Published in final edited form as:

Am J Nephrol. 2014 ; 39(1): 20–26. doi:10.1159/000357409.

BK Virus Replication in Patients with ANCA Associated Vasculitis

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Abstract

Background—BK virus (BKV) is an important cause of renal dysfunction in kidney transplant (KTX) recipients. Immunosuppression intensity is a major risk factor for BKV replication in these patients. The prevalence of BKV replication in immunosuppressed patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) without transplant is not known.

Methods—Consecutive patients (N=37) with a diagnosis of GPA (N=25) or MPA (N=12) without history of KTX were evaluated for plasma BKV replication by quantitative PCR (Group A). Descriptive data were collected. BKV replication in this non-transplant immunosuppressed vasculitis cohort was compared to a historical cohort of vasculitis KTX recipients (Group B). Results: Group A patients had mean disease duration of 75 months. Mean age was 57yrs and 54% female. Mean time from vasculitis onset to BKV testing was 36 months and 19/37 patients were tested within 24 months of induction therapy. At the time of BKV testing, 73% were on prednisone (P) with azathioprine, mycophenolate mofetil (MMF), methotrexate or leflunomide. None of the non-transplanted vasculitis patients had detectable plasma BKV. Among 35 patients in group B, 16 were tested for BKV; 5/16 (31%) had detectable virus in plasma at a mean of 6 months post TX (P=0.002). Most (94%) were on maintenance therapy with MMF, P and tacrolimus.

Conclusion—Immunosuppressed patients with GPA/MPA without KTX had no evidence of plasma BKV. However, BKV was common in GPA/MPA patients after KTX suggesting that

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The author's declare conflict of interest

Duvuru Geetha, MD: Department of Medicine, Division of Nephrology, Johns Hopkins University, Baltimore, Maryland: Has served as consultant and received honoraria from Genentech for educational purposes

The author's declare no conflict of interest

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Parts of this work were presented at the American Society of Nephrology meeting in San Diego, California in November 2012.

replication may be related to differences in immunosuppression, alloimmune activation or differences in host defense mechanisms.

Keywords

ANCA vasculitis; BK virus replication; Granulomatosis with Polyangiitis; Microscopic Polyangiitis; immunosuppression

Introduction

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are rare small vessel vasculitides characterized by cycles of remission and relapse. Circulating antineutrophil cytoplasmic autoantibodies (ANCA) are found in 80 to 94% of these patients which led to the nomenclature, ANCA associated vasculitis (AAV)[1,2]. Renal involvement in AAV is common with 25% of patients developing end stage renal disease (ESRD) and requiring renal transplant [3,4].

The introduction of cytotoxic therapy has changed the prognosis of these diseases from an invariably fatal disease to a manageable chronic illness with a relapsing course. Therapy consists of a staged treatment approach involving two phases: 1) remission *induction* with aggressive immunosuppressive agents, cyclophosphamide or rituximab, in combination with glucocorticoids; and 2) remission *maintenance* with less potent immunosuppressive agents, such as azathioprine or methotrexate. Current standard of care treatment regimens are fraught with morbidities associated with most immunosuppressive agents, namely opportunistic infections [5,6].

BK virus is a human polyomavirus that has emerged as an important cause of renal dysfunction in kidney transplant (KTX) recipients with graft loss in 10–50% of patients with BKV nephropathy [7] and rare reports of specific malignancies in renal transplant recipients in the setting of detectable BKV replication[8–10]. The intensity of overall immunosuppression is a major risk factor for the reactivation of BK virus in KTX recipients. Immunologic control of BKV replication can be achieved by reduction, elimination or switching of immunosuppressive agents. To prevent BKV related adverse outcomes, current guidelines established by an international panel of transplant physicians recommend post-transplant screening for BKV replication in KTX recipients, every 3 months for the first two years and annually thereafter until fifth year post transplantation[11].

Patients with AAV and KTX have many of the same complications with BKV as those without AAV. Among 85 AAV patients who underwent KTX for ESRD, BKV nephropathy was reported in 6 of 85 KTX recipients [12]. Interestingly, individuals with AAV almost universally receive significant immunosuppression due to the nature of their disease, regardless if they are a KTX recipient or not. The prevalence of BK virus replication in immunosuppressed AAV patients *without KTX*, many of whom receive immunosuppressive regimens, is not known. This may have important implications regarding future recommendations for BKV screening in this population.

Materials and Methods

The study protocol was approved by the Johns Hopkins University Institutional Review Board. Patients with a diagnosis of GPA or MPA followed at the Johns Hopkins Vasculitis Center from 2011 to 2012 without a history of kidney transplant were recruited for this cross-sectional analysis (Group A). Patients were clinically classified as GPA or MPA as defined by the Chapel Hill Consensus Conference [13]. All patients were required to be on immunosuppressive drug treatment for either induction or maintenance of remission of their vasculitis.

For comparison, we identified a historical cohort of GPA/MPA patients who had undergone KTX for end stage renal disease between the years 1999 to 2011 from the Hopkins transplant vasculitis database. Patients in this cohort who underwent testing for BKV were identified (Group B) and analyzed to compare the prevalence of BKV replication.

Acquisition of clinical data

Patient demographics, organ involvement at the time of diagnosis, AAV disease duration and details of immunosuppressive drug use were abstracted from the electronic medical record.

Laboratory data

Peak serum creatinine at the time of diagnosis and serum creatinine at 12 months when available and serum creatinine at time of BKV testing were recorded. Presence or absence of c-ANCA, p-ANCA, PR3 ELISA and MPO ELISA at the time of diagnosis was recorded. ANCA testing was done by standard indirect immunofluorescence assay on ethanol fixed neutrophils. PR3 and MPO testing was done by direct enzyme linked immunosorbent assay with commercially available kits. ANCA titer of greater than 10 was considered to be positive for c-ANCA and p-ANCA (reference range 0–10 units). PR 3 and MPO levels of greater than 20 units (reference range 0–20 units) were positive. If the testing for c-ANCA, p-ANCA, PR3 ELISA and MPO ELISA was negative, patients were labeled as having ANCA negative vasculitis.

Testing for BKV replication and TaqMan real-time PCR assay for BKV detection and quantitation

We looked for evidence of BKV replication in plasma using quantitative plasma BK virus PCR assay at a single time point. The study subjects had blood (5ml) collected at their routinely scheduled clinic visit. The serum and plasma were aliquotted into 0.5ml amounts and stored at –80°C.

Evidence of BKV replication was obtained by quantitative real-time PCR of plasma. Two tests of record in the Johns Hopkins Medical Microbiology Laboratory were used to determine replication in the historical cohort. The first, based on amplification/detection of T antigen promoter sequences[14], had a limit of detection of 200 copies/mL and was in place from October 2005-August 2011. The second test, adopted in September 2011 and currently in clinical use, employs commercial primers and probe (artus/Qiagen,

Gaithersburg, MD) to amplify/detect an unspecified BKV genome region and has a limit of detection of 30 copies/mL. The second, more sensitive assay was also used to detect BKV replication in the prospective cohort of GPA and MPA patients who did not undergo kidney transplant.

Statistical analyses

BKV replication prevalence was compared between the non-transplant GPA/MPA vasculitis cohort and the historical cohort of GPA/MPA vasculitis KTX recipients. Descriptive statistics were used to investigate the clinical characteristics of GPA/MPA patients with and without KTX. Continuous variables were expressed as mean value $\pm$ standard deviation. Discrete variables were expressed as proportions. Fisher's exact test of independence for 2×2 tables was used to detect group (transplanted, non-transplanted) differences in prevalence of BKV replication using frequency data (number of patients with BKV replication in plasma).

Results

Demographics and clinical characteristics of GPA/MPA patients without kidney transplant (Group A)

Demographic and clinical characteristics of the thirty seven patients with GPA or MPA who participated in the study are shown in Table 1. The mean age was 5 (SD16) years, females comprised 54 % of patients and majority was Caucasian (92%). Disease phenotype was GPA in 25 patients and MPA in 12 patients. Thirty six patients were ANCA positive (c – ANCA: 21, p-ANCA: 15). The mean disease duration was 75 months. Renal involvement was present in twenty four (65%) of these patients with seventeen having biopsy proven glomerulonephritis.

The details of immunosuppressive drug therapy are listed in Table 2. The mean time from induction therapy to BKV testing was 36 months and 19 of 37 patients were tested within 24 months of induction therapy. At the time of BKV testing, 73% of patients were on a combination of prednisone with azathioprine, mycophenolate mofetil (MMF), methotrexate or leflunomide. 27% were on prednisone (P) monotherapy.

Demographics and clinical characteristics of GPA/MPA patients with kidney transplant (Group B)

Thirty five GPA/MPA patients that had undergone KTX for end stage renal disease due to AAV were identified from the Hopkins transplant vasculitis database. BKV surveillance testing with plasma BKV PCR was started at our institution in 2005. Fifteen patients transplanted between 2006 and 2011 underwent surveillance with quantitative plasma BKV testing every 3 months for the first year post transplant and every 6 months during the second year post transplant with quantitative plasma BK PCR assay. In one additional patient, elevated serum creatinine prompted allograft biopsy and a quantitative plasma BKV PCR assay. The mean duration of vasculitis prior to transplant in these 16 patients was 76 months. The mean age of the 16 patients (8 males and 8 females) tested for BKV replication was 56 years. Disease phenotype was GPA in 8 patients and MPA in 8 patients. Fifteen

patients received induction therapy (12 with anti-thymocyte globulin, 3 with interleukin 2 receptor antagonists (1 with daclizumab and 2 with basiliximab). Fifteen patients received P, MMF and tacrolimus for maintenance immunosuppression while a single patient received sirolimus, MMF and P.

Prevalence of BKV replication

The prevalence of detectable BKV in plasma was different between the prospective non-KTX and historical KTX AAV cohorts (Table 3). None of the non-transplanted vasculitis patients had detectable BKV in plasma. However, 5/16 (31%) transplanted GPA/MPA patients had detectable BKV in plasma or allograft during surveillance or when tested to evaluate allograft dysfunction. Virus was detected at a mean of 15 months post KTX. The median viral load at first detectable viremia was 5160 copies/mL. The immunosuppressive regimen of the five transplanted patients with demonstrable BKV was maintenance therapy with MMF, P and tacrolimus. Four of the five patients received induction therapy (3: anti-thymocyte globulin, 1: basiliximab) All patients underwent reduction of immunosuppressive therapy after detection of viremia with stabilization of allograft function. Four patients cleared viremia at a median of 4.5 months and one patient had low level viremia 14 months post KTX.

Discussion

This study failed to detect evidence of BKV viremia in immunosuppressed GPA/MPA patients without KTX and confirmed the prevalence of this virus in transplanted GPA/MPA patients. These findings are highly suggestive of important underlying differences between these two populations, the etiology of which remains unclear, but could include specific immunosuppressive agents, donor origin of BKV, alloimmune activation or differences in host defense mechanisms. The study limitations include small sample size and disproportional testing for BKV viremia in non-transplanted AAV patients (who were assayed at a single time point), compared to KTX AAV patients (who were assayed serially as part of surveillance screening).

Primary infection with BKV occurs in early childhood and is asymptomatic. The virus then remains latent in urothelium and renal tubular epithelial cells. Asymptomatic viral activation and low level viruria can occur in 5% of healthy individuals. However, viral reactivation is more common after KTX with viruria in 30–60%, viremia in 21% and BKV nephropathy in 1–10% [11,15]. The overall intensity of immunosuppression has been accepted as a risk factor for BKV replication in KTX recipients. Other proposed risk factors include viral tropism for urothelium, human leukocyte mismatches between the donor and recipient, immunosuppressive therapy and other unknown factors[15].

In KTX recipients, BKV viremia and nephropathy has been observed with various immunosuppressive regimens. However, a higher risk of BKV replication is observed with standard dose tacrolimus than cyclosporine when combined with MMF and P [16,17]. In KTX recipients, BKV specific T cell responses in these patients have been shown to be inversely correlated with tacrolimus levels but not with P, mycophenolate levels or other immunosuppressive drugs[18]. Vasudev et al. have shown that reduction of the calcineurin

inhibitor score derived from a scaling system used for immunosuppressive dose reduction for BKV replication but not the overall reduction in unit immunosuppressive score correlated significantly with slowing allograft functional loss in patients with BKV nephropathy[19]. Calcineurin inhibitors inhibit T cell activation while the anti-proliferative agents interfere with T cell proliferation. Additionally, T cell depleting antibody commonly used for induction therapy in KTX recipients has been shown to be an independent risk factor for BKV replication have been [20]. In addition to corticosteroids, the standard treatment regimens in AAV patients without KTX typically include remission induction therapy with cyclophosphamide and rituximab which are relatively B cell specific and remission maintenance therapy anti-proliferative agents like azathioprine and MMF but do not include calcineurin inhibitors. These differences in immunosuppressive drug therapy may explain the absence of BKV replication in AAV patients without KTX.

BKV replication has been reported in other autoimmune diseases and in solid organ recipients other than KTX, however the highest rates of viruria, viremia and nephropathy appear to occur in KTX recipients. A cross-sectional prevalence study in lupus patients showed a high prevalence of BKV viruria but no detectable viremia [21]. Additionally, in one point prevalence study, BKV viruria was documented in 27%, 26% and 8% of kidney, heart and liver transplant recipients while BKV viremia was detected in 12% and 7% of kidney and heart transplant recipients[22]. The pathogenesis of enhanced BKV replication and associated nephropathy in KTX is unclear. Explanations include alloimmune activation in the renal allograft as has been shown in an animal model[23] and kidney damage [24], although factors leading to kidney damage such as cold ischemia time, donor source, donor-recipient HLA matching and rejection episodes leading to kidney damage have not been consistently associated with disease [19,25– 27]. The observed difference in BKV replication between kidney transplant recipients and other immunosuppressed patients may be due to differences in anti-viral T cell immune responses. A study by Bohl et al. provided evidence for donor source of BKV and also showed association of sustained BK viremia with lack of HLAC7 allele[28].

Disruption of the balance between the host immune response and BKV replication is almost certain to play a role. Impaired immune responses to BKV infection in KTX include decreased production of specific antibodies B cells, ineffective immune surveillance by T cells, and diminished dendritic cells [29]. Interestingly, AAV patients have been shown to have decreased dendritic cell numbers during active disease and in remission [30]. Despite this, we did not find any evidence of BKV replication in our immunosuppressed vasculitis patients. Finally, viral factors such as genomic rearrangements in non-coding control regions has been linked to increased replication in KTX recipients [31]

This study is limited by small sample size. The assessment for BKV viremia occurred at a single time point in non-transplanted AAV patients compared to transplanted AAV patients subjected to BKV surveillance screening who were tested for BKV viremia at different time points. The mean time from induction therapy to testing in Group A patients without KTX was 36 months. However, about 50% of patients were tested within 24 months of induction therapy and all patients were on maintenance immunosuppression with majority of patients on combination therapy with two immunosuppressive drugs at the time of BKV testing.

Since BKV replication in KTX recipients is linked to the intensity of immunosuppression, future studies aimed at testing for BKV replication immediately after the induction therapy as well as serial monitoring for BKV viremia in Group A patients might give us a better estimate of BKV replication in this population. The diagnostic PCR assays for BKV are limited by lack of standardized assays. Although, BK viruria occurs earlier than BK viremia, viruria was not tested in this study due to the low positive predictive value of viruria for BKV nephropathy and physiologic fluctuations in urinary BKV load.

This study is the only available study looking at prevalence of BKV replication in immunosuppressed AAV patients without a KTX. It contributes further to our understanding of BKV disease pathogenesis by providing data to support the hypothesis that factors in addition to immunosuppression may be important in replication and nephropathy in KTX.

Acknowledgement

Funding Sources:

Funding for this project was provided by the Donald B. and Dorothy L. Stabler Foundation

Abbreviations

BKV	BK virus
KTX	kidney transplant
GPA	Granulomatosis with Polyangiitis
MPA	microscopic Polyangiitis
ANCA	anti-neutrophil cytoplasmic antibody
AAV	ANCA associated vasculitis
P	prednisone
MMF	mycophenolate mofetil

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Table 1

Demographic and Clinical characteristics of AAV patients without kidney transplant (Group A, n=37)

Mean age at diagnosis, years (SD)	57 (16)
Female (%)	20 (54)
Caucasian (%)	34 (92)
Clinical vasculitis phenotype (%)	
GPA (%)	25 (68)
MPA (%)	12 (32)
ANCA type (%)	
c-ANCA	21 (57)
p-ANCA	15 (40)
ANCA negative	1 (3)
Organ involvement from vasculitis (%)	
Kidney	24 (65)
Lung	19 (51)
Sinus	14 (38)
Joints	11 (30)
Ears	9 (24)
Eyes	8 (22)
Peripheral nerves	5 (14)
Time from diagnosis to BKV testing (months) (SD)	77 (58)
Months from induction therapy to BKV testing (SD)	36(35)
Number of patients tested for BKV within 24 months of induction therapy n (%)	19(51)
Serum creatinine at diagnosis (mg/dl) median (range)	1.4(0.6 to 7.5)
Erythrocyte sedimentation rate at start of induction therapy (mm/hr) median (range) (n=23)	40 (2 to 123)
C-reactive protein at start of induction therapy (mg/dL) median (range) (n=23)	1.2 (0.2 to 9.8)
Serum creatinine at time of BKV testing median (range) (mg/dl)(SD)	1.28 (0.45) 1.2 (0.6 to 2.6)
Number of patients on dialysis at time of BKV testing (n) (%)	1 (3)

Table 2

Demographic and Clinical characteristics of AAV patients with kidney transplant (Group B, n=16)

Mean age at transplant, years	55
Female (%)	8 (50)
Caucasian (%)	10 (63)
Clinical vasculitis phenotype (%)	
GPA (%)	8 (59)
MPA (%)	8 (50)
Organ involvement from vasculitis (%)	
Kidney	16 (100)
Lung	7 (44)
Sinus	4(25)
Joints	5 (31)
Ears	1 (6)
Eyes	1 (6)
Peripheral nerves	1 (6)
Time from vasculitis diagnosis to kidney transplant (months) median (range)	55 (16 to 264)
Donor type (%)	
Diseased Donor	8 (50)
Living related	6 (38)
Living unrelated	2 (12)

Table 3

Details of immunosuppressive drug use

	Group A	Group B
	N=37	N=16
Type of induction therapy n (%)		
Cyclophosphamide/prednisone	21 (57)	
Cyclophosphamide/rituximab/prednisone	2 (5)	
Rituximab/prednisone	4 (11)	
Methotrexate/prednisone	7(19)	
Prednisone	3 (8)	
Anti-thymocyte globulin	0 (0)	12 (80)
Interleukin 2 receptor antagonist	0 (0)	3 (20)
Cumulative Cyclophosphamide dose (grams) median (range) (n=16)	18 (5 to 81)	
Number of Rituximab courses , median (range)	1 (1 to 3)	
Type of drug therapy at time of BKV testing n (%)		
Azathioprine/prednisone	9 (24)	
Azathioprine alone	6 (16)	
Mycophenolate mofetil/prednisone	2 (5)	
Methotrexate/prednisone	5 (14)	
Methotrexate alone	2(5)	
Cyclophosphamide/prednisone	1(3)	
Rituximab/prednisone	1 (3)	
Leflunomide alone	1 (3)	
Prednisone alone	10 (27)	
Mycophenolate mofetil/prednisone/tacrolimus	0 (0)	15 (94)
Mycophenolate mofetil/prednisone/sirolimus	0 (0)	1 (6)

Group A: GPA/MPA patients without kidney transplant

Group B: GPA/MPA patients with kidney transplant

Table 4

Prevalence of BKV replication in transplant AAV and non-transplant AAV

Group	A (without kidney transplant)	B (with kidney transplant)	P value
Positive plasma BK virus PCR	0	5	0.002
Negative plasma BK virus PCR	37	11	
Total	37	16	