Frequency of BK Virus Nephropathy in Graft Dysfunction Biopsies

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Background. *BK virus nephropathy is the most common type of viral disease to occur following renal transplantation. Although its frequency differs according to transplantation center, the rate is between 1.5% and 20%. Diagnosis can be established histologically by renal allograft biopsy. The aim of this study was to determine the frequency of BK virus nephropathy in patients who had had a renal biopsy for graft dysfunction at our center.*

Methods. *Biopsies received in the last 3 years from patients with graft dysfunction were used in the study. We have found the BK virus in biopsies of 5 of 41 patients (11%). All these patients had been treated with immunosuppressive drugs following transplantation surgery. Biopsies were performed because of disturbance of renal function. Only 1 patient had had a urinary examination. Morphological diagnosis of BK virus nephropathy was followed by serological examination.*

Results. *The most frequent morphological changes with BK virus infection in our samples were basophilia, nuclear inclusions, and nuclear enlargement on tubular epithelium. Decoy cells were not found in the biopsy from the only patient who had had a urinary examination. Treatment of the patients with BK virus nephropathy with immunosuppressive drugs has been reduced, and antiviral treatment has been started.*

Conclusion. *BK virus nephropathy should be kept in mind in the differential diagnosis of transplant rejection and drug toxicity.*

The most common viral disease affecting renal allografts is BK virus nephropathy (BKVN).[1–5] BKVN gained clinical attention only in the mid-1990s.[1] Its prevalence at different transplant centers ranges between 1.5% and 20%.[1–9] BKVN affects renal allografts an average 9–12 months after transplantation.[1–3] It has no specific clinical signs and symptoms. Patients present with varying degrees of allograft dysfunction that can be insidious at times.[2]

The BK virus (together with the JC virus and Simian virus 40) belongs to the polyomavirus family of double stranded nonenveloped viruses. After causing a primary infection, which usually occurs early in life without apparent clinical symptoms, polyomaviruses frequently remain in a dormant state in the kidneys and ureters of asymptomatic individuals. Under immunocompromised conditions, latent viruses can be reactivated, and the polyomavirus strain type BK can cause viral nephropathy.

The diagnosis of BKVN must be established histologically by renal biopsy.[1,9–14] The typical sign of polyomavirus nephropathy is nuclear inclusions in tubular epithelial cells. The nature of the viral changes have to be confirmed with immunohistochemical stains, in situ hybridization, polymerase chain reaction (PCR), and electron microscopy.[1–5] BKVN has been successfully treated with antiviral drugs.[12–14]

The aims of this study were to investigate the incidence of BKVN among renal allograft biopsies, to compare our findings with those of other proposed diagnostic tools, and to report the clinicopathologic features of BKVN and the outcomes of patients with BKVN as observed at Marmara University Hospital.

Material and Methods

The 41 patients who received a nonprotocol allograft kidney biopsy in the Pathology Department of Marmara University Hospital between December 2002 and December 2005 were included in the study. All the patients were being treated with a immunosuppressive regimen consisting of a calcineurin inhibitor (cyclosporine, mycophenolate mofetil) and steroids following transplantation surgery. Allograft biopsies were performed if the serum creatinine concentration increased by more than 25% from the baseline value.

A determination of BKVN was made histologically on the basis of findings as described in the literature. BKVN was diagnosed by the presence of 2 characteristic morphologic features: (1) intranuclear viral inclusion bodies in tubular and parietal glomerular epithelial cells and (2) virally induced tubular epithelial cell injury and necrosis. Four variants of viral intranuclear inclusion bodies can often be seen in BKVN: type 1 (the most frequent form), an

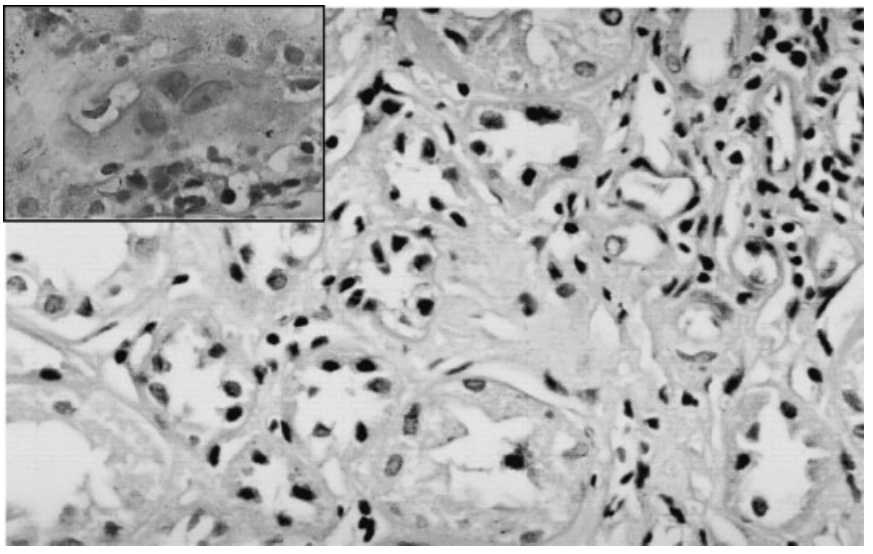

Figure 1. Type 1 nuclear inclusion bodies from a patient with BK virus nephropathy (H&E, original magnification × 400; nuclear inclusion high magnification in upper left).

amorphous basophilic ground-glass inclusion body; type 2, a central, eosinophilic, granular inclusion body surrounded by a clear halo; type 3, an eosinophilic finely granular form lacking a halo; and type 4, a vesicular variant with markedly enlarged nuclei and clumped, irregular chromatin.[4]

In only 1 of the 41 patients had there been investigation of urine cytology, a sample of which was stained by the Papanicolaou method for viewing with light microscopy to determine whether intranuclear viral inclusions (decoy cells) were present. All patients with BKVN had a result positive for the BK virus from a plasma PCR test.

Clinical information for patients was obtained retrospectively from medical charts.

Results

During the 3 years of the study, we found BKVN in allograft kidney biopsies from 5 patients (4 male, 1 female) for an incidence of 11%. The mean age of these patients was 34.6 years (range, 24–50 years). The mean time to diagnosis of BKVN after transplantation was 9.84 months (range 4.2–16.2 months). We found type 1 intranuclear inclusion bodies (*Figure 1*) on all cases slides. Also, we documented that the biopsies from 2 patients had detached tubular epithelial cells in to the tubulus lumen. Three patients had presented with interstitial nephritis. No patient had tubulitis, endarteritis, or specific glomerular changes.

Intranuclear viral inclusion bodies in all samples stained positive for the SV-40 T (BioGenex) antibody (*Figure 2*), and PCR showed all were positive for the BK virus. Mean serum creatinine at the time biopsy was performed was 2.62 mg/dL (*Table I*). The allografts came from 2 living and 3 cadaveric donors. The treatment regimen of our patients was changed to sirolimus and prednisolone 5 mg/day. Creatinine decreased and stabilized. Also, all patients were started on cidofovir and IV Ig.

Only one patient (case 5) had another biopsy, which occurred 3 months later and did not show the histopathologic features of BKVN. After a mean follow-up period of 8.2 months, 1 of the 5 patients had lost his graft (case 3). The other 4 patients are still being followed and currently have stable renal function. Decoy cells were not found in the only patient who had had a urinary examination.

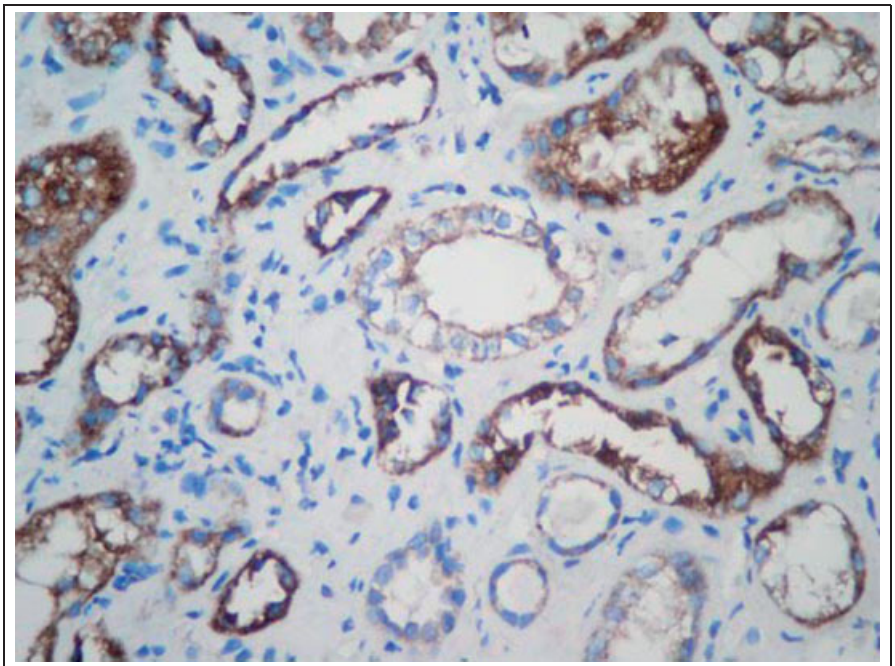

Figure 2. SV 40 immunohistochemical staining from a patient with BK virus nephropathy.

Table I. Characteristics of study patients.

Case No.	Age, Sex	Biopsy Time	Creatinine (during biopsy)	Follow Up	Status
1	24, male	14 mo	1.8 mg/dL	15 mo	stable renal function
2	27, male	6.7 mo	2.2 mg/dL	21 mo	stable renal function
3	44, male	16.2 mo	6.7 mg/dL	8 mo	graft loss
4	50, female	4.2 mo	2.8 mg/dL	16 mo	stable renal function
5	28, male	8.1 mo	1.6 mg/dL	31 mo	stable renal function

Discussion

Nephropathy associated with the polyomavirus type BK has emerged as a cause of allograft failure linked to immunosuppressive regimens.[1–5] According to retrospective studies, BKVN develops in 1%–20% of renal transplant biopsies.[1–12] The incidence of BKVN in our study was 11%, similar to what others have reported in the literature.

BKVN affects renal allografts an average of 9–12 months (range 6–160 months) after transplantation.[2,5,7] Our result, median time 9.84 months, was similar to that reported in the literature.

Among the suggested risk factors for infection with the BK virus are recurrent episode of rejection, male sex, older age, and treatment with newer immunosuppressive drugs.[9] According to Lee et al., PCR positivity for the BK virus is more common for female patients and patients who had a cadaveric donor than for male patients and patients who had a living donor.[9] In the present study most of the patients with BKVN were male and had a cadaveric donor. But we did not have enough cases for a statistical analysis.

The diagnosis of BKVN has to be made by pathological examination. The morphological hallmarks are intranuclear viral inclusion bodies seen exclusively in epithelial cells and focal necrosis of tubular cells. Four variants of intranuclear inclusion bodies can be seen along the entire nephron. Type 1 inclusion is the most frequent.[4] In this study we observed type 1 nuclear inclusion bodies in samples from all 5 patients. BKVN has to be diagnosed by allograft biopsy to rule out other potentially coexisting pathologic conditions such as rejection, drug toxicity, and recurrence of the underlying renal disease.[1,3]

Unless control-protocol biopsies are performed, BKVN in the early stages is rarely found in the absence of the other pathologic conditions.[3] Noninvasive diagnostic tools have been evaluated for their ability to identify patients at risk. Detection of decoy cells in urine has a sensitivity of 100% and a positive predictive value of less than 20% for detecting BKVN.[1,4,7] In the only patient for whom urine cytology was available, we did not observe any decoy cells.

There are no established therapeutic guidelines for BKVN in kidney transplant biopsy. The only therapeutic approach seems to be careful reduction in the doses of immunosuppressive therapy drugs to control the replication of BKVN.[2,5,14] In our study one patient lost his graft 8 months after being diagnosed with BKVN.

As BKVN is an increasing cause of graft loss after kidney transplantation, it should be included in the differential diagnosis of graft dysfunction.

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