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BK Virus Nephropathy and Transplant Outcomes: A Single Centre Study

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ABSTRACT

Introduction

A significant proportion of renal allografts are complicated by BK Polyoma Virus infection which can lead to BK Polyoma virus Nephropathy (BKVN). Early recognition and reduction of immunosuppressants is the mainstay of management of BKVN. We aimed to study the clinical profile of BKVN, management strategies and its outcome at one year of diagnosis.

Methods

A retrospective observational study was done in Tribhuvan University Teaching Hospital, Nepal. Medical records of transplant recipients between August 2008 to April 2024 with BKVN were reviewed. Time since transplant, recipient age and sex, donor age, relation and sex, induction agent and maintenance immunosuppressives, clinical presentation, diabetes, changes in immunosuppressives, other treatments, 1-year creatinine and need for dialysis were studied.

Results

Out of 847 living-donor kidney transplants, 15 (1.77%) had BK virus nephropathy. Thirteen (86.7%) were males; mean age was 42 ± 11.53 years and 5(33.33%) were diabetic. Average HLA mismatch was 3/6. BKVN was diagnosed after a mean period of 16.07±13.24 months after transplant. Thymoglobulin was used as induction agent in 11(73.3%) cases. All the patients were on Tacrolimus, Mycophenolate mofetil and Prednisolone. Average creatinine was 147.93±40.882µMol/L. Patients were managed with reduction in immunosuppressives and fluoroquinolones. Average creatinine after 1 year of diagnosis was increased by 10% to 164.43 ± 101.03µMol/L while one patient required maintenance hemodialysis 3 years later.

Conclusion

BKVN was seen in less than 2% of renal allograft recipients at mean of 16.07 months after transplant with significant renal dysfunction at diagnosis without improvement at one year. One patient required hemodialysis.

Keywords

BK virus; graft failure; kidney transplantation; nephropathy; outcome

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INTRODUCTION

BK polyoma virus (BKPyV) is a double-stranded DNA virus with mostly asymptomatic primary infection with an seroprevalence of >90%.[1,2] After primary infection, the virus establishes a latent phase in renal tubular epithelial cells and urothelium with asymptomatic urinary shedding in about 7% of healthy population.[3] In kidney transplant recipients, active replication of BKPyV can lead to BKPyV-associated nephropathy (BKVN) and subsequent graft dysfunction with rate of graft loss as high as 67% in pre-treatment era.[4,5]

First detected in 1971[6], in kidney transplant recipients, active replication of BKPyV can lead to BKPyV-associated nephropathy (BKVN) and graft dysfunction in almost 67%.[5] Over-immunosuppression is a known risk-factor for the development of BKVN.[7]

For diagnosis, there are polymerase-chain-reaction (PCR) assays and viremia precedes BKVN with biopsy being requisite for definitive diagnosis.[8] Viremia is detected in 10 - 20% of patients, usually in the first-year post-transplant and half of whom, without any intervention, progress to BKVN with a median delay of 2 to 6 weeks.[9] Various risk factors for BKVN have been suggested with the most important being immunosuppressive treatment; tacrolimus and/or corticosteroid-based regimens[9] and the treatment primarily focuses on reducing immunosuppressives.[9,10]

There have been few studies on BKVN in our country. Chettri et.al. studied 60 new-transplant patients who were followed up for a year. The researchers found that recipient diabetes and higher HLA mismatch were risk factors for development of BKVN.[11] Other than this study and a few case reports, there is paucity of data on BKVN in our population. We aimed to study the clinical profile of BKVN, management strategies and its outcome at one year of diagnosis.

METHODS

This was a single-centre retrospective study conducted in Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Prior approval from Institutional Review Committee (IRC) of Institute of Medicine was obtained (Ref 169 (6-11) E2) before commencing the study. All patients who received living-donor kidney transplant between August 2008 and April 2024 and had biopsy proven BK virus Nephropathy were included and the records were reviewed.

Date of transplant, recipient age, recipient sex, donor age, donor sex, relationship with Donor, Blood group compatibility, induction agent and immunosuppressive used at the time of BKVN diagnosis, co-morbid diabetes, other infections during the time of diagnosis, changes in maintenance immunosuppression, other treatments received, renal function 1 year after diagnosis and need for dialysis were studied. Descriptive and inferential statistics were used to analyse the data. IBM-SPSS was used for data analysis.

RESULTS

Patient Characteristics:

In total, 847 living-donor kidney transplantation were performed between August 2008 and April 2024. Of them, 15(1.77%) had biopsy proven BK Virus Nephropathy.

The mean age of patients was 42±11.53 years. Of the cases with BK Nephropathy; 13(86.7%) were male and 5(33.33%) had diabetes.

Donor Characteristics:

Females were the donor in 14(93.3%) cases and the average age at donation was 44.27±8.39 years. Recipients were related by blood in 6(40.2%) cases; others were emotionally/legally related and the average HLA mismatch was 3/6.

Immunosuppressive Treatment:

Induction Therapy:

The induction agent used was Thymoglobulin in 11(73.3%) cases, Basiliximab in 1(6.67%), Grafalon in 2(13.33%) whereas no induction agent was used in 1(6.67%) case.

Maintenance Therapy:

All of the patients were on Tacrolimus, Mycophenolate mofetil (MMF) and Prednisolone at the time of diagnosis. The average 24-hour-Tacrolimus dose was 3.32±2.47mg. The average tacrolimus level was 8.09 ± 1.30 ng/ml [range: 6.13 – 10.40]. The average dose of mycophenolate mofetil

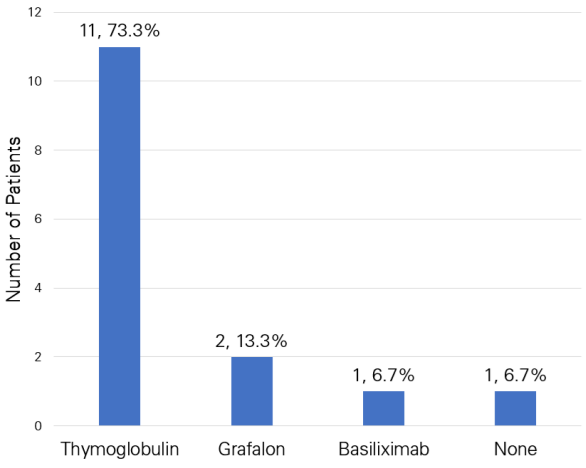

Figure 1. *Induction agent used during transplant of BK virus nephropathy cases (n=15)*

Table 1. Changes in immunosuppression after diagnosis of BKVN (n=15)

Immunosuppressive drugs	Before Diagnosis (Mean ± SD)	After Diagnosis (Mean ± SD)
Tacrolimus	3.32±2.47mg	2.28 ± 1.29 mg
Mycophenolate mofetil	1392.86 ± 212.91mg	660.71 ± 374.77mg
Prednisolone	5mg	5mg

was 1392.86 ± 212.91 mg and that of prednisolone was 5 mg (Table 2).

Development of BK Virus Nephropathy

BKVN was diagnosed after a mean period of 16.07±13.24 months [Range: 6-51 months] after transplant. Diagnosis was based on clinical suspicion in most (11 of the 15) cases whereas in 4 cases, it was diagnosed on protocol allograft biopsy. Proteinuria was seen in 2 cases.

Polymerase chain reaction (PCR) test was positive before biopsy in 3(20%) cases who subsequently underwent allograft biopsy while for 8 cases, PCR was done after biopsy with titer ranging from Negative (in one case with diagnosis of BKVN on protocol biopsy) to more than 5,000,000 copies . One patient had to be treated for rejection after the diagnosis of BKVN (after reduction in immunosuppressives). The average creatinine at diagnosis was 147.93 ± 40.88µMol/L.

Management

Following diagnosis, all of the patients underwent reduction in immunosuppressive drugs (Table 2). The new 24-hour-dose of tacrolimus was 2.28 ± 1.29 mg, mycophenolate mofetil was 660.71 ± 374.77mg while prednisolone dose was unchanged at 5 mg. So, on average, tacrolimus dose was reduced by 31.32%, that of mycophenolate was reduced by 52.56% while prednisolone was unchanged. Mean tacrolimus trough level of 3 consecutive follow up after reduction was 5.19 ± 1.20 (3.16-7.50). Regarding MMF , initially the dose of the drug was reduced by 1/3rd and on follow up if there were signs of clinical deterioration, it was completely withheld and re-introduced only if the titer of BK virus PCR was negative or if there were concerns of rejection.

One patient was treated with IVIG (300mg/kg every 3 weeks while 11 (73.3%) received fluoroquinolone (Ciprofloxacin 500mg once daily) antibiotic in addition to above.

Outcome and Graft loss:

Average creatinine after 1 year of diagnosis was 164.43 ± 101.03µMol/L .There was, in average, 10% increase in creatinine at 1 year after the diagnosis of BKVN. Of the 15 patients, 1 patient required maintenance hemodialysis 3 years after diagnosis. She was a case of neurogenic bladder with history of recurrent urinary tract infection. Her creatinine at diagnosis was 208µMol/L which increased to 429µMol/L 1 year after diagnosis. Her average tacrolimus level prior to diagnosis was 8.13ng/ml which was reduced and was 6.1ng/ml and her MMF was withheld. She was receiving fluoroquinolone for recurrent UTI which was continued. She didn't receive adjunctive treatment and follow up BKPyV titer was not done due to financial constrain. Due to uremic symptoms, she was initiated on hemodialysis.

DISCUSSION

In this single center study, we had 847 renal allograft recipients who received living-donor kidney over a period of 16 years. Of them, 15 (1.77%) had biopsy proven BKVN. In a study by Gras J., et. al. aimed at identifying risk factors for biopsy proven BKVN among transplant recipients, of the 1737 patients, there were 64 cases i.e. prevalence of 3.7%. Other studies show a prevalence of 5-6%.[12,13] The prevalence of BKVN is lower by comparison in our population . This could be because of virtual absence of deceased donor kidney transplant in our population as prevalence of BKVN in studies conducted among living-donor transplant cases has been reported to be much lower (1.49%) in observational studies conducted in our neighbouring country, India.[14] Similarly, better matching of the donor and recipient with mother and wives being the most common donor and only 8 cases of deceased donor kidney transplant as reported in a study by Shah DS, et al might be the cause for this lower prevalence[15]

The mean age of the patients was 42±11.53 years (Median: 40 years) and there was male predominance with 13(86.7%). In some studies, the median age of patients was 50 years but it has been reported at any age; even in pediatric population[16] and this result is reflection of the usual transplant population in our setting as seen in the study by Shah DS, et.al who reported 79% of the transplant recipients being male.[15]

Of the 15 patients, 5 (33.33%) had diabetes. In the core of development of BKVN is the presence of

immune impairment which may be independently seen in diabetes and this has to be considered significant as prevalence of diabetes in post-transplant patient has been reported to be around 20% [17] suggesting a higher prevalence of diabetes in patients with BKVN . Given the different nature of this study, head to head comparison, however, cannot be made.

Most of the donor were females with average age of 44.27±8.39 years at donation . The average HLA mismatch was 3/6. In studies, it has been noted that while specific HLA alleles might not be associated with BKVN, HLA mismatching has significant association with BKVN [18]

The average time of diagnosis of BKVN after transplant was 16.07±13.24 months [Median: 9 months; Range: 6-51 months] of which 20% had positive DNA PCR test before the biopsy was done. In the study by Gras J., et. al., the median time to diagnosis of 11 (5-14.5) months[19]. BKVN usually occurs after a period of sustained progressively worsening viremia with majority presenting within the first year and highest incidence in the first 2-6 months[20]. This was different in our population as only 53% of the cases had BKVN diagnosis within a year after transplantation while the rest had their diagnosis after 1 year . This difference could be because of the lack of routine search for the cases earlier because of the relatively costly tests leading to time delay in diagnosis.

The average creatinine was 147.93 ± 40.88µMol/L which increased by 10% to 164.43 ± 101.03µMol/L one year after diagnosis of BKVN . As BKVN is usually asymptomatic and often times presents only as a gradual increase in serum creatinine with pathological picture of tubulointerstitial nephritis which can very well mimic rejection[21], this data is of significant value in our population.

Most of the patients received thymoglobulin as induction agent during transplantation. While individual induction agent has not been significantly associated with eventual development of BKVN, potent immunosuppressive has been well hypothesized to be a risk factor for development of BKVN.[4]

All of the patients were on 3 immunosuppressive regimens at the time of diagnosis consisting of tacrolimus, mycophenolate mofetil and prednisolone and had reduction in tacrolimus dose by 31.32%, and reduction of mycophenolate mofetil dose by 52.56% following diagnosis. While reduction in immunosuppressive medications was as per international guidelines, 73.3% received fluoroquinolone antibiotics. One patient had persistent and increasing viremia and worsening of renal function despite reduction in immunosuppressive medications, fluoroquinolone antibiotic and received IVIG as adjunctive therapy. Regarding fluoroquinolone antibiotics, studies have shown no significant effect on reducing the ill-effect of BKVN with fluoroquinolone antibiotics[22] and some studies even revealing increased incidence of drug resistant infections[23]. The lower incidence of graft loss in our population suggests exploring this further.

Regarding graft failure, 1 patient required maintenance hemodialysis 3 years after diagnosis. This was a case of neurogenic bladder with history of recurrent urinary tract infection. In a study by Gately R., et. al., graft loss occurred in 35% of the 460 cases of BKVN patients in the population of 14,697 transplant recipients[24]. Other studies reveal the prevalence of BKVN to be 1-10% with graft loss in approximately 50% of cases.[25]

CONCLUSION

BKVN is a known complication in kidney transplantation with potential for irreversible graft loss. In our population, the prevalence of BKVN has been seen to be lower (1.77%) with time to develop and diagnose BKVN being 16.07 months on average which is longer than seen in other studies. Reduction in immunosuppressives, in select cases, other adjunctive treatment including IVIG have used as mainstay of treatment for BKVN.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

This study was done with the supervision of Prof. Dr. Dibya Singh Shah, Head of Department and Prof. Dr. Mahesh Raj Sigdel who helped with the topic selection, literature review, critical analysis of the results as well as preparation of Manuscript.

Dr. Mandira Phuyal and Dr. Anand Mishra contributed to the data collection and analysis.

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