RISK FACTORS FOR BK VIRUS NEPHROPATHY IN RENAL TRANSPLANT RECIPIENTS - THE ROLE OF URETERAL TRAUMA.

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Executive Summary

BK virus associated nephropathy (BKVAN) is an important emerging infectious disease in the renal transplant population. The risk factors for the development of BKVAN are not clearly defined.

I propose that trauma to the donor ureter due to the placement of indwelling stents is an independent risk factor for the development of BKVAN. Stent placement may facilitate the ascending spread of BKV from latent sites in the urinary epithelium to the renal cortex, where active disease can develop in a susceptible host.

In 2002 14,523 kidney transplants were performed in the United States. The unadjusted graft survival at 3 years is approximately 83%. BKVAN is a rare condition with a prevalence of 2-6%, and it generally develops within the first two years after transplantation. BKVAN has a poor prognosis and up to 40% of affected patients lose graft function within one year. Current strategies to treat BKVAN including reduction of immunosupression and use of anti-viral drugs have not been very successful.

This paper discusses the design, conduct and analysis of a case –control study that was conducted to test the hypothesis that stent placement is a risk factor for BKVAN. The objectives of the study are to provide data to support this hypothesis as well as to provide more information about the clinical course and outcomes of this rare disease.

Analysis of the study results reveals a statistically significant association between stent use and BKVAN. This novel finding is clinically important as it may lead to changes in existing surgical practices in kidney transplantation. These results will help to guide the design of larger prospective clinical trials that are necessary to confirm the association between stent use and BK virus associated nephropathy.
Introduction

Over the past two decades the incidence of infectious complications following organ transplantation has declined. However, in recent years BK virus associated nephropathy (BKVAN) has emerged as an important complication of renal transplantation. This disease can cause premature allograft failure in renal transplant recipients.

BK virus is a small non-enveloped DNA virus belonging to the polyomavirus family. This family includes two human pathogens, JC virus and BK virus, both of which were first isolated from immunocompromised patients (1). BK virus was first isolated in 1971 from the urine of a Sudanese renal transplant patient (with the initials B.K.) who presented with ureteral stenosis (2). Human infections with BK virus are common in childhood and are largely asymptomatic. Seroconversion occurs in more than 90% of cases by the age of 20 (3). After primary infection the virus remains latent in the urinary epithelium and lymphoid cells. Reactivation may occur in the presence of intense immunosuppression associated with conditions like organ transplantation, primary immunodeficiency diseases, human immunodeficiency virus infection and following immunotherapy for malignancy.

In the field of kidney transplantation, the emergence of BKVAN in the 1990s seems to coincide with the widespread use of newer potent immunosuppressive drugs such as tacrolimus and mycophenolate mofetil (MMF). Cases of BKVAN have been reported from most major transplant centers around the world. However the risk factors associated with the development of BKVAN are not clearly defined. The disease may or may not be related to the use of a specific immunosuppressive agent. It is also interesting to note that there is a relative absence of BKVAN in recipients of non-renal transplants who receive therapy with similar immunosuppressive agents.
The disease can affect up to 6% of all kidney transplant recipients. BKVAN can develop at varying times in the post transplantation period (average 40 weeks, range 6-150 weeks) (4, 5). Clinically BKVAN presents with acute allograft dysfunction manifested by a rise in the serum creatinine (Scr). Diagnostic tests that are being used currently include urine cytology and viral assays. However to confirm the diagnosis of BKVAN a renal biopsy which demonstrates classical histopathological and immunohistochemical findings is necessary. At present there is no effective treatment for BKVAN. Several investigators have tried antiviral therapy and modification of the immunosupression regimen to delay the progression of this disease. The prognosis of BKVAN is poor and progression of the disease to irreversible graft failure has been reported in up to 45% of all cases. (5,6,7)

**Objectives**

The primary objective of this study is to investigate the association between ureteral trauma secondary to the use of indwelling stents and the development of BKVAN in renal transplant recipients.

**Secondary Objectives**

1) To determine other risk factors for BKVAN in renal transplant recipient.

2) To describe the clinical course and outcomes of patients with BKVAN.

3) To compare graft survival in patients with BKVAN and controls without BKVAN.

**Hypothesis**

Ureteral trauma is an independent risk factor for the development of BKVAN. It facilitates the ascending route of spread of BK virus from the urothelium to the renal cortex, where active disease may develop in a susceptible host.
Pathogenesis of BK Virus Associated Nephropathy

The risk factors for BKVAN in renal transplant recipients are unknown. It is likely that BKVAN is the result of a poorly defined multifactorial process. Recently a second hit hypothesis has been proposed (8). The first “hit” involves the transplantation of a kidney that is loaded with latent BK virus. Under the influence of intensive immunosuppression in the post transplantation period, a second hit appears to be necessary for the replication of the latent virus. These second hits may include diverse causes of allograft injury such as acute rejection, acute tubular necrosis and ureteral trauma. The role of ureteral trauma in the pathogenesis of BKVAN has not been previously investigated.

Differentiating tubular cells such as those recovering from rejection episodes or ischemia-reperfusion injury in a renal allograft recipient treated with highly potent immunosuppressive drugs may provide the necessary cofactors for replication of the virus. This has been demonstrated in an animal model (20). Active viral replication is followed by tubular cell lysis.
and development of invasive disease manifested characterized by interstitial inflammation and acute tubular necrosis.

The specific purpose of this study is to determine the role of ureteral trauma in the pathogenesis of BKVAN. The best-known site of BK virus latency after a primary infection is the urogenital tract. Viral sequences can be detected in up to 50% of human kidneys (26) and BK virus associated ureteral stenosis has been reported in renal allograft recipients (27,28). Hence it appears that if the virus remains in the lower urinary tract, patients remain asymptomatic or develop pyuria and rarely ureteric stenosis. When the virus spreads to the renal cortex and is reactivated then symptomatic disease that manifests as acute renal failure is possible. In biopsy specimens the virus has been shown to be abundant in the medulla and distal tubule cells. This finding also suggests that the virus spreads from the lower urinary tract to the renal cortex.

However, it is unclear how or why the BK virus spreads from the urothelium to the renal cortex. Ureteral trauma induced by the placement of indwelling stents may play a role in facilitating ascending spread of the BK virus from the urothelium to the renal cortex.

**Ureteric Stents and Kidney Transplantation**

Urological complications after kidney transplantation like obstruction of the ureter and urine leakage at the vesicoureteric anastomosis can cause significant morbidity and mortality. With improvements in surgical techniques the incidence of these complications has decreased to 5-10% (9).

Placement of ureteric stents is common practice in renal transplantation. Retrospective studies have suggested that this practice is beneficial and decreases the incidence of urine leaks (10). However randomized controlled clinical trials of routine stenting in low-urological-risk kidney transplantation show that the procedure is unnecessary and does not reduce the risk of urological
complications (11). At present selective stenting based on the judgement of the surgical team is recommended in renal transplantation.

At our institution the decision to use a ureteric stent is made by the transplant surgeon at the time of surgery. The usual indications for stent placement during kidney transplantation at this institution include:

1) Lack of urine output or decreased urine flow from the transplanted kidney after the anastomosis is completed.

2) Certain characteristics of the recipient bladder including a thin bladder wall, a large floppy bladder or small, shrunken and scarred bladders.

3) Individual preference of the operating surgeon.

Flexible silastic stents with a 6 French diameter and a length of 16-20 cm are usually used. The stents are removed after 4-6 weeks. This procedure is usually performed by outpatient cystoscopy in the urology clinic.

**Histology of the Ureter**

The ureter consists of intricately arranged bundles of smooth muscle within an inner lining of lamina propria and urothelium and an outer sheath of fibrous tunica adventitia (figure 1). The indwelling stent lies in close contact with the uroepithelium for several weeks. The biomaterial in the stent can cause changes in the urinary epithelium. In animal models the biological reactions to double -J stents include superficial epithelial destruction with erosions and ulcerations of the transitional epithelium and inflammatory reactive changes. The latter include mononuclear inflammatory infiltrate in the epithelium and lamina propria, edema of the lamina propria, mucous metaplasia and transitional epithelial hyperplasia.
These changes were noted after intubation of the animal ureters for 6 weeks (12,13,14). Similar reactive urothelial changes are expected to occur in the transplanted donor ureter as a result of mechanical trauma and chemical inflammation secondary to the intra-operative placement of indwelling stents. Following these reactive urothelial changes, epithelial regeneration occurs.

We postulate that regenerating and differentiating uroepithelial cells may mediate enhanced entry of BK virus into cells by upregulating cell surface receptors. Very little is known about the behavior of the BK virus at the cellular level. However the cellular interactions of the Simian Virus 40(SV 40) have been well described (21,22)

The SV40 virus is a polyoma virus that infects Rhesus monkeys. It shares 69% DNA sequence identity with the BKV (23). The SV40 specific receptor comprises MHC class 1 proteins (16). It has recently been recognized that SV40 enters the host cell through caveolae (22). Caveolae are small (50-70nm) flask-shaped vesicles present in the cell surface of many cell types (24) Drachenberg, et al have reported that the process by which BK virus enters the renal tubular cell
is morphologically very similar to the caveolae dependant endocytosis of SV 40 (25). The virus can then spread from cell to cell in the uroepithelium by a receptor-mediated mechanism. This process allows the virus to spread from the collecting ducts to cells for which the BK virus is tropic like tubular cells and parietal epithelial cells. (18) Hence this mechanism facilitates the ascending route of viral spread from the urothelium to the renal cortex. However receptor mediated viral entry into a cell is not sufficient to cause viral replication. Instead additional second hits like allograft injury secondary to acute tubular necrosis and acute rejection may be necessary to trigger viral replication.

**Methods**

**Study Design:** A matched case control study was used to test the hypothesis that ureteric trauma due to stent placement is associated with BKVAN.

**Setting:** Renal transplant clinics at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center. One hundred and seventy eight kidney transplants were performed at this institution in 2002.

**Subjects.**

Twenty cases of BK virus associated nephropathy (BKVAN) were identified by retrospective analysis of all kidney transplant recipients at Johns Hopkins Hospital between January 1996 and August 2003. A case was defined as a renal transplant recipient who had histological evidence of BKVAN in a kidney biopsy performed in the post-transplant period for allograft dysfunction. The histological diagnosis was made by the observation of BK virus induced cytopathic changes in the renal tubular epithelium and confirmed by electron microscopy and immunohistochemical stain for the BK virus (SV 40 antibody; Access Biomedical, Campo CA).
The morphological hallmarks of BKVAN are intranuclear viral inclusion bodies and focal necrosis of tubular cells (figure 2). The intranuclear inclusion bodies are seen exclusively in epithelial cells and appear as amorphous basophilic ground-glass structures. Inclusion bearing cells are abundant in the medulla and distal tubules. Diagnostic confirmation is performed by electron microscopy or immunohistochemistry. Ultrastructurally BK virus presents as viral particles measuring between 30 and 50 nm in diameter. Immunohistochemistry is done using commercially available antibody that detects the SV 40 large T antigen. This antigen is common to BK, JC and SV 40 viruses (figure 3)

Controls

The patients with BKVAN (n=20) were compared with a control group that consisted of 46 patients who were biopsied during the same time period and were negative for BKVAN by
histology and immunohistochemistry.

**Matching**
The two groups were matched for transplant date, biopsy date and immunosuppressive regimen. The controls received their kidney transplant and underwent kidney biopsies within three months of the date that the cases underwent these procedures. All the patients received immunosuppression with a standard 3 drug regimen including, Tacrolimus, Mycophenolate Mofetil and Prednisone.

**Data Collection**
Data was collected by retrospective chart review after approval from the Institutional Review Board (IRB). Data collected from both groups included demographics, type of transplant, HLA match, type and dose of immunosuppression, use of indwelling ureteric stents, history of delayed graft function, acute rejection episodes, pretransplant diabetes mellitus and cold ischemia times. The baseline serum creatinine, creatinine at the time of diagnosis of BKVAN and the status of graft function at the most recent follow up or in October 2003 was also evaluated.

**Statistical Analysis**
Comparison was performed between patients with BKVAN and control patients without BKVAN. The continuous variables were compared using t-tests. Categorical variables were expressed as proportions and compared using the Chi-Square statistic. STATA (Version 7.0, College Station, Texas) statistical software was used for this study.

The primary outcome variable was development of BKVAN. Multivariate conditional logistic regression models were used to study the adjusted relationship between stent use and the development of PVN (Table 2).

Kaplan-Meier survival curves were used to compare each group with regard to the incidence of
Sample Size Calculation

- Proportion of controls with stents – 30%
- Proportion of cases with stents – 70% (assumption)
- Using Alpha 0.05 and Power 0.80
- Allocation ratio – 2 (case/control)
- Estimated samples sizes:
  - Cases –21
  - Controls - 42

Results

To obtain data about the use of stents, a random sample of 177 renal transplant recipients was selected from the entire kidney transplant population at Johns Hopkins Hospital between 1995 and 2000. Ureteric stents were placed in 30% of patients at the time of transplantation. Stent use was more common in deceased donor transplants. However there was no statistically significant difference in the incidence of stent use in deceased donor versus living donor transplants (37% vs. 25% p 0.06)

During the study period the incidence of BKVAN at this institution was 2%. The baseline characteristics of sixty-six transplant recipients are presented in table 1.

The group of patients with BKVAN included 16 men (80%) and 4 women (20%). The male predominance was statistically significant (p=0.03). The mean age was 51.2 years (range 25-73).

Twelve patients (60%) were Caucasian and seven (35%) were African American. Fourteen transplants were from deceased donors and six from living donors (1 ABO incompatible donor, 4 living related donors and 1 living unrelated donor).

The mean cold ischemia time in the deceased donor transplants was 22.8 hours and indwelling double-J ureteral stents were placed in 15 patients (75%) during surgery. After transplantation nine patients (45%) had delayed graft function and required dialysis during the first week.
Table 1. Baseline Characteristics of Cases and Controls.

<table>
<thead>
<tr>
<th></th>
<th>CASES N=20</th>
<th>CONTROLS N=46</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE in years</td>
<td>51.2</td>
<td>51.5</td>
<td>NS</td>
</tr>
<tr>
<td>Males (%)</td>
<td>80%</td>
<td>50%</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>60%</td>
<td>67.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Black</td>
<td>35%</td>
<td>30.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Deceased Donor Transplant</td>
<td>70%</td>
<td>41.3%</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Average HLA Mismatch</td>
<td>3.35</td>
<td>3.04</td>
<td>NS</td>
</tr>
<tr>
<td>Average CIT/Deceased Donor Tx</td>
<td>22.8 hours</td>
<td>28.3 hours</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>History of Diabetes (%)</td>
<td>6 (30)</td>
<td>19 (41.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Stent Placed (%)</td>
<td>15 (75)</td>
<td>16 (34.8)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Delayed Graft function (%)</td>
<td>9 (45)</td>
<td>8 (17.4)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>History of Acute rejection (%)</td>
<td>8 (40)</td>
<td>20 (43.5)</td>
<td>NS</td>
</tr>
<tr>
<td>History of Urinary Obstruction (%)</td>
<td>3 (15)</td>
<td>5 (10.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Average MMF dose (g)</td>
<td>1.84</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Average Prednisone Dose (mg)</td>
<td>11.07</td>
<td>13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Average Tacrolimus level (ng/ml)</td>
<td>10.43</td>
<td>9.84</td>
<td>NS</td>
</tr>
<tr>
<td>CMV infection (%)</td>
<td>5</td>
<td>8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Exposure to Anti- Lymphocyte Antibodies (%)</td>
<td>25</td>
<td>28.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean number of SM pulses</td>
<td>2.8</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Exposure to Solumedrol Pulses (%)</td>
<td>50</td>
<td>41.3</td>
<td>NS</td>
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</table>

Controls are matched based on time of transplantation, time of biopsy and immunosupression. Control biopsies were negative for PVN. P values may be underestimated because of matching.

All patients received maintenance immunosupression with Tacrolimus, prednisone and mycophenolate mofetil. Azathioprine was used in one patient instead of MMF. Eight (40%) of the patients developed acute rejection prior to developing BKVAN. Ureteral obstruction was observed in three patients. The diagnosis of BKVAN was made at an average of 14.6 months post transplantation (range 4.2-40.7 months)
Primary Outcome – stent use and BKVAN

In this case control study, use of ureteric stents at the time of kidney transplantation was found to have a statistically significant association with the subsequent development of BKVAN (Odds Ratio 5.6, 95 % CI 1.54 to 22.9, p=0.003). Stents were used in 75% cases and only 35% of the control patients. Stent use appears to increase the risk of BKVAN by at least 54%.

Regression Analysis

Both logistic regression and conditional logistic regression analysis was performed and the results are presented in tables 2 and 3.

The outcome variable used was the presence or absence of BKVAN as defined by histological and immunohistochemical criteria which have been discussed earlier. Only two predictor variables were included in the model; age group (>57 years) and the presence or absence of DGF. Delayed graft function is considered to be an important confounding variable in the relationship between stent use and BKVAN. It represents several variables that contribute to poor immediate function of the allograft, including a high terminal creatinine in the donor kidney, prolonged cold and warm ischemia times, etc.

The statistically significant association between stent use and BKVAN persists after adjusting for DGF and age. Due to the small sample size the reported confidence intervals lack precision. Renal transplant recipients with a history of stent use have at least a two-fold increase in the risk of BKVAN after adjusting for DGF and age.
<table>
<thead>
<tr>
<th></th>
<th>UNIVARIATE</th>
<th></th>
<th>MULTIVARIATE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR, 95% CI</td>
<td>P</td>
<td>OR, 95% CI</td>
<td>P</td>
</tr>
<tr>
<td><strong>STENT</strong></td>
<td>16.9 (2-142)</td>
<td>0.009</td>
<td>81.1 (2.1-3175)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>DGF</strong></td>
<td>3.4 (0.73-15.4)</td>
<td>0.12</td>
<td>0.2 (0.02-3.3)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>AGE &gt;57 YEARS</strong></td>
<td>0.99 (0.95 - 1.04)</td>
<td>0.76</td>
<td>0.42 (0.08-2.16)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 2. Conditional Logistic Regression Results.

<table>
<thead>
<tr>
<th></th>
<th>UNIVARIATE</th>
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<th>MULTIVARIATE</th>
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<tbody>
<tr>
<td></td>
<td>OR, 95% CI</td>
<td>P</td>
<td>OR, 95% CI</td>
<td>P</td>
</tr>
<tr>
<td><strong>STENT</strong></td>
<td>5.6 (1.73 - 18.3)</td>
<td>0.004</td>
<td>4.97 (1.12- 22.1)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>DGF</strong></td>
<td>3.89 (1.21- 12.5)</td>
<td>0.02</td>
<td>1.39 (0.32 - 5.99)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>AGE &gt;57 YEARS</strong></td>
<td>0.99 (0.96 - 1.0)</td>
<td>0.98</td>
<td>0.75 (0.23 - 2.49)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Table 3. Logistic Regression Results.

**Secondary Outcomes**

**Other risk factors for BKVAN**

No significant differences were found between the ages of patients in both groups. Males were more likely to develop BKVAN (p=0.03) and BKVAN was more common in deceased donor transplants (P=0.03).

Delayed graft function, which was defined as the need for dialysis in the first week post–transplant was more common in the BKVAN group (45% vs. 17.4% p=0.02). There was no evidence that a particular immunosuppressive agent was responsible for BKVAN as there was no difference in the dose of MMF, Prednisone and Tacrolimus levels between the BKVAN group and the control group. In addition there was no difference between the two groups with regard to exposure to Anti-lymphocyte antibodies or Solumedrol pulse therapy. The incidence of acute rejection was similar in both groups. No other significant differences were found between the two groups.
Clinical course and outcomes

After the diagnosis of BKVAN was confirmed immunosuppression was reduced in 18 patients and remained unchanged in 2 patients. Immunosuppression was reduced in a uniform manner. The dose of MMF was either reduced by 50% or the drug was stopped. Tacrolimus dose was reduced in 17 patients to obtain trough levels of 5-7ng/ml. In one patient cyclosporine was substituted for Tacrolimus. The prednisone dose was reduced to 5-7.5 mg /day in all patients.

The mean serum creatinine at diagnosis of BKVAN was 2.81(range 1.4- 5.1 mg/dl). After a mean observation period of 32 months postransplantation, six (30%) of patients had lost their grafts. In these patients graft loss occurred 9.43 (range 1.1 to 24.3) months after the diagnosis of BKVAN was made. The mean serum creatinine in the remaining 14 patients is 2.64 (range 0.9 to 4.5mg/dl) after an average follow up period of 17 months. Rejection diagnosed by allograft biopsy developed in 20% of the cases after reduction of immunosupression. In the patients who did not lose graft function there is significant renal dysfunction; 45% have a serum creatinine (Scr) >2mg/dl (table 4). However when compared to the Scr at the diagnosis of BKVAN the renal function remained relatively stable in 71% (10/14) of the patients, with a Scr range of 0.9-2.7mg/dl.

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
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<tbody>
<tr>
<td>Graft Loss</td>
</tr>
<tr>
<td>Death with functioning graft</td>
</tr>
<tr>
<td>Functioning graft with Scr&gt;2mg/dl</td>
</tr>
<tr>
<td>Functioning graft with Scr&lt;2mg/dl</td>
</tr>
</tbody>
</table>
**Graft Survival**

Graft loss is defined as a decline in renal function leading to initiation of dialysis. Graft loss occurred in 30% cases and 4.4% controls after a mean follow up of 34 months.

Kaplan-Meier analysis demonstrates that at any given time point the BKVAN group has significantly decreased graft survival (p 0.0002 using log rank test).

The hazard ratio for graft loss and BKVAN is 10.5 (95% CI 2.22 to 49, p 0.003)

**Figure 5.**

Graft survival analysis. Comparison between patients with BKVAN and disease free Controls (P = 0.0002). The hazard ratio for graft loss and BKVAN is 10.5
DISCUSSION

BKVAN is an important cause of premature graft loss in kidney transplant recipients. The disease appears to be more common in elderly Caucasian males with a history of delayed graft function. However multiple factors lead to the development and progression of BKVAN in the setting of intense immunosuppression.

This study has revealed a novel association between ureteral trauma due to stent placement and the subsequent development of BKVAN. It is the first study in the kidney transplantation literature to address this issue. The next question that needs to be answered is whether this association is causal or not. There is clearly a temporal relationship between stent placement and BKVAN and this association is biologically plausible.

However due to the observational nature of this study it is possible that the observed association is due at least in some part to confounding variables. Regression analysis was used to account for 2 known confounding variables namely age and DGF, but there are probably other unknown variables that influence this relationship. Another limitation of the study is the choice of controls. They may not be entirely representative of the general transplant population, because I only selected patients who had renal allograft biopsies. Hence the controls are more likely to have had some form of allograft dysfunction, which led to the biopsy itself. One way to deal with this problem would be to include renal transplant recipients who have never been biopsied as controls. However unless newer diagnostic techniques are developed, it is not possible to rule out BKVAN without doing a biopsy first.

The results of this study should help investigators to develop prospective clinical trials to confirm the association between ureteral trauma and BKVAN. Based on these results alone it is not possible to make recommendations for clinical practice. However the routine practice of
stenting in kidney transplantation of low–risk patients needs to be reevaluated.

Another important clinical finding in this study is that judicious reduction of immunosuppression has a role in the management of BKVAN. This treatment option appears to be a reasonable one for the short-term preservation of graft function especially if the diagnosis of BKVAN is made before significant renal dysfunction develops. Moreover the effects of newer therapies for BKVAN have to be compared with the option of careful reduction in immunosuppression.
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