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Prevalence of polyoma BK virus infection among living-donor renal transplant recipients

M. El Ansary, S. Abd Elhamid, G. Saadi, W. Ismail, N. Ibrahim, N. Bahaa El-Din, S. Alhsyek. Prevalence of polyoma BK virus infection among living-donor renal transplant recipients.
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Abstract: *Background.* Polyomavirus nephropathy (PVN) mainly caused by BK polyomavirus (BKPyV) remains the most common productive viral infection of the kidney in immunosuppressed patients. The diagnosis of PVN is based on the detection of BK viruria and BK viremia in conjunction with histological findings in the graft biopsy.
Methods. Our study was aimed to estimate the prevalence of productive BKPyV infection among renal transplant patients within the first year post-transplant and identify those at risk of developing PVN. Our cross-sectional study was conducted on 134 kidney transplant patients. Evidence of BKPyV replication was assessed by viral quantification of blood and urine samples of studied patients using a quantitative real-time polymerase chain reaction (Q-PCR) PCR), detection of decoy cells in urine cytology smears, histological examination of graft biopsies from Q-PCR BKPyV-positive patients, and immunohistochemical staining by simian virus 40 (SV40) antibody.
Results. Significant BKPyV infection was prevalent in 8% (n = 11) of our patients, with a peak of BKPyV infection about 8 months post transplant. BKPyV viral load by Q-PCR assay in these patients varied from 1350 to 20,000,000 (1.35×10^3 to 2×10^7) copies/mL for urine samples and 935 to 18,920 (9.35×10^2 to 1.89×10^4) copies/mL for blood samples. All the 11 patients were positive for decoy cells but only 3 developed PVN based on histology and positive SV40 staining. BKPyV infection was more prevalent in older patients. All patients responded to reduction in their immunosuppressive regimens, apart from 2 patients who required replacement of calcineurin inhibitors-based regimen with mammalian target of ramapycin inhibitors with an overall good response.
Conclusion. Protocol screening programs based on detection of viral replication by viruria, viremia, and decoy cells in urine are necessary to shed light on patients with high virus replication and hence increased risk of developing PVN, and to allow early diagnosis and intervention.

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Key words: polyomavirus; BK nephropathy; quantitative PCR; immunohistochemistry; renal transplantation

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The prevalence of polyomavirus nephropathy (PVN) in kidney transplant recipients is estimated to be between 1% and 10% and may cause graft dysfunction and loss (1). BK polyomavirus (BKPyV) infection directly correlates with long-term intense immunosuppression, often including tacrolimus (TAC) and mycophenolate mofetil (MMF); other factors include previous acute rejection episodes, induction therapy, and older age in males (2). BKPyV replication can be easily detected by examination of urine cytology for identification of decoy cells (3), which are epithelial cells with enlarged nuclei and large basophilic ground-glass intranuclear

inclusions of viral particles, or by ultrastructural detection using electron microscopy of tubular casts formed of viral particles known as "Haufen"; the latter is considered to be diagnostic (4). Also quantification of BK viral DNA of serum and urine by quantitative real-time polymerase chain reaction (Q-PCR) are useful in diagnosing and monitoring kidney transplant recipients for BKPyV infection (5). Regular screening for BKPyV reactivation, mainly during the first 2 years post transplant, with subsequent reduction in immunosuppression is considered the best option to avoid disease progression (2). A definitive diagnosis of PVN is made by renal allograft biopsy, also called "Definitive PVN." PVN is defined morphologically by intrarenal polyomavirus replication, mainly in tubular epithelial cell nuclei, and varying degrees of tubular cell injury ranging from early and minimal to marked with marked cell lysis and acute tubular necrosis (6). Patients with PVN do not show symptoms of a generalized infection, the urine sediment is bland, and renal function can be normal. Minimal and early stages of PVN present with normal renal function and may not show intranuclear viral inclusion bodies or significant acute tubular necrosis. In such cases, a diagnosis can only be established by immunohistochemistry, usually with an antibody directed against the simian virus 40 (SV40) T antigen or by *in situ* hybridization (7). In the absence of definite histologic evidence obtained by biopsy, findings of sustained urine viral replication (>2 weeks) and significant BK replication (plasma DNA PCR load >10,000 copies/mL) with or without kidney dysfunction, can define BK nephropathy and, in this case, it is known as "Presumptive PVN" (8, 9).

The target of this study was the estimation of the incidence of BKPyV infection among renal transplant patients presenting with graft dysfunction within the first year post transplant, with determination of who developed PVN and BKPyV-induced graft loss.

Patients and methods

Patients

Our cross-sectional study was conducted on a total of 134 adult living-donor renal allograft recipients, transplanted between January 2013 and June 2015 in Kasr El-Aini Renal Transplant Unit, Cairo University, Egypt. Donors were selected based on ABO blood group and human leukocyte antigen compatibility; all of them had negative cross-match tests. Mean age of enrolled patients was 47.72 years $\pm$ 12.70, and patients were 88 males (66%) and 46 females (34%).

All patients were subjected to detailed history-taking, concerning mainly the presence of fever or not, urinary manifestations like dysuria and hematuria, and duration of renal transplantation. Basic laboratory investigations included complete blood count, serum creatinine levels, and creatinine clearance. Extra laboratory investigations for suspected patients included calcineurin inhibitors (CNI) drug levels, urine cytology for detection of decoy cells, quantification of BKV viral load by Q-PCR technique, and renal biopsy for patients with evidence of BKPyV replication by Q-PCR.

According to the Q-PCR results, the patients were then divided into 2 groups based on BKPyV status (group I composed of 11 BKPyV-positive patients while group II encompassed 123 BKPyV-negative patients).

Immunosuppressive regimens

The standard immunosuppressive regimens for all patients were as follows: CNI, either cyclosporine (CsA) or TAC. CsA was given at initial 3 months at dose of 200–300 ng/mL, at 4–18 months the dose was 150–200 ng/mL, at 19–36 months it was 100–150 ng/mL, after that the patients were maintained on 80–100 ng/mL. TAC was given at first 3 months at dose of 10–15 ng/mL/day, at 4–18 months it was reduced to 8–10 ng/mL/day, and finally the patients were maintained on 5–7 ng/mL/day. In addition, the patients received antiproliferative drugs: MMF at dose of 2 g/day or mycophenolate sodium at dose of 750 mg twice daily. Also all patients received steroids at dose of 20 mg/day for 70 kg adult patient given 2 weeks postoperatively then tapered to 15 mg/day at 3–6 months and 10 mg at 6–12 months, and finally they were maintained at a dose of 5–7.5 mg/day.

Methods

Sample collection

Urine samples were collected for detection of decoy cells by cytology and detection of BKV by Q-PCR technique. From each patient 3 mL of venous blood was collected by sterile venipuncture under complete aseptic conditions in EDTA tubes for the study of BKV by Q-PCR technique. Blood and urine samples for quantification of BKV load were collected from transplanted patients complaining of urinary manifestations and/or with elevated serum creatinine level and diminished creatinine clearance values according to the method described by Anzivino et al. (10).

DNA extraction from blood and urine samples

For blood samples, blood is collected in 4-mL Vacuntainer® tubes containing EDTA (BD Becton Dickinson S.p.A., Milan, Italy) and DNA was extracted from the whole blood. For urine samples, 1 mL of each urine sample was collected without preservatives. Centrifugation at 14,000 RPM for 10 min for turbid urine samples was done, and clear samples were processed without centrifugation. DNA from both blood and urine samples was extracted using the Mag NA Pure Compact Nucleic Acid Isolation Kit I (03730964001; Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions and stored at −20°C until use.

Q-PCR for BKV

DNA samples extracted from all urine and blood samples were analyzed using the BKV Q-PCR Alert Kit (Nanogen Advanced Diagnostics S.p.A., Lombardy, Italy), it is a quantitative amplification assay designed for the diagnosis and monitoring of BKPyV infection in DNA samples. This technique, based on TaqMan-MGB® (Minor Groove Binder) technology, was performed using a Real-Time PCR System (PICO REAL 24 Thermo Scientific TCR 0024, Vantaa, Finland). The amplification reaction is carried out both for a region of the gene that encodes BKV TAg and for the promoter region and 5′UTR of the human beta globin (β-globin) gene. β-globin gene is amplified simultaneously with the target sequence to verify successful DNA isolation and exclude false-negative results. Our reaction volume is composed of 20 μL containing 5 μL (50 ng/μL) of total purified DNA, BKV Q-PCR Alert AmpliMIX (specific primer oligonucleotides mixture), BKV Q-PCR Alert AmpliPROBE (mixture of fluorescent probes labeled with FAM/MGB-NFQ specific for BKV DNA and fluorescent probes labeled with VIC/MGB-NFQ specific for human β-globin gene), and Q-PCR Alert AmpliMASTER (optimized reagent mixture with Uracil-N-glycosidase, an enzyme to inactivate contamination from amplification product, and ROX fluorophore, as the passive reference for the normalization of the fluorescence). Thermal cycling was carried out according to the following steps: an initial denaturation at 95°C for 10 min, followed by 45 cycles of 95°C for 15 sec and 60°C for 1 min, at the end of which the fluorescence was read. Amplification data were analyzed with software provided by the manufacturer. The standard curve for this quantitative amplification assay is obtained using the BKV Q-PCR Standard, 4 stabilized serial dilutions at known titer (range: 10^2–10^5 plasmid copies) of a plasmid containing part of the BKV genome region encoding for TAg. The number of viral copies in each sample was calculated from the standard curve. The Q-PCR results for urine and blood specimens were expressed as copies of viral DNA per milliliter (copies/mL) of sample. A Control lane was included in each run for its validation.

Urine cytology

Cytology smears from urine samples of 60 patients were performed, all of which had presented with graft dysfunction. Standard smears were prepared from fresh voided morning urine samples, fixed in alcohol, and stained with Papanicolaou stain. Smears were examined for decoy cells, all 4 types reported in literature (3) and, when present, the number of decoy cells per 10 high-power fields (hpf) was counted. Patients with > 5 decoy cells per 10 hpf in the smears were considered to be high risk/positive (3).

Renal graft biopsies

Indication renal graft biopsies were obtained from group I patients (positive BKPyV replication by Q-PCR) as all of them presented with impaired graft function, mainly increased serum creatinine levels. Biopsies were routinely processed, cut in 2–3 μm thick sections with 25–30 serial sections per biopsy, and stained with hematoxylin and eosin, Masson trichrome, and periodic acid-Schiff stains. Immunohistochemistry for C4d (Spring Bioscience, Pleasanton, California, USA) and SV40 (Cell Marque, Rocklin, California, USA) were performed for all biopsies. Not included in the study were indication biopsy results within the study period, from some of group II patients (2%) with various causes of graft dysfunction, mainly drug toxicity and acute rejection. All biopsies were scored according to the Banff classification and, in the presence of PVN, severity was classified according to the latest recommendations of the Banff PVN working group (11). Based on morphology, PVN can be classified into disease grades 1–3 based on the severity of polyomavirus replication and the Banff "ci" interstitial fibrosis scores, with disease resolution and favorable outcome in early disease grade 1 and a high risk of graft failure in grade 3. Presence of associated interstitial inflammation as well as concurrent acute/active T-cell-mediated or antibody-mediated rejection was documented.

Statistical analysis

Statistical analyses for subjects' demographic, clinical characteristics, and laboratory data were done using SPSS 15.0 software (SPSS, Chicago, Illinois, USA). Numerical data were expressed as mean and standard deviation for continuous variables or median and range for non-normally distributed data. Qualitative data were expressed as frequency and percentage for categorical variables.

Declaration of ethics

Oral and written informed consent was obtained from all patients according to Helsinki guidelines of research ethics.

Results

The baseline demographic, clinical, and laboratory data of the patients in the study groups are listed in Table 1. Regarding demographic features, the 2 groups were comparable in respect to gender; meanwhile, the mean age value was different between the 2 groups, with more frequent BKPyV infection among older patients in group I than in group II (39.18 ± 9.02 vs. 32.52 ± 9.56). On clinical examination, renal and anemic manifestations were more evident in patients of group I, with less frequency among group II patients. Mean value of duration of renal transplant was higher in group II than group I (13.9 ± 8.25 vs. 10.6 ± 5.3) and frequency of fever was comparable between both groups. Regarding baseline laboratory data, all patients of group I suffered from impaired kidney functions and lowering of creatinine clearance and hemoglobin levels than group II patients (mean creatinine value 1.8 ± 0.59 and 1.05 ± 0.35, mean creatinine clearance level 54.96 ± 18.41 and 86.65 ± 18.28, and mean hemoglobin level 10.05 ± 4.65 and 12.33 ± 4.35, respectively). BKPyV viral infection was noticed in 11 (8%) of all patients, with mean value of peak BKPyV infection at 7.9 ± 1.8. BKPyV viral load in urine samples, estimated by Q-PCR, varying from 1350 to 20,000,000 (1.35×10^3 to 2×10^7) copies/mL to mean value of 2,259,004.54 ± 5,929,031.55 copies/mL and median of 9000 copies/mL. BKPyV viral load in blood samples was positive in 7 of 11 patients, and ranged from 935 to 18,920 (9.35×10^2 to 1.89×10^4) copies/mL with mean value of 10,342.14 ± 7181.12 copies/mL and median of 5000 copies/mL (Table 2).

Descriptive statistics of BK polyomavirus (BKV)-positive and -negative patients regarding demographic, clinical, and laboratory data

Characteristics	Group I (BKV+ patients) (*n* = 11)	Group II (BKV− patients) (*n* = 123)
Age, years		
Range	29–55	21–45
Mean ± SD	39.18 ± 9.02	32.52 ± 9.56
Gender		
Males, *n* (%)	7 (64)	81 (66)
Females, *n* (%)	4 (36)	42 (34)
Duration of renal transplant (months)		
Range	7–18	9–22
Mean ± SD	10.6 ± 5.3	13.9 ± 8.25
Renal manifestations, *n* (%)		
Present	9 (82)	2 (2)
Absent	2 (18)	121 (98)
Fever, *n* (%)		
Present	1 (9)	6 (5)
Absent	10 (91)	117 (95)
Anemic manifestations, *n* (%)		
Present	7 (64)	4 (3)
Absent	4 (36)	119 (97)
Creatinine (mg/dL)		
Range	1.2–3.2	0.7–1.4
Mean ± SD	1.8 ± 0.59	1.05 ± 0.35
Creatinine clearance (mL/min)		
Range	23.5–72.8	75.52–110.29
Mean ± SD	54.96 ± 18.41	86.65 ± 18.28
Hb (g/dL)		
Range	10.20–11.70	11.90–13.90
Mean ± SD	10.05 ± 4.65	12.33 ± 4.35

SD, standard deviation; Hb, hemoglobin.

Table 1

Biopsy results from all 11 patients are summarized in Table 2. Of the 11 patients, only 3 showed evidence of viral replication within the renal parenchyma, mainly evident by marked tubular injury, various intranuclear viral inclusion bodies with tubular cell lysis, and variable degrees of inflammatory infiltrate, mainly formed of lymphocytes and plasma cells, but without tubulitis in tubules and with no evidence of viral injury

Group I (BK polyomavirus-positive) patients' characteristics

Pt	Demographic data		Laboratory data										
						BKV replication by Q-PCR				Biopsy findings		
	Age (yrs)	Gender	Creat. at biopsy	Creat. clear. at biopsy	Time post Tx (months)	Urine	Blood	Decoy cells	Standard IS	LM	C4d	SV40
1	35	M	1.4	72.8	7	9000	3500	5	TAC, MMF, ST	ATIN	–	–
2	29	M	1.3	69.5	10.5	5000	4320	3	TAC, MMF, ST	TCMR	–	–
3	55	F	1.9	35	9	1,500,000	13,950	6	TAC, MMF, ST	PVN	–	+
4	33	F	1.5	70.2	7	4500	<18	5	TAC, MPS, ST	ATI	–	–
5	53	M	2.3	39.22	5.5	1,730,000	15,820	4	CYA, MPS, ST	ABMR	+	–
6	41	M	1.6	70.5	8	3200	<18	2	TAC, MMF, ST	BLAR	–	–
7	47	M	3.2	23.5	6	20,000,000	18,920	8	TAC, MMF, ST	PVN	–	+
8	29	F	1.2	65.9	9.5	1350	<18	4	TAC, MMF, ST	ATI	–	–
9	33	F	2.4	33.7	8.5	1,557,000	14,950	5	TAC, MMF, ST	PVN	–	+
10	37	M	1.8	55.9	9	9000	<18	3	CYA, MPS, ST	TMA	–	–
11	39	M	1.6	68.35	11	30,000	935	2	CYA, MMF, ST	ATI	–	–
Mean ± SD	39.18 ± 9.02		1.8 ± 0.59	54.96 ± 18.41	7.9 ± 1.8	2,259,004.54 ± 59,29,031.55	10,342.14 ± 7181.12	4.27 ± 1.79				
Median	–		–	–	–	9000	5000	–				

Pt, patient; yrs, years; Creat. clear., creatinine clearance; Tx, transplantation; BKV, BK polyomavirus; Q-PCR, quantitative polymerase chain reaction; IS, immunosuppression; LM, light microscopy; Cd4, T-helper cell; SV40, simian virus 40; M, male; TAC, tacrolimus; MMF, mycephenolate mofetil; ST, steroids; ATIN, acute tubulointerstitial nephritis; F, female; TCMR, T-cell-mediated rejection; PVN, polyomavirus nephropathy; MPS, mycophenolate sodium; ATI, acute tubular injury; CYA, cyclosporine; ABMR, antibody-mediated rejection; BLAR, borderline acute rejection; TMA, thrombotic microangiopathy.

Table 2

and hence no associated T-cell-mediated rejection was determined. All 3 cases were C4d negative and showed no significant microvascular inflammation, Banff microvascular inflammation sum score <2. One case showed mild fibrosis (Banff ci score: 1). All 3 cases were graded as PVN stage 2. SV40 staining showed strong positive nuclear staining in scattered tubules (Fig. 1).

Discussion

Viral infections, especially cytomegalovirus and polyomavirus, are becoming very prominent with the use of potent immunosuppressive therapies (12). The prevalence of BKV viruria and BKV viremia in renal transplant recipients is around 40% and 12% respectively (13). PVN, which affects about 8% of recipients, manifests as an asymptomatic gradual rise in serum creatinine levels and results in allograft loss or permanent dysfunction in 40% to 60% of cases (12). The diagnosis of PVN is based on detection of viruria, viremia, and histologic findings from a kidney biopsy (14). To the best of our knowledge, this is the largest and may be the first report of the incidence of BKPyV viral infection as well as definite PVN among Egyptian living-donor renal transplant recipients. Our study utilized living donation, which reduces the recipient's waiting times with a longer (over 20 years vs. 13 years for deceased kidneys) and a better graft function (living-donor organs always start functioning immediately, whereas deceased-donor kidneys can take from a few days to a few weeks to start functioning) (15). Our results showed an incidence of BKPyV viral infection among our renal transplant patients of 8% (n = 11). Three of the 11 patients progressed to PVN, but none of them developed irreversible graft loss. Our findings agree with those of many researchers; Pham et al. (16).

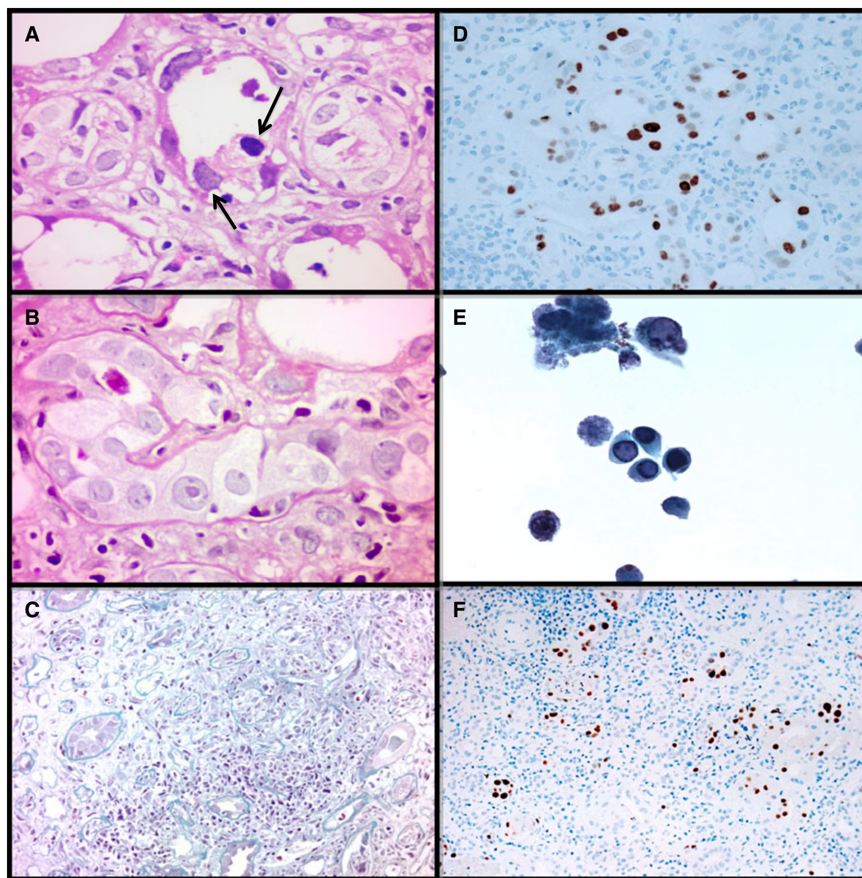

Fig. 1. (A) Intranuclear viral inclusions (arrows) and marked cell lysis in adjacent tubule, hematoxylin and eosin stain. (B) Other forms of polyoma viral inclusions, periodic acid-Schiff stain. (C) Low-power view of interstitial inflammation and fibrosis, Masson trichrome stain. (D) Positive intranuclear inclusions for SV40 from Patient 3. (E) Abundant decoy cells in cytology smears from Patient 7. (F) Low-power view showing scattered positive SV40 intranuclear inclusions among inflammatory infiltrate, from Patient 7.

stated that the incidence of PVN in kidney transplant recipients ranges from 1% to 10%. Also, Hirsch et al. (17), van Aalderen et al. (18), and Bassil et al. (19). reported that PVN occurs in 4% to 12% of kidney transplant patients; this was 2% within our study group. In our study, the mean time post transplant to the peak of BKPyV infection was 7.9 ± 1.8 months. This time matches several studies that showed occurrence of BKPyV infection within the first year post transplant, with a peak incidence at 9 months (20, 21). In our study, all BKPyV-positive cases showed positive decoy cells in urine preparations, with mean value of 4.27 ± 1.79 cell/10 hpf, thus making them an important simple, cheap, and non-invasive screening diagnostic modality for clinical assessment of risk. Our BKPyV viral load mean and median values for urine and blood samples estimated by Q-PCR were 2,259,004.54 ± 5,929,031.55 and 10,342.14 ± 7181.12 copies/mL, respectively, median 9000 and 5000 copies/mL, respectively; this was in accordance with Abdel Halim et al. (22), who stated that BK viremia was considered significantly positive when it exceeded 10,000 copies/mL. Furthermore, Drachenberg et al. (23) found that significant BKPyV replication (plasma DNA PCR load >10,000 copies/mL), with or without kidney dysfunction, defines presumptive BK nephropathy. In our study, viruria was detected in all of our patients; however, viremia was detected in 7 of the 11 patients. This directed our interest to examine for BK viruria by Q-PCR primarily in urine; with the advantage of a high negative predictive value to rule out PVN, viruria is usually reported 12 weeks before developing viremia and nephropathy, but it carries the disadvantage of having a low positive predictive value for PVN and requiring BK viral load differences >2 log10 copies/mL to be significant (5). From the above findings, we and others suggest that quantitative measurement of viremia is not indicated in patients without viruria (5).

Our study showed more prevalent BKV infection among older patients. This was in accordance with the data obtained by Dharnidharka et al. (24) and Prince et al. (25), who found that older age group is a potential risk factor for the reactivation of BKPyV infection, with more liability of development of PVN. Renal and anemic manifestations were more evident among BKPyV patient groups, with less frequency among group II patients. All patients of group I suffered from increased serum creatinine, and lowering of creatinine clearance and of hemoglobin levels than group II patients. These findings were in agreement with Abdel Halim et al. (22), who assessed basal graft function by measurement of glomerular filtration rate; they found its reduction to 35.4 ± 18.8 mL/min/1.73 m^2 at 1 year.

Immunosuppression with TAC and MMF has been considered the most important risk factor for BKPyV infection (26). However, it might occur with any triple-drug regimen, and perhaps the overall load of immunosuppressive drugs is the most important risk factor (27). There is a paucity of data evaluating the effectiveness of anti-BKV therapies in patients with established BKPyV viremia. Vincenti et al. (28). reported immunologic non-inferiority at 6 months post transplant between TAC-MMF vs. CsA-MMF in a large prospective randomized trial of *de novo* renal transplant patients randomized to CsA microemulsion (CsA-ME, using C [2] monitoring) or TAC, with mycophenolate sodium, steroids, and basiliximab. Early management of BKPyV viremia and PVN is essential to avoid graft loss (29, 30). All our patients were primarily managed for their BKPyV viremia with reduction in the doses of immunosuppressive regimens: CNI (CsA or TAC) and MMF doses were reduced by half; however, the 2 non-responders were shifted to mammalian target of rapamycin (mTOR) inhibitors (sirolimus replaced CNI or everolimus replaced MMF). The 2 patients responded without progression to graft dysfunction and loss. This result matches the studies using drugs that specifically target the Akt and mTOR pathway and could reduce BKPyV pathogenesis (31). Because both sirolimus and leflunomide possess immunosuppressive activity, treatment of BK reactivation using this combination may control BK replication (32).

Unlike our treatment plan, Hirsch et al. (33). suggested that CsA-mycophenolic acid had lower rates of viremia than TAC-mycophenolic acid at month 6 (10.6% vs. 16.3%, $P = 0.048$) and 12 (4.8% vs. 12.1%, $P = 0.004$) and lower plasma BKV loads at month 12 (3.9 vs. 5.1 log[10] copies/mL; $P = 0.028$). Also, Hirsch et al. (34) compared the effects of mTOR inhibitors and CNI on BKPyV replication in primary human renal tubular epithelial cells. Sirolimus impaired BKPyV replication, with a 90% inhibitory concentration of 4 ng/mL, by interfering with mTOR-SP6-kinase activation. Sirolimus inhibition was rapid and effective up to 24 h post infection during viral early gene expression, but not thereafter, during viral late gene expression. The mTOR C-1 kinase inhibitor torin-1 showed a similar inhibition profile, supporting the notion that early steps of BKPyV replication depend on mTOR activity. CsA also inhibited BKPyV replication, whereas TAC activated BKPyV replication and reversed sirolimus inhibition. FK binding protein 12 kDa (FKBP-12) siRNA knockdown abrogated sirolimus inhibition and increased BKPyV replication

similar to adding TAC. Thus, sirolimus and TAC exert opposite effects on BKPyV replication in renal tubular epithelial cells by a mechanism involving FKBP-12 as a common target. Immunosuppressive drugs may therefore contribute directly to the risk of BKPyV replication and nephropathy besides suppressing T-cell functions.

Conclusion

BKPyV infection is a threatening issue for renal transplant patients, especially with the advent of newer more potent immunosuppressive agents. It may cause PVN with subsequent allograft dysfunction and loss, so diagnosing, treating, and distinguishing PVN from acute rejection is essential for proper management and enhancing kidney allograft survival. Proper diagnosis is based on detection of viruria, viremia, and histologic findings from a kidney biopsy. However, the optimal screening method and timing to detect BKPyV remain challenging. Furthermore, cutoff values, especially for quantitative tests, need to be defined and standardized. Protocol screening programs based on detection of viral replication by viruria, viremia, and decoy cells in urine are necessary to shed light on high-risk patients and allow early diagnosis, reduction in immunosuppression therapy, and establishment of the optimal combination of immunosuppression in those patients.

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