

BK virus infection following live related renal donor transplant; a single center experience

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Abstract

BK virus (BKV) nephritis is an important infectious complication following kidney transplantation. It can lead to premature graft loss and impact survival. The overall increase in the use of potent immunosuppressants has been implicated in its higher incidence. The diagnostic techniques have improved but the treatment is still elusive. We present a case series of four patients with BKV nephropathy and their therapeutic management.

Introduction

BK virus (BKV) is a double stranded DNA virus belonging to the Papova family. The virus remains latent in the urogenital tract and is an important cause of renal allograft dysfunction (1). The use of newer, more potent immunosuppressive agents has been implicated in its increased incidence. The diagnosis is based on a combination of the presence of urinary decoy cells, virus in the urine or blood, and the gold standard characteristic histological findings on allograft biopsy (2,3). Early detection, prompt diagnosis, and a careful reduction in immunosuppressant therapy have been associated with good outcomes.

Case series report

A retrospective analysis of four cases of proven BKV nephropathy (BKVN) among 118 live related renal transplant recipients was done.

Patient 1

A 56-year-old male with focal segmental glomerulosclerosis received renal transplant from his wife (HLA mismatch 1/6). He was induced with thymoglobulin and put on triple immunosuppression with steroid, tacrolimus and mycophenolate mofetil (MMF). Around 22 months after, he had an asymptomatic rise in the creatinine level. Urine was positive for decoy cells and BKV DNA polymerase chain reaction (PCR) was positive in the blood. Renal Biopsy revealed intranuclear basophilic and gelatinous-appearing viral

Core tip

BK virus (BKV) nephropathy remains a serious opportunistic infection occurring after renal transplantation, with allograft loss occurring in approximately 50% of cases. A high degree of suspicion and prompt testing is required for its early diagnosis. A graded reduction in calcineurin inhibitor (CNI) dosage, stopping of antimetabolites and frequent monitoring is the key to stabilize renal function. The use of other agents should be individualized as there is no proven clinical benefit through randomized controlled trials.

inclusions with interstitial inflammation, tubular atrophy, and fibrosis with positive SV 40 staining (Figure 1). MMF was withheld and tacrolimus was tapered gradually and a trial of quinolones and leflunomide was given. As there was no improvement in the graft function, high dose IV immunoglobulin (IVIG) was given. His graft function recovered partially.

Patient 2

A 23-year-old female with renal coloboma syndrome received a renal transplant from her mother (2/6 HLA mismatch). Thymoglobulin was administered for induction and she was put on steroid, tacrolimus and azathioprine. She presented with a sudden increase in serum creatinine value 14 months post-transplant and was diagnosed with BKVN by allograft biopsy, Decoy cells in urine and the demonstration of BKV by



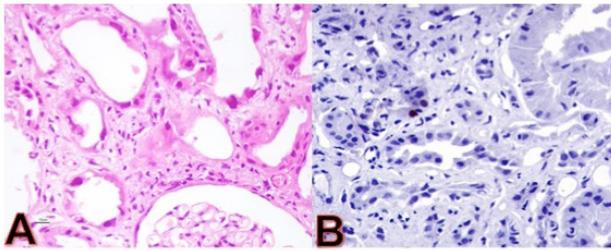


Figure 1. (A) Viral cytopathic changes observed in tubular epithelial cells accompanied by interstitial inflammatory cell infiltrates. (B) Positive immunostaining with cross-reacting monoclonal antibodies against the LT antigen of simian polyomavirus SV40.

PCR in blood. Azathioprine was stopped, tacrolimus was gradually brought down and leflunomide was added. She had complete recovery of graft function.

Patient 3

A 48-year-old male with diabetic nephropathy received a renal transplant from his sister (HLA mismatch 4/6). He was induced with basiliximab and was put on triple immunosuppression with steroid, tacrolimus and MMF. He presented with an asymptomatic rise in serum creatinine 2 years post-transplant. Diagnosis of BKVN was made by renal histology, presence of decoy cells in the urine and BKV viremia detected by PCR. Management consisted of stopping of antimetabolite and gradual reduction of tacrolimus. Quinolones and leflunomide were added as graft function continued to deteriorate. Subsequently IVIG was also given. Despite these modalities, the patient lost his graft within a year.

Patient 4

A 30-year-old male with chronic interstitial nephritis received a renal transplant from his sister (3/6 HLA mismatch). Immunosuppressive therapy consisted of thymoglobulin induction, steroid, azathioprine and tacrolimus. He had an increase in serum creatinine 47 months after transplantation. Allograft biopsy was suggestive of BKVN and acute humoral rejection. Azathioprine was stopped, tacrolimus was reduced and emergent plasmapheresis was done for the acute humoral rejection. But graft function deteriorated rapidly and he became dialysis dependent within a month after diagnosis.

Results

The baseline characteristics of our patients is summarized in [Table 1](#). Our case series consists of four patients of BKVN diagnosed within a mean time of 2 years post-renal transplant.

All of them were diagnosed with BKVN on the basis of decoy cells in the urine, BK viremia by PCR and the gold standard of renal biopsy with characteristic features of BKVN.

The treatment consisted of careful monitored reduction in calcineurin inhibitor (CNI) dosage and stopping antimetabolites in the first instance. A trial of quinolones, leflunomide and IVIG was given to those who did not re-

spond to the reduction in immunosuppression.

One patient had a combination of BKVN with acute antibody mediated rejection. Thus a therapeutic challenge as anti-rejection measures could potentially worsen BKVN. Two of the patients showed renal recovery and are under regular follow-up to look for recurrence.

Discussion

BKV which was first detected in 1971, causes nephritis and poses a threat to the renal allograft function. The factors responsible for its higher incidence and pathogenesis is still being studied. A multitude of factors including use of stronger, more potent immunosuppressants, greater awareness among nephrologists and better tools for its diagnosis have been proposed (4).

The pathogenesis has been attributed to many factors including ineffective T cell response, absence of humoral immunity to BKV, DNA sequence differences of the virus itself and also alloimmune activation (4).

The approximate incidence ranges from 2%-10% with about 20% occurring in the first year of transplantation (1,4,5). The change and reduction in immunosuppression which impacts the outcome suggests the role of over immunosuppression in the pathogenesis. But the lack of exact epidemiological data, makes it difficult for the treating physician to balance the immunosuppression with the risk of acute rejection (5).

The most common presentation is renal dysfunction with a slow progressive increase in the creatinine level (5,6), which was also the case in our patients. Rarely patients can also have ureteric obstruction and cystitis. Protocol biopsies have detected BKVN in the absence of a rise in creatinine level (6).

Many risk factors for BKVN like over immunosuppression, acute rejection episodes, HLA-mismatch, the absence of HLA C7 expression in the organ donor and/or the recipient, the utilization of ureteral stents, long cold-ischemia time, donor and/or recipient BKV seropositivity, male gender and donor age greater than 65 years have been proposed but not been conclusively proven (7). Fifty percent of our patients lost their graft and in the remaining the stabilization of graft function took a period of 3-6 months. This is almost similar to the data analyzed by Vasudev et al (7).

Though multiple factor interplay is required for BKVN, it has been observed only in immunosuppressed patients and the reduction/discontinuation of immunosuppressive agents aids in its recovery and stabilization of renal function. No particular drug has been identified in its higher incidence (8).

Renal biopsy is the gold standard for the diagnosis of BKVN (9). All our patients demonstrated the characteristic features of polyomavirus-associated nephropathy (PVAN) such as viral cytopathic changes observed in tubular epithelial cells accompanied by interstitial inflammatory cell infiltrates and a positive immunostaining with cross-reacting monoclonal antibodies against the large T antigen of simian polyomavirus SV40 ([Figure 1](#)). This can

Table 1. Clinical, histopathological and outcome of patients with BKV nephropathy

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Age and gender of the recipients	56, male	23, female	48, male	30, male
Native disease	Focal segmental glomerulosclerosis	Renal coloboma syndrome	Diabetic nephropathy	Chronic Interstitial nephritis
Age and gender of donor	54, female	45, female	55, female	47, female
Number of HLA mismatches	5	2	4	3
Induction	Anti-thymocyte globulin	Anti-thymocyte globulin	Basiliximab	None
Triple immunosuppression with tacrolimus based regimen	Yes	Yes	Yes	Yes
Time of diagnosis of BKVN (in days)	227	170	306	571
Creatinine at diagnosis (mg/dl)	1.9	1.3	2.1	5.9
Urine decoy cells	Yes	Yes	Yes	Yes
BKV in serum by PCR	Yes	Yes	no	No
Renal biopsy	SV 40 positive polyoma inclusions with dense lymphoplasmacytic infiltrates	SV 40 positive polyoma inclusions with dense lymphoplasmacytic infiltrates	Lymphoplasmacytic infiltrates and polyoma inclusions	Lymphoplasmacytic infiltrates and polyoma inclusions and C4d dense positivity in peritubular capillaries
Recovery	Partial	Complete recovery	Graft loss	Graft loss

be further graded into PVAN A, B and C based on the degree of interstitial fibrosis (9).

Other modes of diagnosis include viral serologies, urine cytology and molecular methods of nucleic acid testing. BKV DNA extraction from both urine and plasma can be demonstrated and various cut offs have been proposed based on the mode of extraction (9).

Decoy cells in the urine which are detached tubular epithelial or urothelial cells containing intranuclear BKV inclusion bodies indicate a high degree of viral replication. It is a relatively easy and cost-effective screening test but some series have reported a low sensitivity and positive predictive value. Viruria precedes viremia by an average of 2-10 weeks (9).

All patients should be screened for BKVN monthly for the first three months and thereafter every 3-6 months in the first two years. Any allograft dysfunction or when treatment of suspected acute rejection is contemplated, tests to diagnose BKVN using molecular methods may be appropriate (9).

In less equipped centers urine cytology and an urgent renal biopsy for changes of BKVN is an appropriate modality (9). The first step in the management of BKVN is the pre-emptive stoppage of MMF/azathioprine and the graded reduction of CNI. There is no standard guideline on how much of the immunosuppression should be reduced and is left to the clinician's discretion (6,9).

Several drugs like cidofovir, leflunomide and fluoroquinolones have been studied but there is no positive data on their role in curing BKVN. IVIG has shown to be effective in vitro but clinical studies are required to demonstrate a direct benefit (9).

The combination of acute antibody mediated rejection with BKVN is really a therapeutic dilemma. Atsumi et al (10) reported that the treatment of acute rejection takes precedence over BKVN treatment in the rare instance of both together.

Modifying immunosuppression in BKVN, avoiding fur-

ther allograft dysfunction, and delaying the progression of renal failure remains the main focus of therapy. Early detection of BKVN by regular surveillance for viremia/viruria enables modification of immunosuppression in individual cases where adequate reduction of immunosuppressive therapy fails to induce clearance of BKV, thus adjunctive cidofovir or leflunomide therapy could be attempted (6,8,9).

Retransplantation can be considered following graft loss due to BKVN. However pre-emptive reduction in immunosuppression, the controversial issues of induction and the BKV Plasma viral load monitoring have to be considered (9).

Conclusion

BKVN remains a serious opportunistic infection occurring after renal transplantation, with allograft loss occurring in approximately 50% of cases. A high degree of suspicion and prompt testing is required for its early diagnosis. A graded reduction in CNI dosage, stopping of antimetabolites and frequent monitoring is the key to stabilize of renal function. The use of other agents should be individualized as there is no proven clinical benefit through randomized controlled trials.

Authors' contribution

All authors wrote the manuscript equally.

Conflicts of interest

None to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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