathioprine) can be recommended with subsequent CI dose modification (ciclosporin or tacrolimus), if viruria persists[77]. In the case of ongoing viraemia, the antimetabolite is completely discontinued. However, it can be removed as an initial therapeutic measure along with the reduction of the CI dose[52], as the administration of antimetabolite mycophenolate leads to an increase in the incidence of BKV viruria[24]. Even in patients after concomitant renal and pancreatic transplantation, reduction of immunosuppression in BKV viraemia and BKVN seems to be an effective and efficient method of preventing deterioration of renal function, without influencing the prognosis of pancreatic graft[78].

However, reducing immunosuppressive therapy may not always be without undesirable consequences and some studies mention this risk. In particular, long-term modified immunosuppression in the treatment of BKVN may be associated with a higher incidence of chronic rejection and the rise of de novo DSA formation in a recipient with persistent BKV viraemia[74,79]. Bioptically verified acute cellular or humoral rejection represents, according to one of the studies, a higher risk of graft loss than it was observed in BKVN alone[41].

The universally accepted algorithm recommended for BKV reactivation screening involves a series of repeated monthly examinations during the first half year after kidney transplantation followed by further tests at 9, 12, 18 and 24 months. The rationale behind this approach is the fact that 85% of all BKV viraemia cases develop in the first 3 to 4 months after transplantation[23]. This standard scheme should always be supplemented by an examination in the event of detection of otherwise inexplicable graft dysfunction. However, the optimal screening method and the threshold for evaluating the results of various tests as clinically significant are not clear. Multidisciplinary recommendations by experts suggest urinary DC or PCR detection of urinary BKV DNA or VP-1 mRNA are acceptable methods[9]. Specific quantitative diagnostic tests using quantitative PCR with threshold values for suspected disease should be used to confirm the results. More than 10^7 copies/mL of viral DNA in urine or urinary VP-1 mRNA with an amount greater than 6.5 x 10^5 copies/ng of total RNA are considered significant viral DNA secretion in urine analysis and more than 10^4 copies/mL if plasma DNA testing is used. However, some authors consider plasma BKV viraemia higher than 500 copies/mL significant and recommend such patients for biopsy[41]. If full blood is used in PCR screening, consideration should also be given to the possible institutional variability in the sensitivity and specificity of PCR methods[52]. The presence of more than 10^3 copies/mL is considered to be significant when examined from whole blood and when correlated with the development of graft dysfunction should be an indication for biopsy[77]. Of note, as previously mentioned, the PCR results of the whole blood test can be falsely negative and plasma PCR-BKV has a stronger positive predictive value[57].

Screening and an early intervention may significantly reduce BKVN. If performed routinely, it will help detect BKV replication even before graft damage. If pathological changes associated with BKVN develop, the management of renal damage is more difficult[41,80]. The effect of the measures is monitored by plasma PCR-BKV until its negativity. Viraemia should disappear within six months after the reduction of immunosuppressive therapy; the average time of its resolution is four months[9]. In the case of persistence of BKV viraemia or further progression of graft dysfunction, repeated biopsy is indicated in order to avoid the acute rejection as a complication. The administration of antiviral agents is indicated in the case of confirmation of BKVN persistence[52].

BKVN ANTI-VIRAL THERAPY

Antiviral agents

IVIG

Opinions differ on the use of IVIG as an antiviral agent in BKVN. The rationale behind this treatment is based on the fact that currently commercially available immunoglobulin preparations may contain antibodies against BKV and JCV, since these viruses are ubiquitous in the general population. However, there is no general acceptance[68] of the neutralizing effect of these antibodies against all major BKV genotypes[81], and the data demonstrating the effectiveness of IVIG in patients with BKVN is limited and inconsistent[82]. In clinical practice, the effect of these specific antibodies in enhancing the overall antibody response to inadequate cellular responsiveness may be beneficial even with its debatable anti-BKV activity[13]. Thus, IVIG may be useful, especially in individuals with hypogammaglobulinemia, where it can contribute to passive anti-BKV immunity and also act as an immunomodulatory. IVIG may also be helpful in the prevention and treatment of graft rejection in the context of reduced immunosuppression and the often difficult histological differentiation of these two acute pathologies[83], whereas other immunosuppressive therapies could exacerbate the course of BKV infection. A response to questions about the protective effect of anti-BKV neutralizing antibodies in preventing the development of BKVN could be provided by an ongoing observational study of the University Hospital, Strasbourg (ClinicalTrials.gov, identifier: NCT02826811).

Leflunomide

Leflunomide has both immunosuppressive and antiviral effects, including an effect on CMV viral replication.

While its exact mechanism of action remains unclear, it has been used in BKVN therapy with inconsistent results and numerous adverse reactions. In one study investigating the 4-year graft survival in patients with significant BKV viraemia and/or histologically verified BKVN detected in the first year after renal transplantation, no significant differences were seen in the treatment associated with the reduction of immunosuppressive therapy and concomitant leflunomide use, when compared to the group without BKV viraemia[84]. However, the randomized trial did not show an effect of leflunomide monotherapy in terms of improvement of renal function compared with a simple immunosuppressive reduction[85]. One series of refractory BKVN cases documented that leflunomide combined with everolimus can lead to virus removal and graft function stabilization[86]. Currently, there is an open-label, randomized, multicentric study evaluating the potential of leflunomide administered with orotic acid in terms of the clearance of BKV viraemia (ClinicalTrials.gov, identifier: NCT01620268).

Cidofovir and Brincidofovir (CMX-001)

The antiviral agent cidofovir is effective in the treatment of CMV infection and shows activity against polyomaviruses. Its benefit in patients with BKVN was tested particularly in uncontrolled, non-randomized studies with very good documented survival of grafts. However, unambiguous clinical evidence that cidofovir monotherapy reduces BKV load is missing, as this reduction has always been associated with the simultaneous minimization of immunosuppressive therapy[87]. The mechanism of action of cidofovir against BKV is unclear and its administration has been associated with nephrotoxicity in the form of proteinuria and subacute tubulointerstitial nephritis with terminal renal failure. Because of the risk of significant toxicity, cidofovir should be used with caution and only if other interventions fail.

Brincidofovir, a lipid ester of cidofovir, has reduced nephrotoxicity but maintains its anti-BKV activity in vitro. It has also been studied in BKVN after renal and hematopoetic stem cell transplantation[88] with reasonable outcomes. Overall this therapy was well tolerated by patients and quantitatively reduced the BKV viral load, but with some patients experiencing dose-limiting gastrointestinal toxicity.

Quinolone antibiotics

Anti-BKV activity of quinolone antibiotics was repeatedly reported in the past, and quinolones were used in BKVN therapy. However, subsequent randomized trial did not demonstrate the efficacy of levofloxacin neither in the prevention of the development of BKVN in the immediate post-transplantation period nor in the treatment of active BKV viraemia[89]. Currently, a randomized, blinded study of ciprofloxacin is being conducted at Houston Methodist Hospital, Texas, assessing its efficacy in the prevention of BKV infection in the early period after renal transplantation (ClinicalTrials.gov, identifier: NCT01789203).

Alternative methods in immunosuppressive therapy adjustments

In addition to standard immunosuppressive agent reduction, alternative treatments associated with modifications in immunosuppressive therapy may be effective in the treatment of BKV viraemia and BKVN. A positive effect may develop upon converting from tacrolimus to a small dose of ciclosporin, when the suppressive effects of ciclosporin on BKV replication are employed and mycophenolate levels are concomitantly reduced. Currently, a prospective observational study is being conducted at Loma Linda University Medical Center, which should evaluate the effectiveness of this conversion from tacrolimus to ciclosporin in patients with BKV viraemia and BKVN (ClinicalTrials.gov, identifier: NCT02758288).

An effective measure could also be the complete elimination of CI from immunosuppressive protocols. These can be replaced with mTORi, possibly with antimetabolite discontinuation. This reduces the anticipated long-term nephrotoxic effect of CI (ref.[90]), and the complete discontinuation of the CI or at least their dose reduction may thus delay the loss of graft function. This strategy was also tested in a pilot study of ABO incompatible kidney transplants, where conversion of tacrolimus to everolimus was performed after the mean of 141 days following transplantation due to active BKV replication. This conversion was not associated with a higher incidence of rejection episodes and the viral load decreased in most patients[91]. Currently, there are two studies evaluating the potential of mTORi in patients with BKV reactivation. An extensive study in patients with BKVN converted from ciclosporin or tacrolimus to everolimus is being conducted at the University of California (ClinicalTrials.gov, identifier: NCT01624948). The second, open, randomized, prospective study based on tacrolimus substitution with sirolimus in the prevention of BKVN in patients with BKV viraemia was completed at Columbia University (ClinicalTrials.gov, identifier: NCT01649609) and its results are expected.

Any currently used protocol based on the reduction or modification of immunosuppression or the administration of antiviral therapy requires the evaluation of the effect of the chosen procedure by comparing the basal viral load and its changes after the treatment. From this aspect, PCR testing every 2-4 weeks until the eventual disappearance of BKV viraemia seems optimal.

Possibilities of BKVN immunotherapy

Since post-transplantation reactivation of BKV is closely related to a deficient response of the immune system to the presence of the virus, the possibility of targeted anti-BKV immunotherapy is currently being studied. The facilities of T-cell immunotherapy are being investigated, where candidate T-cells can be isolated from the patient's own blood using in vitro techniques. The isolated T-cells are then expanded in vitro against the target BKV antigens, and these activated responder T-cells are subsequently re-administered to the recipient. However, the problem of such a process is product generation time and undesirable delay in treatment. Immediate availability

of virus-specific T-cells could be provided by specific cell banks supplied from suitable HLA-matched donors[92].

The specific viral epitopes optimal for targeted T cell expansion are currently the subject of research[93]. Genetic modifications to the responder T cells can allow them to survive longer, and they can subsequently also act as a prevention of the disease[41]. The obtained data suggest that adoptive transfer of BKV-reactive T lymphocytes has the potential to improve BKV-associated disability and may provide a significant therapeutic benefit for patients with BKVN or haemorrhagic cystitis. Further research into complex determinants of immunogenic T cell epitopes for BKV antigens and optimization of T cell expansion protocols should assist in the development and subsequent practical use of these immunotherapeutic procedures in the treatment of BKV associated diseases[3].

RENAL RETRANSPLANTATION

Data describing the outcomes of renal rentransplantation in patients whose first graft failed due to BKVN is currently scarce. However, in limited studies short-term graft survival remains comparable to the general kidney transplant population using standard induction and maintenance immunosuppressive protocols. Repeated transplantation in such patients warrants a thoughtful approach taking into account both infectious as well as immunologic risks. In general, it is recommended to wait until the recipient does not have active viral replication as confirmed by plasma BKV-PCR. Successful retransplantation performed despite positive BKV viraemia was reported in a patient receiving simultaneous renal and hepatic transplantation[94]. However, the outcome could be affected by the lack of induction therapy and lower doses of subsequent maintenance immunosuppression. An alternative approach is nephrectomy of the failed graft at the time of retransplantation, but this procedure remains controversial. Prophylactic nephro-ureterectomy is not recommended in the absence of BKV replication; prudent maintenance immunosuppressive therapy and close postransplantation monitoring of BKV viraemia are desirable[41]. Some centers choose more gentle immunosuppression in these patients; however, the use of antithymocyte immunoglobulin in the induction did not increase the incidence of BKV viruria and viraemia in one of these studies[23]. If we can choose from multiple kidney donors, we consider the donor with the lowest antibody titre against BKV. Donor BKV seroreactivity was namely found to be the strongest pre-transplant risk factor associated with the development of BKV viraemia in the recipient based on a multivariate analysis. Thus, donor screening should be considered as a routine test before kidney transplantation and/or retransplantation[41].

CONCLUSION

BKVN is a serious complication endangering the function of the kidney graft especially during the first year after transplantation and should be considered whenever renal function deteriorates. With an increasing number of retransplantations and incompatible transplants, it is likely that its incidence will increase.

In the absence of BKV specific antiviral therapy, active BKV replication screening in the post-transplantation period is an essential prophylactic procedure to prevent graft damage. It allows for preemptive reduction of immunosuppressive therapy in case of the detection of significant BKV viraemia and the prevention of the development of clinically significant nephropathy. This strategy has proven to be effective in reducing early graft loss due to BKVN, despite the increased risk of alloimmune activation and acute rejection. Post-transplant screening of BKV replication should also be used in organ recipients in non-renal transplantations due to possible BKV reactivation with renal impairment in these patients.

In individuals with clinically manifest BKVN where graft dysfunction, despite the maximal reduction in immunosuppressive therapy, is progressing over several weeks or months, we use non-specific antiviral therapy, although its benefit has not been clearly verified. The goal thus still remains to find an effective, well-tolerated and easy-to-use antiviral agent that can be used in the prophylaxis and therapy of BKV viraemia and BKVN, similarly to our ability to treat CMV infection and CMV diseases. Promise for the future may also be found in BKV-specific immunotherapy research, and the possibilities of genotypic-specific anti-BKV vaccination are also being explored.

In patients with graft failure due to BKVN, we postpone retransplantation until BKV viraemia disappear. The nephro-ureterectomy of the previous transplanted kidney is not recommended in the absence of BKV replication.

It is clear that the management of BKV-associated diseases currently differs in individual centres and the results of randomized controlled trials will be essential to define optimal treatment strategies for the renal recipients with BKV reactivation.

Search strategy and selection criteria

Our research strategy was focused on presenting a current and comprehensive summary of recent information on epidemiology and pathogenesis of BKV infection in kidney transplant patients, risk factors for its development, clinical manifestation varieties and diagnostic options, and also on the not very clear screening, prophylactic and therapeutic approaches to manage BKV replication or nephropathy.

Scientific original or review articles from 1974 to 2017 were searched using PubMed and the Web of Science database. All searches were up to date as of December 2017. The search terms were “BK virus clinical trials“, “BK virus infection“, “BK virus nephropathy“, “BK virus retransplantation“, “BK virus therapy“, “JC virus infection“, “kidney transplantation“, “polyomavirus infection“

and "SV40 virus infection". Only English-written articles were used to prepare this review.

ABBREVIATION

BKV, BK virus; BKVN, BK virus nephropathy; CI, Calcineurin inhibitors; CMV, Cytomegalovirus; DC, Decoy cells; DSA, Donor specific antibodies; HB, Haufen bodies; HHSV, Human herpes simplex virus; HLA, Human leukocyte antigen; IVIG, Intravenous immunoglobulins; JCV, JC virus; mTORi, Mammalian target of rapamycin inhibitor; NK, Natural killers; PCR, Polymerase chain reaction; SV40, Simian virus 40.

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