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Pathogenicity of BK virus on the urinary system

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Introduction The polyomaviruses are omnipresent in nature. The major sites of BK virus appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells.
Material and methods A literature search according to PRISMA guidelines within the Medline database was conducted in July 2019 for articles presenting data about BK virus in urologic aspect without setting time limits, using the terms 'BK virus' in conjunction with transplantation, nephropathy, stenosis, cancer, bladder, prostate, kidney.
Results The BK virus usually stays latent, however, its replication may become active in various clinical situations of impaired immunocompetence such as solid organ transplantation, bone marrow transplantation, AIDS, pregnancy, multiple sclerosis, administration of chemotherapy or biologic therapy. BK virus is associated with two main complications after transplantation: polyomavirus-associated nephropathy in kidney transplant patients and polyomavirus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplant patients.
Conclusions The aim of this article was to present available data on urologic aspects of BK virus infection, its detection methods and available treatment.

Key Words: polyomavirus ‹› BK virus ‹› urology ‹› haemorrhagic cystitis
‹› polyomavirus associated nephropathy

INTRODUCTION

According to the International Committee on Taxonomy of Viruses, polyomaviridae is a family with 89 recognized virus species contained within four genera, as well as 9 species that could not be assigned to any genus [1]. Among all polyomaviridae 13 species are known to infect humans [2, 3]. Most of these viruses are very common in the human population, yet, involvement of these viruses in human pathologies is rare. The polyomaviruses are omnipresent in nature and species specific – they infect humans (JCV, BKV), monkeys (simian virus 40 *SV*40), and mice (mouse polyomavirus) [4].
BK virus (BKV) is a ubiquitous polyoma virus, often acquired during childhood with a 80–90% seroprevalence rate among adults. The major sites of BKV appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells. It usually stays latent, however, BKV replication may become active in various clinical situations of impaired immunocompetence such as solid organ transplantation, bone marrow transplantation, AIDS, pregnancy, multiple sclerosis, administration of chemotherapy or biologic therapy [5]. Nowadays, with the use of potent immunosuppressive agents and enhanced viral surveillance protocols, the BKV has arisen as an important cause of morbidity in renal transplant recipients.
BKV is associated with two main complications after transplantation: polyomavirus-associated nephropathy (BKVAN) in 1 to 10% of kidney transplant pa-

tients [6–9] and polyomavirus-associated haemorrhagic cystitis (BKVHC) in 5 to 15% of allogeneic hematopoietic stem cell transplant (HSCT) patients [10, 11, 12]. Also, other complications such as ureteral stenosis and some cancers are related to BKV infection [4, 13–16]. Despite being rare, BKV associated pathologies also occur in patients with non-kidney solid organ transplantation (SOT) or with inherited, acquired or drug-induced immunodeficiency [13, 17]. Besides BKVAN and BKVHC they include pneumonitis, retinitis, liver disease and meningoencephalitis [18].

The aim of this article is to present available data on urologic aspects of BK virus infection, its detection methods and treatment.

Evidence acquisition and evidence synthesis

A literature search according to PRISMA guidelines within the Medline database was conducted in July 2019 for articles presenting data about BK virus in urologic aspect without setting time limits, using the terms 'BK virus' in conjunction with transplantation, nephropathy, stenosis, cancer, bladder, prostate, kidney. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Autoalerts in Medline were also run, as well as reference lists of original articles and review articles for further eligible data. The search was limited to English literature. Articles that did not address the topics were excluded, and the full text of the remaining articles was subsequently reviewed.

The BK virus

The term 'BK' originated from a patient's initials, in whom the virus was first detected in 1971. The 'first' patient underwent renal transplantation 3 months earlier and presented with anuria and pain over the graft [19]. Diagnostic workup revealed ureteric obstruction that was later corrected surgically. Examination of biological samples and of the ureteral segment excised during surgery exposed a previously unknown virus. With time, other research confirmed an association between renal transplant recipients' morbidity and BKV incidence [20–23].

Genome

Polyomaviruses are small (45 nm) non-enveloped viruses that are composed of 72 capsomeres with icosahedral symmetry, harbour a circular double-stranded DNA, and belong to the Polyomaviridae family with Polyomavirus as the only genus.

The BK virus's genetic material contains three main domains: (1) an early region composed of replicative genes – large tumour antigen (T antigen) and small tumour antigens (t antigen); (2) a non-coding control region (NCCR) adjacent to the early region containing transcription factors for the early and late genes and (3) a late region encoding the viral capsid proteins (VP1,VP2, VP3) [18, 24]. The BKV genome is in 75% homological with the JC virus genome and in 70% with SV40 virus genome [24]. BKV has four serologic types based on sequence variation in the genomic region of VP1, which can be further divided into various subtypes. Type I presents the highest prevalence of 70–80% and is followed by type IV (10–20%), with some geographical distinctions [25, 26]. Apart from the VP1 region subdivision, there are also other subclassifications of BKV due to the variation in the NCCRD [5]. However, despite many subtypes of BKV being described, the clinical implications of infection with the different genotypes of BKV are still unknown [27].

Epidemiology

It is estimated that BK virus seroprevalence concerns 50% of children under 5 years old and up to 90% of the adult population [16, 28]. The primary BKV infection often occurs around the age of 3 to 4 years old [29]. The virus can be transmitted via various routes including: faecal-oral, respiratory, through blood transfusions, organ transplantation, transplacentally and through seminal fluid [30]. After infection (with or without trivial symptoms), BKV is not completely eliminated from the host and may be detected in renal tubular epithelial cells, where it remains latent lifelong with replication controlled by the immune system [31]. Other locations of the virus include the liver, lungs, brain and lymph nodes. Asymptomatic and clinically insignificant viruria occurs in healthy patients with occurrence up to 20%, with higher incidences during immunosuppressed states and in pregnancy [16, 30].

In renal transplantation, reactivation of latent virus starts soon after immunosuppression implementation, and is observed in up to 30–50% of kidney recipients within the first three months. The precise mechanism of infection reactivation is not well elucidated [32]. The risk of reactivation depends on the microbiologic features of the virus, the presence of inducing factors for the activation of virus in tissues (kidney injury, graft rejection, ischemia, drug toxicity), the amount of virus present, the nature of the person's immune deficits (e.g. serological status), total burden of immunosuppression and host–graft relationship variations [18, 33].

Clinical presentations

BK Virus Nephropathy

BKVAN concerns mostly patients after kidney transplantation. Despite the fact that 30–50% of all renal recipients develop temporary BK viruria and approximately one-third present viremia, only 1–10% of patients progress to BKVAN [34, 35]. Rarely, BKVAN may also appear in native kidneys of other organs recipients – lung, heart, liver and pancreas, as well as bone marrow stem cell [36–44].

Symptomatology of BKVN is nonspecific and may vary from asymptomatic infection to elevated serum creatinine. Among bone marrow transplant recipients, haemorrhagic cystitis is the most common feature of BKV infection.

In renal transplant recipients the deterioration of allograft function is often the first and the sole sign of BKVAN. In more than 50% of kidney transplant recipients, BKVAN leads to graft failure and in 30 to 80% of cases – graft loss [37, 45]. The majority of BKVAN cases occur within the first 12 months after transplantation, however, 25% of cases may be diagnosed long after transplantation.

Multiple complementary risk factors contribute to disease progression. From amongst viral-related factors, serotype and genomic mutations (NCCR rearrangements) were proven to be relevant. Also, recipient characteristics (older age, male gender, ethnicity, HLA-C7 negativity, BK-virus seronegativity before transplantation, low number of BKV-specific T-cells and co-morbidity with diabetes mellitus), previous acute rejection episodes, delayed graft function, ureteral injury during transplantation procedure were describe to increase the risk of BKVAN with donor-related factors including BKV seropositivity and donor-recipient HLA mismatching [16, 46, 47]. In addition to the above, the total degree of immunosuppression is thought to be the most important factor promoting BKV reactivation and no single immunosuppressive agent was proven to increase the rate of BKVAN. However, patients receiving tacrolimus-based immunosuppression have been reported to have higher rates of BKVAN than those on cyclosporine or sirolimus [5, 48, 49].

Diagnosis of BKVAN

Historically, the diagnosis of polyomavirus infection was based on the demonstration of rising antibody titers (which was later proved not to be clinically relevant), cytologic evaluation of urine sediment, viral isolation from urine and blood and electron/immuno-electron microscopic studies of urine and immuno-histochemical staining for SV40 LTag (Simian Vacuolating Virus 40 T Antigen) in kidney biopsy.

Cytologic evaluation of urine sediment can demonstrate viral inclusion bearing epithelial cells, so called 'decoy cells' (characterized by a ground-glass appearance with an enlarged nucleus, which is occupied by a homogeneous basophilic inclusion surrounded by chromatin). They are present in 40% to 60% of renal transplant recipients, although positive predictive value is approximately 20% with negative predictive value of 100% [50]. Virus particles are also detectable by direct negative staining electron microscopy (BKV-clusters – 'haufen') [22, 51].

BKV infection after kidney transplantation may progress gradually from initial viruria through viremia and in a subgroup of 20–40% of viremic patients to histological changes classified as BKVAN [52]. Currently, BKVAN diagnosis is based on PCR-based viral load analysis in the plasma and urine. Both quantitative and qualitative tests are being used, with later being much more sensitive. Sustained high urine viral loads of $>7_{\log}10$ copies/ml correlate with the onset of viremia [53].

Sustained plasma BKV-DNA load higher than $4_{\log}10$ copies/ml is considered as presumptive BKVAN [54, 55, 56]. Literature data indicate that the urine BKV DNA $>7_{\log}10$ copies/ml and/or plasma BKV DNA $>4_{\log}10$ copies/ml indicate possibility of BKVAN even in the absence of demonstrable BKV replication in renal biopsies [12, 57, 58]. It was also reported that measurement of messenger RNA for BK virus VP1 in urine can mirror active viral replication [59, 60].

Although helpful in identifying patients at increased risk, laboratory assays including quantitative PCR testing are not perfect in rendering a definitive diagnosis of BKVAN.

Biopsies in patients with presumptive BKVAN are obtained routinely to confirm a diagnosis of definitive BKVAN and evaluate the degree of tissue injury. The term 'definitive' BKVAN describes only patients with biopsy-proven BKV-related nephropathy [61]. BKVAN is characterized by subacute virus-induced tubular injury, inflammation, and progressive nephron damage. Histologic markers of BKVAN include viral cytopathic effect with large, homogenous intranuclear inclusions, mainly in tubular epithelium with no necrosis. BKVAN include ischemic glomerulopathy, dilation of glomerular capillaries or mild increase in mesangial matrix, also cytopathic effect in parietal Bowman capsule, crescents or glomerulonephritis is present [62, 63]. Diagnostic confirmation obtained by immunohistochemistry (IHC) with a positive SV40 LTag staining reaction is required. Presence of SV40 LTag in epithelial cell nuclei is

often but not always accompanied by the typical intranuclear viral inclusion bodies [52].

Screening for prevention

It is widely known that early intervention in the situation of BKV infection/reactivation in immunocompromised patients is effective in preventing the development of severe complications. Because of this, BKVAN surveillance is therefore recommended for renal transplant recipients.

Screening for BKV infection may be performed by means of urine cytology (decoy cells) or preferably by PCR assessment of urine and/or plasma.

It has to be remembered that methods of screening are burdened with the same problems as diagnostic methods such as interassay variation, interobserver variability and lack of universal standardization. For that reason the optimal frequency and method for BKV surveillance are not clear.

The screening schedules vary between different centres. According to the 2019 American Society of Transplantation Infectious Diseases Guidelines screening for BKV replication should be performed in all kidney recipients monthly until month 9, and then at least every 3 months during the first two years post-transplant, and then with decreasing frequency until the fifth year post-transplant, yet, the screening procedures may be employed more frequently in special circumstances (any unexplained graft dysfunction, in regions with higher BKVAN incidence) [53, 57, 64–67]. In recipients with viral urine load $>7_{log10}$ copies/ml and/or urine cytology >3 decoy cells HPF evaluation of viremia is required. In case of viremia $>4_{log10}$ copies/ml confirmation by kidney biopsy and reduction of immunosuppression should be considered [52].

Treatment

BK virus pathogenicity is for a great part due to the importance of its replication, supported by immunosuppression (iatrogenic, secondary to HIV infection, etc.). Therefore, an early diagnosis and a rapid restoration of immunity leading to limitation of viral replication, is currently the most effective way to control the disease [68].

Stepwise immunosuppression reduction is recommended for kidney transplant recipients with viruria $>3_{log10}$ copies/ml for 3 weeks or increasing to $>4_{log10}$ copies/ml and in all cases of for biopsy proven BKVAN [53].

Although there is no standard way to reduce immunosuppression, most centres start from discontinuation of mycophenolate mofetil/sodium or aza-thioprine and reduction of calcineurin inhibitor dose by 25% to 50%. Switching from tacrolimus to cyclosporine A (trough levels 100-150 ng/ml) may be also effective as well as switching to mTOR inhibitors [69]. It is recommended to monitor the response by viruria and viremia assessment every 2–4 weeks. After this, clearance of viruria and viremia in achieved in most of the patients, yet, the kidney allograft function do not always return to normal levels [70, 71].

Additional administration of antiviral therapy such as cidofovir at low doses, leflunomide, quinolones, artesunate and intravenous immunoglobulins was reported, but the, above mentioned agents were not clearly proved to be more efficacious than screening and reduction of immunosuppressive therapy [72–81].

Ureteral stenosis

Ureteral stenosis with fibrosis, and ulceration of the donor ureter after renal transplantation associated with BKV infection, although rare (2 to 6%), is a challenging complication which often requires surgical correction [21, 82, 83]. It is usually clinically asymptomatic with progressing oliguria and impaired renal function. Classic colic symptoms or discomfort over the graft are not present in all cases, since the transplanted kidney is denervated [84].

Risk factors of stenosis development do not vary from general risk factors of BKV infection reactivation. It was reported that use of ureteral stents after transplantation increase rate of polyomavirus nephropathy. It was also shown that stent placement, yet not the time of removal, was lined to BKV viruria. In light of those observations routine placement of ureteral stents during transplantation is a subject of debate [85–88]. Additionally, ischemia of the ureter resulting from stripping, long ureter or imperfect uretero-vesical anastomosis may play role in BKV related stricture.

Treatment include administration of medical regiments similar to those used in BKVAN. In cases of obstructive nephropathy the proper renal drainage by DJ catheter or percutaneous nephrostomy is required. Further endoscopic dilatation, long-term stenting and/or surgical resection of strictured segment are possible therapeutic options.

BK Virus haemorrhagic cystitis

Haemorrhagic cystitis (HC) is a complication of BKV infection mainly related to hematopoietic stem cell transplant, yet, it may also appear in other immunocompromised patients [89, 90]. BKV viruria is pres-

ent in the majority of bone marrow transplant recipients and about 10–30% of patients develop clinically significant HC mainly shortly after the procedure [12, 91, 92, 93].

Various risk factors of HC incidence and severity have been identified including donor–recipient gender mismatches, bone marrow as a stem cell source, class II and III of thalassemia, use of busulfan plus cyclophosphamide plus ATG in the conditioning regimen, graft-versus-host disease (GVHD), use of prednisolone and cyclosporine as prophylaxis treatment of GVHD, and gancyclovir and intravenous immunoglobulin (IVIg) as antiviral drugs [91].

HC may present with haematuria of varying severity, lower urinary tract symptoms (dysuria, urgency, frequency) and suprapubic pain. In more advanced cases, blood clots can deposit in the urinary tract leading to acute urinary retention, obstructive uropathy and finally, renal function impairment. Clinical severity of HC can be graded according to the following criteria: grade 0 (no haematuria), grade I (microscopic haematuria), grade II (macroscopic haematuria), grade III (macroscopic haematuria with presence of blood clots), and grade IV (macroscopic haematuria with clots and renal impairment due to urinary obstruction) [11, 94].

The diagnosis is often done by exclusion basing on clinical presentation and BKV viral load and urine analysis. It is worth mentioning that plasma BKV load in HC may be undetectable [94].

Definitive therapeutic options for HC are not well established. Treatment is mainly symptomatic with hyperhydration, forced diuresis and pain management. Therapy similar to that used in BKVN may be administered, including modification of immunosuppressive medications and the use of cidofovir, leflunomide, and fluoroquinolone antibiotics. Some cases of sever bleeding require catheter placement, bladder irrigation, hyperbaric oxygen and in some life-threatening situations, blood transfusions and endoscopic treatment with electric/laser fulguration, vascular embolization or cystectomy if needed [95]. In patients with obstructive nephropathy, DJ or PCN placement may be necessary.

Oncogenesis

Patients after renal transplantation harbour a higher risk of cancer when compared with the general population, and an immunosuppressed state has been linked with an increased risk of virus-related malignancies [96]. However, despite the fact that BKV DNA has been discovered in a various tumour tissues, the relation between BKV infection and malignancy (especially prostate and bladder cancer) is a subject of intense discussion [97]. It is unclear whether this is the result of a predisposition for viral uptake into tumour cells or rather a causative mechanism. Moreover, multiple in-vitro and in-vivo animal studies show clear oncogenic impact of BKV in creatures ranging from mice to raccoons [98]. Yet, the results of those studies cannot be translated directly into humans.

It has been postulated that the oncogenic role of BKV is based on the expression of early coding viral replication proteins - large T antigen and small T antigen, which can begin neoplastic transformation of infected cells. T antigens are identified to be prooncogenic due to their ability to inactivate tumour suppressor proteins, such as p53 and pRb (retinoblastoma protein). By that, BKV pushes the infected cell into an 'S' cell cycle phase and inhibits its apoptosis ability. It further leads to increased cell proliferation, immortalization and neoplastic transformation [5, 99–101]. Other BKV pro-oncogenic mechanisms are also proposed and include induction of telomerase activity, deregulation of multiple crucial signalling pathways for proliferation (phosphoinositide-3 kinase–Akt/ protein kinase B, Wnt, and Ras/Raf/mitogen-activated kinase signalling pathways, STAT3, Notch, and hepatocyte growth factor receptor signalling pathway), and finally, induction vascular endothelial growth factor expression [98, 102–105]

The majority of reports regarding association of urothelial cancer (both bladder and upper urinary tract) and BKV infection are case reports of immunocompromised patients [106–109]. It has to be emphasised that almost all of the described tumours are high-grade, highly aggressive with morphological features resembling the bladder cancers of SV40 transgenic mice (developed by the pathway of p53 and pRb inactivation) [98, 110, 111]. In a recent population-based study on 55 697 transplant recipients, the risk of bladder tumours was found to be 1.7-fold higher in patients treated for presumed BKV nephropathy compared with transplant recipients without prior BKV infection [112]. Similarly, a study on 2000 patients found a 12-fold elevated risk of bladder cancer in kidney transplant recipients with evidence of BKV-associated decoy cells in urine, BK viremia, or biopsy-proven BKVN [113]. What is also worth mentioning, it is postulated that detection of BKV in bladder cancers from transplant recipients is more frequent than in bladder cancer in the general population [114]. Yet, some studies show a relatively high incidence of bladder carcinoma also in immunocompetent patients with cytological evidence of BK infection [115]. In case of prostate cancer, recent studies provide some evidence for a link between BKV infection/expression and cancer development not only in state of immuno-

suppression, but also in general population [116]. BKV particles are being found in cancerous cells, and moreover, in higher loads when compared with healthy tissue [117, 118]. Interestingly, BK virus was also more often observed in patients with lower Gleason scores. Additionally, BKV DNA was less frequently detected in overt, more advanced cancers which supports so called hit-and-run hypothesis (the virus activity paves the way for tumorigenic transformation only at early stages of the disease) [119]. What is worth revealing, in the study by Kaller et al., it was found that preoperative seropositivity to BKV LTag significantly reduced the risk of biochemical recurrence, independently of established predictors of biochemical recurrence such as tumour stage, Gleason score and surgical margin status [120]. However, it has to be remembered that available studies are burdened with many limitations and their findings do not provide any solid evidence for a relationship between BKV and prostate cancer. It is still unclear if there is any causative mechanism of BKV virus for prostate cancer and conclusions should be careful [121].

When kidney cancer is analysed, the incidence seems to not be clearly BKV – dependent [112]. Scarce case reports describe possible association, however, the case number is very low, and therefore, the conclusions should be drawn with caution [122, 123, 124].

CONCLUSIONS

The polyomaviruses are omnipresent in nature and the major sites of BK virus appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells. The virus usually stays latent, however, its replication may become active in various clinical situations of impaired immunocompetence and produce graft and life threatening complications. Because of the fact, that both diagnosis and treatment of BKV induced toxicity are difficult, strict surveillance and early intervention are therefore recommended for transplant recipients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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