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Original Article

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BK Virus Nephropathy in Renal Transplantation: Case Series and Review of the Literature

İsmail Baloğlu[1], Kültigin Türkmen[1], Hacı Hasan Esen[2], Nedim Yılmaz Selçuk[1], Halil Zeki Tonbul[1]

[1]Division of Nephrology, Necmettin Erbakan University School of Medicine, Konya, Turkey
[2]Department of Pathology, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey

Abstract

Objective: BK virus nephropathy (BKVN) is an important cause of kidney transplant failure. In this study, we aimed to evaluate our center's experience with BKVN in patients who had undergone renal transplantation and also discussed important aspects of the disease in this patient population.
Materials and Methods: In this study, 8 patients with BKVN were evaluated retrospectively, having been selected from a group of 330 patients (178 females, 152 males; mean age: 48.37±13.25 years) who had undergone renal transplantation between 2007 and 2017 and were followed up at our center.
Results: BKVN was detected in 8 of 330 renal transplantation patients (4 females, 4 males; mean age: 51.25±11.14 years). Their immunosuppressive regimen consisted of tacrolimus (FK), mycophenolate mofetil (MMF), and methylprednisolone. To reduce immunosuppressive dose, FK was discontinued in 3 patients, and they were switched to everolimus. In 2 of 7 patients, MMF was discontinued, and they were switched to azathioprine. FK or MMF doses were reduced in the8 patients with BKVN. Out of the 8 patients, cidofovir was administered to 1 patient, whereas intravenous immunoglobulins were administered to 3 patients. Additionally, pulse steroid treatment was administered to 1 patient who was diagnosed with acute rejection based on allograft biopsy findings. Among the 8 patients with BKVN, 1 (12.5%) experienced graft loss and was returned to hemodialysis treatment.
Conclusion: Although new alternative treatments are available, immunosuppressive dose reduction is still considered the most effective treatment. Therefore, we believe that effective screening and preemptive strategies should be defined more clearly instead of focusing on treatment strategies.
Keywords: Renal transplantation, BK virus, BK virus nephropathy

Corresponding Author: İsmail Baloğlu ✉ i_baloglu@hotmail.com
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INTRODUCTION

In organ transplant recipients, viral infections have become more important and prevalent due to iatrogenic immunosuppression. One of the causes of such viral infections is the BK virus, which was isolated in 1971 by Gardner et al. (1) from the urine of a patient with a ureteral stricture. BK virus (Polyomahominis 1) is a non-enveloped DNA virus belonging to the papovavirus family (2). Primary infections typically occur without specific signs or symptoms in approximately 60%-90% of the population. The virus persists in the urinary tract epithelium and may get reactivated under immunosuppressive conditions (3, 4).

Although BK virus nephropathy (BKVN) rarely occurs in renal allograft recipients after kidney transplantation, when it does occur, it causes various complications, such as ureteric stenosis, transient renal function deterioration, widespread viral nephropathy, and irreversible graft failure (5, 6). In addition, the prevalence of BKVN, which

is a major cause of graft loss, is between 1% and 10% in renal transplant recipients (3, 7). Although multiple factors related to the patient, graft, or extreme immunosuppression are implicated in BKVN, the factors that are truly responsible are not well known (8, 9). At the same time, although not an established protocol for treatment, reducing the dose of immunosuppressive drugs and facilitating the administration of immunoglobulins and various antiviral drugs are the usual methods of therapy (10).

In the present study, we aimed to investigate the incidence of BKVN in our center and to evaluate the diagnostic and therapeutic methods for BKVN in the light of current literature.

MATERIALS AND METHODS

The study protocol was approved by the Medical Ethics Committee of the Necmettin Erbakan University (School of Medicine, Konya, Turkey). Written informed consent was obtained from all subjects included in the study. This was a cross-sectional study comprising 330 patients (178 females, 152 males; mean age: 48.37±13.25 years) who underwent renal transplantation between January 2007 and December 2017 and followed up at our center. A review of medical records (including information on age, sex, transplantation dates, posttransplantation follow-up duration, time to BKVN diagnosis after transplantation, time between BKVN diagnosis and the last visit to transplantation outpatient clinic, immunosuppressive treatment regimens during and after BKVN, and serum creatinine levels at BKVN diagnosis and at the last visit) of BKVN patients was performed.

Screening for BKVN was performed using polymerase chain reaction (PCR) for BK virus DNA in the blood. The final diagnosis was established by detecting characteristic cytopathic changes associated with BK virus on renal biopsy and performing an immunohistopathological examination (11).

Statistical Analysis

Clinical and experimental data were analyzed using The Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 software (IBM Corp.; Armonk, NY, USA). Descriptive statistics for each variable were determined. Data were expressed as mean±standard deviation.

RESULTS

The evaluated patients had received renal transplantation from 40% of live donors and 60% of cadaveric donors. Their immunosuppressive regimen consisted of tacrolimus (FK), mycophenolatemofetil (MMF), and methylprednisolone (PRD).

BKVN was detected in 8 of the 330 renal transplantation patients (4 females, 4 males; mean age: 51.25±11.14 years). Thus, the incidence of BKVN was 2.4% in our center. Patients had received renal transplantation from living (2 patients) and cadaveric (6 patients) donors. Their mean follow-up duration was 58±13 months, and the mean time to BKVN diagnosis after transplantation was 25±20 months. The mean creatinine level at diagnosis was 1.68±0.35 mg/dL. The clinical and laboratory characteristics of the patients are shown in Table 1.

PCR was used to screen for the presence of BK virus DNA in the patients' blood. BKVN diagnosis was confirmed on the basis of the results of transplanted kidney biopsies that were all performed at our center. In addition, while acute rejection findings were observed in 1 patient's biopsy results, suspicious rejection findings were observed in 2 patients' biopsy results.

After the diagnosis of BKVN, to reduce the immunosuppressive dose, FK was discontinued in 3 patients, and they were switched to everolimus. In 2 of 7 patients, MMF was discontin-

Table 1. Clinical and laboratory characteristics of BKVN patients

Patient	Age	Sex	Donor type	Induction regimens for Tx	Immunosuppressive regimens before BKVN	Creatinin levels at BKVN diagnosis (mg/dL)	Post-transplantation follow-up duration (month)	Tx-BKVN Duration (month)
1	62	Female	Cadaveric	Basiliximab	FK+MMF+PRD	1.35	33	7
2	62	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.29	76	28
3	32	Female	Living	ATG	FK+MMF+PRD	2.10	71	35
4	45	Male	Living	ATG	FK+MMF+PRD	1.43	15	4
5	62	Female	Cadaveric	Basiliximab	FK+MMF+PRD	2.29	54	22
6	54	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.78	121	68
7	41	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.54	84	29
8	52	Female	Cadaveric	ATG	FK+MMF+PRD	1.72	13	10

FK: tacrolimus; MMF: mycophenolate mofetil; PRD: methylprednisolone; BKVN: BK virus-associated nephropathy

Table 2. Clinical outcomes of patients with BKVN

Patient	Post-BKVN follow-up Duration (month)	BKV-DNA levels at BKVN diagnosis (copy/mL)	BKV-DNA levels at lastevaluation (copy/mL)	Creatinin levels at BKVN diagnosis (mg/dL)	Creatinin levels at last evaluation (mg/dL)	Immunosuppressive regimens after BKVN	Additional treatment for BKVN
1	26	28760	0	1.35	1.02	Everolimus+ MMF + PRD	
2	48	11360	110	1.29	1.34	FK + MMF + PRD	
3	36	720	0	2.10	1.48	FK + MMF + PRD	
4	11	23400	993	1.43	2.56	Everolimus + Azathio-prine + PRD	Cidofovir + IVIg
5	15	8910	HD	2.29	HD	Everolimus + MMF + PRD	IVIg + Pulse PRD
6	53	3680	0	1.78	1.63	FK + MMF + PRD	
7	55	456	0	1.54	1.42	FK + MMF + PRD	
8	3	2957114	1819	1.72	1.43	FK + Azathioprine	IVIg

BKVN: BK virus-associated nephropathy

Table 3. Clinical outcomes of patients with BKVN

Patient	Post-BKVN follow-up Duration (month)	BKV-DNA levels at BKVN diagnosis (copy/mL)	BKV-DNA at last levels evaluation (copy/mL)	Creatinin levels at BKVN diagnosis (mg/dL)	Creatinin levels at last evaluation (mg/dL)	Treatment for BKVN
1	26	28760	0	1.35	1.02	RID
2	48	11360	110	1.29	1.34	RID
3	36	720	0	2.10	1.48	RID
4	11	23400	993	1.43	2.56	RID+Cidofovir + IVIg
5	15	8910	HD	2.29	HD	RID+IVIg+pulsePRD
6	53	3680	0	1.78	1.63	RID
7	55	456	0	1.54	1.42	RID
8	3	2957114	1819	1.72	1.43	RID+IVIg

BKVN: BK virus-associated nephropathy

ued, and they were switched to azathioprine. FK or MMF doses were reduced in all the 8 patients. Of these 8 patients, cidofovir was administered to 1 patient, whereas intravenous immunoglobuline (IVIgs) were administered to 3 patients. Additionally, pulse steroid treatment was administered to 1 patient who was diagnosed with acute rejection based on allograft biopsy results (Table 2).

Patients were followedup for BKVN manifestations for a mean duration of 30±20 months (3-55 months). Among the 8 patients with BKVN, 1 (12.5%) experienced graft loss and was returned to hemodialysis treatment. The finalmean creatinine level in the other 7 patients was 1.66±0.48 mg/dL. In the evaluation of the last PCR performed for the 7 patients, the mean BK virus DNA load was 417±717 copy/mL (0-1819 copy/mL) (Table 3). A control biopsy was performed in a patient with increased creatinine levels, and it was observed that the viral cytopathic effect persisted despite the decrease in the plasma BK virus DNA load (Figure 1).

DISCUSSION

Our study results showed numerous major findings regarding BKVN. First, the incidence of BKVN in our center was 2.4%. Second, a reduction in immunesuppressive dose was sufficient to treat BKVN in most patients. Third, the viral cytopathic effect can persist despite a decrease in the plasma BK virus DNA load. Fourth, we concluded that effective screening and preemptive strategies for BKVN need to be identified.

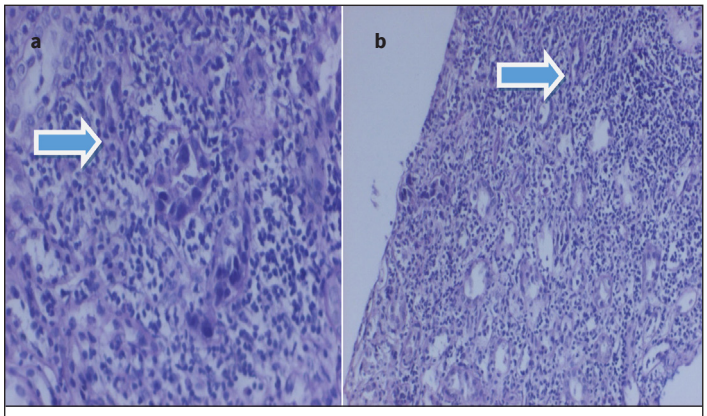

Figure 1. a, b. a) Image of BKVN in transplanted kidney biopsy at diagnosis time. b) The viral cytopathic effect was found to be continued at the control biopsy.

Recently, there has been a cumulative increase in the incidence of BKVN in renal transplant recipients. The etiology of this increase probably involves the interaction of multiple risk factors, including immunosuppression, patient determinants, the transplanted organ, and the virus itself. The incidence of BKVN in transplantation centers worldwide is between 2% and 9.3% (12-14), and the incidence (2.4%) observed in our center was consistent with that reported previously. Although an increase in the incidence of BKVN has been reported, there is no optimal method for diagnosis and screening of the same (15). BK viremia is usually detected within the first 3-4 months of transplantation. Therefore, based on the available literature, the suggested reasonable approach is that all transplantation patients be screened monthly for the first 6months. In addition, screening should be performed whenever kidney allograft dysfunction occurs (16). BKVN diagnosis can be presumed by observing an increase in the plasma BK virus DNA load or by the characteristic histological findings observed on renal biopsy.

BKVN is a major cause of graft loss in transplant recipients (15). Overall, the incidence of allograft failure ranges from 15% to 50% in the affected individuals (4, 17, 18). In 2006, Wadei et al. (19) analyzed data from 55 patients with biopsy-proven polyomavirus-associated nephropathy and found the frequency of graft loss to be 15%. Similarly, Ramos et al. (8) found the frequency of graft loss to be 16.4%. In our center, the rate of graft loss among patients with BKVN was 12.5%. Male gender, advanced age, HLA incompatibility, and early graft rejection have been reported as major risk factors for the development of BKVN (20, 21). However, female to male patient ratio was equal in our subjects, none of whom were of advanced age. Additionally, early rejection and HLA incompatibility were not detected in any patient. Concurrent acute rejection associated with BKVN is a common problem (22). On the other hand, it is well known that pulse steroid treatment for acute rejection increases the risk for BKVN, whereas reducing immunosuppressive dose to treat BKVN increases the risk for acute rejection (23). In our center, only 1 patient—in whom concurrent BKVN and acute rejection were confirmed via biopsy—was administered pulse PRD and IVIg treatment, followed by immunosuppressive dose reduction. However, graft loss occurred in this patient despite treatment, and he was returned to hemodialysis support.

Intense immunosuppression is perceived as a major risk factor for BKVN (24, 25). In recent years, a majority of patients with renal transplantation have been receiving a combination of FK and MMF. The prevalence of BKVN has increased after the use of these powerful immunosuppressant drugs (24). A prospective study conducted by Brennan et al. (26) has demonstrated that the use of FK-MMF-corticosteroid combinations is associated with an increased risk of BK virus replication and thus BKVN. In 2003, Mengel et al. (14) reported that there is a 13-fold greater risk of BKVN development in patients receiving a FK+MMF+PRD regimen. Therefore, the most common approach in BKVN treatment is reducing immunosuppression (27). Similarly, in our center, in accordance with previous data, all the patients with BKVN were receiving a FK+MMF+PRD regimen at the time of BKVN diagnosis. We also reduced the immunosuppressive doses of all patients with BKVN. However, it should be noticed that BKVN has been observed in patients exposed to drugs other than FK or MMF (28). Hence, no specific immunosuppressive drug can be exclusively associated with BKVN.

Cidofovir is a nucleotide analog that has recently been shown to be beneficial in the treatment of BKVN (10, 29). However, the underlying mechanism of inhibition of BKV replication by cidofovir is uncertain because the primary target for cidofovir inhibition is viral DNA polymerase, whereas BK virus does not specifically encode DNA polymerase (30). In addition, this agent is potentially highly nephrotoxic, causing proteinuria and renal failure (31). We used cidofovir (0.5 mg/kg, once in 2 weeks) in one patient at our center, in addition to immunosuppressive dose reduction and IVIg treatment. However, because of the increase in creatinine levels in this patient, the drug was discontinued.

Ig therapy is used as an alternative treatment for BKVN because it comprises BKV-neutralizing antibodies against all major genotypes (32). On the other hand, a study has shown that these antibodies may not exert neutralizing effects (33). Hence, immunoglobulin treatment may be a valuable option for treating BKVN, particularly in cases with both BK infection and graft rejection (34). We used IVIg treatment in 3patients with acute or concurrent suspicious rejection findings. A decline in the plasma BK virus DNA load was detected in 2 patients. However, a decline in creatinine levels was observed in only one patient.

Leflunomide is another treatment option that exerts both immunosuppressive and antiviral effects (35). Although its mechanism of action against BK virus is unknown, improvement or stabilization of the condition has been observed in patients with BKVN in a previous case series (36). However, the availability of limited number of studies and the potential for hematologic and hepatic toxicity preclude the routine use of leflunomide for the treatment of BKVN.

Comoli et al. (37) have shown that CD-3T cells play a critical role in the initiation and progression of BKVN. In another study, Comoli et al. (38) have reported that both CD8 and CD4T cells are involved in the recognition and elimination of BK virus (39, 40). It has also been verified that CD4T cells exhibit a specific multifunctional antiviral activity in BK virus infections (41, 42). The virion protein 1 of BKV stimulates the CD-4T-cells via the major histocompatibility complexI (43). CD-4T-cells may control BKV infection via the secretion of tumor necrosis factor-alpha, interferon-γ, and interleukin-2 (44). In patients with BKVN, the number of CD-4T-cells in the transplanted kidney also increase. Taking these reports into consideration, we speculate that Tlymphocyte-mediated immune responses can play an important role in the pathogenesis of BKVN.

In recent years, a study has shown that the percentage of Blymphocytes in kidneys transplanted to patients with BKVN is significantly increased (45). In addition, in another study, it was also found that BKVN progression is significantly associated with an increase in CD-20 cells and plasma cells (CD138-positive) (46). Therefore, humoral immunity was thought to be related to the pathogenesis of BKVN, but the exact immunopathological mechanisms remain uncertain. Part of the virus may increase the production of B-cell activating factor, thereby increasing the Blymphocyte count, which may in turn activate the Nuclear Factor kappa B (NF-κB) signaling pathway after the initiation of infection (47). However, whether BKV causes damage to the allograft via this mechanism has not been proven. Our study has some limitations. First, all the patients enrolled in the study were of Turkish ethnicity. Second, our study had a single-center design and a relatively small sample size.

CONCLUSION

Immunosuppressive dose reduction is still considered to be the most important treatment for BKVN. In addition, the viral cytopathic effect can persist independent of the plasma BK virus DNA load. Therefore, BKVN should be closely monitored, and effective screening and preemptive strategies should be defined for it in future studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Necmettin Erbakan University (School of Medicine, Konya, Turkey).

Informed Consent: Written informed consent was obtained from the patients who were included in this study.

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