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Clinical manifestations of BK virus infection in pediatric kidney transplant patients

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Background: Polyomavirus BK (BKV) infection is an important cause of graft loss in kidney transplant patients.
Purpose: The purpose of this study was to evaluate clinical findings and risk factors for BKV in pediatric patients after kidney transplantation.
Methods: This retrospective single-center study included 31 pediatric kidney transplant recipients from January 2002 to December 2017. Two patients received 2 transplantations during the study period, and each transplant was analyzed independently. Total number of cases is 33 cases with 31 patients. BKV infection was confirmed from blood samples via periodic quantitative polymerase chain reaction.
Results: The mean age at kidney transplantation was 11.0±4.7 years, and the male-to-female ratio was 2.7:1. Three patients had a past medical history of high-dose chemotherapy and autologous stem-cell transplantation for solid tumors. Nine patients (27.3%) developed BKV infection. The median period from kidney transplantation to BKV detection in blood was 5.6 months. There was no statistically significant difference in estimated glomerular filtration rate between patients with and those without BKV infection. Among 9 patients with BKV viremia, 7 were treated by reducing their immunosuppressant dose, and BKV was cleared in 6 of these 7 patients. In the other 2 BKV-positive patients, viremia improved without immunosuppressant reduction.
Conclusion: BKV infection is common in children with kidney transplantation and might not have affected short-term renal function in our patient sample due to early immunosuppressant reduction at the time of BKV detection.

Key words: BK virus, Kidney transplant, Child

Key message
Question: The purpose of our study was to evaluate the outcomes for polyomavirus BK infection in pediatric kidney transplantation patients.
Finding: There were no biopsy-proven nephropathy cases. Among 9 patients with viremia, 6 had azotemia, for whom the therapeutic approach was based on immunosuppressant reduction.
Meaning: Polyomavirus BK infection in pediatric patients might not have affected short-term renal function because of early detection and rapid immunosuppressant reduction.

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See commentary "Monitoring BK virus infection in pediatric kidney transplant recipients" in Volume 62 on page 414.

Introduction

Infection is one of the major complications following kidney transplantation (KT).[1] Recently, polyomavirus BK (BKV) infection in patients with KT has emerged as a significant clinical risk because it is associated with increased graft failure risk.[2] BK virus is a nonenveloped double-

strand DNA virus that is classified in the Polyomaviridae family.[3] Around 60%–90% of the general population is asymptomatically seropositive.[2] Primary BKV infection initiates in the respiratory tract, and is typically asymptomatic in healthy people, but it can be activated and cause a variety of clinical conditions in immunocompromised patients, including renal dysfunction and graft failure.[2]

Long-term use of immunosuppressants is mandatory for patients after undergoing KT. Insufficient immunosuppressant administration can cause acute rejection, while an oversuppressed immune state can lead to BKV reactivation and subsequent nephropathy and graft failure.[4] Several factors, such as the number of immunosuppressants taken, ischemic damage, donor kidney status, number of HLA matches, presence of BKV antibodies in the donor and recipient, and acute rejection by KT patients, have been suggested to be associated with BKV infection, but the significance of each is controversial.[4,5]

BKV infection usually manifests as hemorrhagic cystitis, ureteral stenosis, and interstitial nephritis.[5] Regular monitoring for BKV in blood and urine is necessary to detect infection and prevent renal dysfunction. BKV testing should be accompanied by azotemia detection.[5] The primary treatment for BKV is reduction of immunosuppressive drugs. When BK nephropathy is confirmed by renal biopsy, common therapies include leflunomide, cidofovir, ciprofloxacin, and intravenous immunoglobulin.[6]

There are limited data regarding clinical manifestations of BKV and, thus, no clear guidelines exist for BKV monitoring and treatment in pediatric KT patients. Therefore, the purpose of our study was to evaluate the clinical findings, risk factors, and outcomes for BKV infection in pediatric KT patients.

Methods

1. Subjects

The medical records of 33 transplants in 31 pediatric patients who received KT between January 2002 and December 2017 at Samsung Medical Center, a tertiary referral center located in Seoul, Korea, were retrospectively reviewed. Two patients received 2 transplantations during the study period, and each transplant was analyzed independently.

Data on the following demographic characteristics were collected: sex, cause of end-stage renal disease, the date of transplantation, donor type, age at transplantation time, and immunosuppressant for induction and maintenance. All data were obtained from electronic medical records in accordance with the ethics principles for medical research involving human subjects, as established in the Helsinki Declaration of 1975 and revised in 2000. The Institutional Review Board of Samsung Medical Center approved this study (IRB No. 2018-06-087). Informed consent was waived by the IRB.

2. Definitions

Virus in the urine (viruria) was detected via the following steps: (1) detect decoy cells via urine cytology; (2) confirm presence of Haufen, which are icosahedral aggregates of polyomavirus particles, by electron microscope;[7] and (3) detect BKV DNA via urine polymerase chain reaction (PCR). We defined BKV viruria as a viral load $>10^7$ copies/mL in PCR of urine, and viremia was defined as a viral load $>10^4$ copies/mL in the blood. BKV nephropathy can be diagnosed by renal biopsy, and typical findings include intranuclear viral inclusion by SV40 stain.[8] Interstitial white blood cell infiltration with tubular damage can also be observed. We divided patients into a BKV infection group and a BKV noninfection group, where BKV infection was defined as BK viremia and/or BK nephropathy. The estimated glomerular filtration rate (eGFR) was calculated using a modified Schwartz equation.[9]

3. BKV screening

Both urine and blood PCR were performed every month for 6 months after transplantation, and then every 3 months for up to 1 year posttransplantation. A year after transplantation, screening was performed every 6 months. If patients showed signs of azotemia, which is not conducive to supportive management, BKV screening was performed.

4. Statistical analyses

To compare between the BKV-positive and BKV-negative groups, continuous data were analyzed by Wilcoxon rank-sum test, while categorical data were analyzed by Fisher exact test. Multivariate logistic regression models were fit to identify predictors for BKV infection. All analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). A P value <0.05 was considered statistically significant.

Results

1. Clinical manifestations

The mean age at transplantation was 11.0±4.7 years, and the male-to-female ratio was 2.7:1. Patients' clinical characteristics are described in Table 1. Twenty patients (60.6%) received maintenance immunosuppressive therapy with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. Thirteen patients (39.4%) received the same immunosuppressive therapy after KT, but the steroids were proactively withdrawn. In this study, 3 patients with a prior history of solid tumors who received high-dose chemotherapy and peripheral stem-cell transplantation had been exposed to long-term immunosuppressant before KT.

Nine patients (27.3%) developed BK viremia with BK virus DNA loads of $>10^4$ copies/mL on PCR, and the median onset of viremia was 5.6 months after transplantation. There were no biopsy-proven

BKV nephropathy cases in our patient sample. Nineteen patients showed no evidence of viremia or viruria, while 6 patients showed evidence of viruria without viremia.

Outcomes for graft functionality at 6 and 12 months after transplantation were analyzed and compared between patients who did and did not develop BKV infection (Table 2). There was no statistically significant difference in eGFR between the 2 groups. Among patients who developed BK viremia 12 months after KT, the mean tacrolimus serum level was 6.5 ng/mL and the MMF dose was 526 mg/m^2/day. There was no difference between the 2 groups in tacrolimus levels and MMF dose at 6 and 12 months after KT. We also screened for coinfection with cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), and human herpes virus-6 (HHV-6) at the time of BK screening. Among patients with BKV infection, CMV and EBV infection was present in 4 (44.4%) and 2 patients (22.2%), respectively. HSV and HHV-6 were each present in 1 patient, respectively (11.1%).

Table 1. Clinical characteristics of enrolled patients who received kidney transplantation (n=33)[a]

Variable	Value
Male-to-female ratio	2.7:1
Cause of end-stage renal disease	
Glomerulonephritis	14 (42.4)
Congenital anomalies of the kidneys or urinary tract	8 (24.2)
Tumor	4 (12.1)
Unknown	7 (21.2)
First transplantation	30 (90.9)
Donor	
Living	15 (45.4)
Cadaveric	18 (54.5)
Age at the time of first transplantation (yr)	11.0±4.7
Induction immunosuppression	
Basiliximab	27 (81.8)
Polyclonal antibodies	3 (9.1)
Others	3 (9.1)
Maintenance immunosuppression	
Tacrolimus+mycophenolate mofetil+steroids	20 (60.6)
Tacrolimus+Mycophenolate mofetil+early steroids withdrawal	13 (39.4)

Values are presented as number of cases (%) or mean±standard deviation.
[a]Total number of cases is 33 cases with 31 patients. Two patients received 2 transplantations during the study period, and each transplant was analyzed independently.

2. Risk factors

Several demographic and clinical factors were analyzed to assess a possible association with BKV infection, and there was no significant difference between the 2 groups (Table 3). However, the mean serum level of tacrolimus at the period of virus detection in blood was 9.5 ng/mL, which was relatively high and could affect the virus infection (Table 4). We also investigated underlying disease because several patients had previously undergone peripheral blood stem-cell transplantation to treat a malignancy. Three of the patients with prior malignancies received long-term immunosuppressant and stem-cell transplantation, and 2 of these patients were diagnosed with BKV infection.

3. Clinical outcomes

Among 9 patients with viremia, 3 did not develop any symptoms of viral infection, and 6 had azotemia according to laboratory findings. Among the viremia patients, kidney biopsy was performed in 2 patients with severe azotemia, and they were diagnosed as having an acute cellular rejection of the transplanted kidney. These 2 patients underwent methylprednisolone pulse therapy, and viremia was screened after the improvement of azotemia. The therapeutic approach for the viremia patients was based on immunosuppressant reduction, and the tacrolimus dose was reduced in 7 patients, targeting a trough-level range of 3–5 ng/mL. We maintained the dose of MMF, and tried to reduce the dose of steroid if the patient was still using steroid. If kidney function had become worse, we

Table 2. Comparisons of clinical presentations between BK viremia-positive and BK viremia-negative

Variable	BK viremia-positive (n=9)	BK viremia-negative (n=24)	*P* value
Tac level 6 months after KT (ng/mL)	6.5±2.2	6.8±1.5	0.571
Tac level 12 months after KT (ng/mL)	6.3±1.4	5.9±1.8	0.706
MMF dose 6 months after KT (mg/m^2/day)	525.6±132.8	623.7±343.5	0.983
MMF dose 12 months after KT (mg/m^2/day)	413.0±159.8	560.7±308.1	0.258
eGFR 6 months after KT (mL/min/1.73 m^2)	70.3±39.6	59.7±26.4	0.557
eGFR 12 months after KT (mL/min/1.73 m^2)	64.1±27.4	58.6±23.3	0.617
Graft dysfunction	3 (33.3)	2 (8.3)	0.591
Coinfection			
Cytomegalovirus	4 (44.4)	7 (29.2)	0.425
Epstein-Barr virus	2 (22.2)	3 (12.5)	0.645

Values are presented as means±standard deviations or numbers (%).
Tac, tacrolimus; KT, kidney transplantation; MMF, mycophenolate mofetil; eGFR, estimated glomerular filtration rate.

were planning to perform kidney biopsy to exclude other conditions such as rejection or calcineurin inhibitor nephrotoxicity. After reducing their medications, viremia cleared in 6 patients. The one patient with remaining azotemia (eGFR = 60 mL/min/1.73 m^2) was planned for kidney biopsy. During follow-up, BK virus titer in blood had been rapidly rising at that period, and EBV viremia persisted. In those reasons, we underwent a change in immunosuppressant, from tacrolimus to sirolimus, to avoid tacrolimus-associated calcineurin inhibitor nephrotoxicity and BK nephropathy before the kidney biopsy. After 2 weeks on sirolimus, this patient's BK virus disappeared and the azotemia improved. In the 2 viremia patients whose immunosuppressant was not reduced because of low virus titer with no clinical symptoms, spontaneous regression occurred without intervention. Median time from the detection of BK viremia to clearing viremia was 3.9 months. Especially, the time for disappearance of BK viremia in 2 patients who had received PBSCT was 23.9 months and 33.6 months, respectively which was longer comparing with the other patients. The median time for clearing of virus in other patients is 2.9 months (Table 4).

For the patients who presented only viruria, we maintained the dose of immunosuppressant and checked the virus titer in urine and blood, because virus titer from urine was low (less than 1×10^4 copies/mL). For 2 patients who presented high virus titer in urine (40,900,000 copies/mL, 12,450,000,000 copies/mL), the dose of tacrolimus was reduced, and after reducing tacrolimus, the virus in urine disappeared.

Discussion

In this study, BKV prevalence was 27.3%, which reaches the upper limit of previously published data for pediatric populations.[10] According to previous studies on BKV infection in pediatric KT patients, prevalence ranged from 16%–26%.[11-14] The median time to viremia detection from the transplantation date was 5.6 months, which was longer than previously published data,[14-16] where the median time to detection was between 2 and 3 months after KT. The reason for the longer median time in our study is because one viremia patient was diagnosed with BKV 106.5 months after KT, which is extraordinarily late.

We did not include viruria patients in the BKV infection group because viruria alone does not progress to nephropathy and can

Table 3. Univariate analysis of risk factors associated with BK viremia

Variable	BK viremia-positive (n=9)	BK viremia-negative (n=24)	*P* value
Recipient age (yr)	10.3±5.4	10.9±4.8	0.6534
Cadaveric donor	5 (55.6)	12 (50.0)	1.0000
Chemotherapy and stem-cell transplantation	2 (22.2)	8 (33.3)	0.1644
Use of steroids in maintenance	9 (100)	23 (95.8)	0.2809
Ureteral stent	2 (22.2)	2 (8.3)	0.2809
Acute rejection	1 (11.1)	5 (20.8)	0.4030
Tac level 12 months after KT (ng/mL)	6.3±1.4	5.9±1.8	0.7057
MMF dose 12 months after KT (mg/m^2/day)	413.0±159.8	560.7±308.1	0.2577

Values are presented as means±standard deviation or number (%).
Tac, tacrolimus; KT, kidney transplantation; MMF, mycophenolate mofetil.

Table 4. Characteristics of patients with BK viremia

No.	Sex	Age at TPL (yr)	Underlying disease	Donor	Acute rejection	Coinfection	T-6 mo eGFR (mL/min/1.73 m²)	T-virus detection (mo)	T-virus clearing (mo)	Tac level (ng/mL)
1	F	8.0	Tumor	Living	Yes	None	154.4	12.8	23.9	8.0
2	M	17.8	GN	Cadaveric	No	None	67.3	2.2	3.0	15.8
3	M	14.6	CAKUT	Cadaveric	No	CMV	25.4	7.7	4.8	6.8
4	M	6.6	Tumor	Cadaveric	No	CMV	52.1	67.8	2.8	4.2
5	F	4.2	GN	Cadaveric	Yes	CMV, EBV	74.8	106.5	5.5	22.1
6	M	5.1	Tumor	Living	No	EBV	108.6	2.2	33.6	11.9
7	F	17.7	GN	Cadaveric	No	None	37.1	5.6	1.0	7.1
8	F	6.3	Unknown	Cadaveric	No	None	65.2	2.9	1.0	6.8
9	M	12.6	GN	Living	No	CMV	47.9	4.1	1.0	3.2

TPL, transplantation; T-6 mo eGFR, estimated glomerular filtration rate at the time of 6 months after transplantation; T-virus detection, first time of BK viremia detection after transplantation; T-virus clearing, time of BK virus disappearance in blood after detection of BK viremia; Tac level, tacrolimus serum level at the time of virus detection; GN, glomerulonephritis; CAKUT, Congenital anomalies of the kidneys or urinary tract; CMV, cytomegalovirus; EBV, Ebstein-Barr virus.

clear without treatment.[17] Detectable virus in the blood is more predictive of BKV nephropathy than viruria alone. According to a BKV monitoring algorithm, after testing for blood BK via PCR and renal function at 1, 2, 3, 6, and 12 months after KT, renal biopsy is recommended if blood BK PCR is positive and serum creatinine levels are elevated. High virus titer in urine is suggestive of the large amount of virus burden in the body and could progress to viremia. In that reason, the regular monitoring of virus titer in urine and blood should be performed. When blood BK is positive but serum creatinine is normal, the recommendation is for immunosuppression decrease with follow-up every 2 weeks until blood samples are clear.[17]

In our study, there was no sex or age difference between the groups with and without BK viremia. Rocha et al.[18] reported that males exposed to higher tacrolimus levels are at higher risk of developing BKN. Younger recipients, especially those <8 years old, and patients who received their kidney from a cadaveric donor are known to be at higher risk for BKV infection as well. Younger age is thought to be a risk factor because of age-based immune-related activities. Schmidt et al.[19] reported that the frequency of BKV-specific CD4 T cells was low in children between 0 and 10 years, and BKV-specific IgG levels showed an age-dependent increase, reaching maximum levels between 20 and 30 years. Their findings suggested that BKV-specific cellular and humoral immunity is age dependent, and that younger recipients might be more vulnerable to BKV infection.[19] Receiving a kidney from a cadaveric donor is thought to elevate risk for BKV infection because of the higher ischemic time during organ harvest and transport, prior to KT. Longer ischemic time might lead to tubular injury, which could trigger BKV replication. We found no difference in donor type between the 2 groups in this study, and this might be because our transplantation program includes a rapid transport system and short operating hours. Our study suggests that prolonged exposure to immunosuppressant before KT can be another risk factor for BKV infection. Among 3 patients with prior malignancy and chemotherapy, 2 were diagnosed with BKV and EBV coinfections. Even though the number of patients with malignancy was too small to analyze statistically, we can nevertheless argue that long-term use of immunosuppressant and nephrotoxic agents by patients with malignancies increases the risk for BKV infection.

It is remarkable that BKV infection might not have had an effect on renal function in this study. It is possible that regular screening for BKV in urine and blood resulted in early detection and rapid immunosuppressant reduction. Immunosuppressant reduction is the main treatment strategy for BKV infection. In our study, immunosuppressant reduction resulted in viremia clearance in 6 patients (85.7%). The patient whose medication was changed from tacrolimus to sirolimus also recovered from viremia. When azotemia persisted, a renal biopsy was considered to check for the possibility of acute rejection, BKV nephropathy or nephrotoxicity due to tacrolimus exposure. Instead of a biopsy, sirolimus induction was administered, and the patient's azotemia improved and viremia cleared. Wali et al.[20] reported that a sirolimus-based immunosuppression rescue therapy could be a new direction for therapeutic interventions for KT recipients with BKV nephropathy.

This study has a few limitations. First, we had no access to donor information, which limits our knowledge of potential risk factors. Second, because of our small sample size, our analyses did not have enough power to test for statistical significance. Third, the kidney biopsy was not performed in patients with BK viremia, and the clinical significance of BK viremia might be unclear in this study.

In conclusion, BKV infection in pediatric KT patients might not have affected short-term renal function in our patient sample because early BKV detection and rapid and appropriate immunosuppressant reduction may have prevented graft failure. Also, sirolimus intervention may offer an alternative treatment for BK viremia.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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