Early Diagnosis of BK Virus Infection and Kidney Allograft Prognosis

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Abstract

Delayed diagnosis of BK virus replication involves long-term graft prognosis. Early diagnosis allows an early treatment approach in order to avoid the development of BK nephropathy. There are still doubts about the best diagnostic methods and treatment strategies.

Aims: Prevalence analysis of BK virus infection, diagnostic test employed and treatment strategies in a series of renal transplants. We also analyze the factors associated to BK virus infection.

Methods: Prospective analysis of 117 renal transplants performed between January 2009 and December 2011 in our Unit. Periodic urinary cytologies were made to diagnose the presence of decoy cells from the first month, every three months during the first year, every six months during the second year, and annually until the fifth year. If decoy cells were detected, serum and urine polymerase chain reaction of BK virus were performed. Biopsy was performed in six patients (if viremia > 10,000 copies/ml and/or graft function deterioration).

Results: Decoy cells were presented in 32 (27.2%) patients. Thirteen patients presented with viremia and viruria. In cases of positive polymerase chain reaction, mycophenolate was reduced or suppressed and calcineurin inhibitor dose was reduced. Biopsy was performed in six patients and BK virus nephropathy was found in five patients. In three patients, treatment with cidofovir and/or leflunomide was used.

After a follow-up of one year, only two patients maintained viruria and viremia and one of these failed as a consequence of BK virus nephropathy.

Conclusions: An early diagnosis of BK virus replication and consequent changes in immunosuppression are useful to prevent the development of BK virus nephropathy and improve graft prognosis. (Trends in Transplant. 2013;7:70-3)

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Key words

Introduction

In the past decade, following the introduction of more powerful immunosuppressive drugs, polyomavirus-associated nephropathy (PVAN) has become an important cause of posttransplant renal failure. This problem was probably misdiagnosed in the past, leading to graft failure. PVAN occurs in 1-10% of renal allograft recipients, causing graft loss in 50-100% in the case of a late diagnosis.

The BK virus (BKV) is a polyomavirus, highly prevalent (> 85%) in the general population. Primary infection occurs during childhood and usually remains asymptomatic or with unspecified clinical features; BKV remains latent in tubular epithelial cells of the urogenital tract. Symptomatic BKV reactivation is uncommon in immunocompetent populations; however, immunosuppression favours BKV replication. BKV viruria develops from lysis of tubule cells and leakage of virus into the lumen. Damage to the urogenital basement membrane occurs with high levels of BKV viruria, which allows vascular spread and development of BKV viremia. Prolonged BKV viremia may result in PVAN.

BKV infection can be detected by viral serology, urine cytology, and nucleic acid testing methods such as quantitative real time polymerase chain reaction (PCR) assay in urine or serum samples. Allograft histology is needed for PVAN diagnosis, consisting in the presence of cytopathic changes characterized by basophilic nuclear viral inclusion in epithelial cells (tubular, Bowman's capsular), accompanied by inflammatory cell infiltrates. The inflammatory injury is similar to that found in acute rejection episodes. The immunohistochemical stain for SV40 LT-ag can identify polyomavirus and exclude acute cell-mediated rejection.

A histological grading system has been proposed that considers three patterns: pattern A, which shows cytopathic changes and no or mild tubular atrophy and interstitial fibrosis (IFTA) and inflammation; pattern B, which is a combination of cytopathic changes plus areas of focal or multifocal IFTA and inflammation (B1, B2, B3); and pattern C, characterized by only a few cytopathic changes and severe IFTA and inflammation associated to irreversible damage. Considering the relevant consequences of BKV replication, general screening for BKV infection has been recommended in kidney transplant recipients, although different protocols for BKV diagnosis have been described.

The aim of this study was to analyze the prevalence of BKV infection in a series of kidney transplant patients. We describe the diagnostic protocol and treatment strategies employed, as well as graft outcome and factors related to BKV replication.

Methods

We undertook a prospective analysis of 117 consecutive renal transplants performed in our Unit from January 2009 to December 2011.

We designed a screening protocol for BKV infection, based on urinary cytology to diagnose the presence of decoy cells. Urinary cytology was determined at the first month, every three months during the first year, then every six months during the second year, and annually until the fifth year posttransplantation. If decoy cells were detected in a single sample, a PCR BKV in serum and urine samples was performed. A renal biopsy was made if BKV viremia was higher than 10,000 copies/ml and in case of renal dysfunction.

After BKV replication was diagnosed, we reduced the immunosuppression treatment and monitored PCR in serum and urine every
three months until one year post-diagnosis. We used adjuvant therapy in case of PVAN with no improvement of renal function.

Results

The mean follow-up of the series was 32.05 ± 10.62 months (range, 14-50.2). The mean donor age was 51.08 ± 21.46 (range, 1-79), and the mean recipient age was 52.26 ± 12.83 (range, 19-78); 65% of patients were male and 10.7% were human leukocyte antigen (HLA) pre-sensitized. All of them received tacrolimus as calcineurin inhibitor and we used reduced doses of polyclonal antibodies as induction in 61.2%.

Cytology was performed in the 117 patients, and decoy cells were detected in 32 (27.2%) patients; PCR was obtained in these 32 patients: 13 showed viremia and viruria, three only viruria, and in 16 patients PCR was negative. Median time of BKV detection by PCR was four months.

Biopsy was performed in six patients and PVAN was diagnosed in five of them. The PVAN-B2 pattern was present in four cases, and PVAN-A pattern in one patient.

In case of positivity of BKV PCR, immunosuppression was minimized. We switched the objective level of tacrolimus from 6-8 to 4-6 ng/ml, and mycophenolate was reduced in four patients and suppressed in 10 patients. No acute rejection episodes were diagnosed after immunosuppression reduction.

We used adjuvant therapy in three cases: cidofovir was used in two patients and cidofovir plus leflunomide in one patient.

After one year follow-up, only two patients maintained viruria and viremia and only in one of them the graft failed as a consequence of PVAN.

Older donor age (p = 0.05) and recipient age (p = 0.01) were related to BKV infection. Other variables such as treatment with polyclonal antibodies, donor and recipient gender, and HLA mismatching showed no differences.

Discussion

In the present study, we showed the importance of early diagnosis of BKV infection. It is currently known that early identification of patients with BKV infection is the key to avoiding the development of PVAN1-3.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for BKV detection suggested monthly screening using nucleic acid testing for the first 3-6 months, and every three months until the end of the first year7. We decided to begin screening for BKV infection using urinary cytology, a routine test at our hospital, which is less expensive than PCR. However, urinary cytology has a lower positive predictive value and less sensitivity than BKV PCR8 so we decided to confirm the diagnosis using BKV PCR. Other groups that used similar protocols waited for two or more positive cytologies before making BKV PCR9.

In our series, viral reactivation was higher during the first six months. It has been described that BKV plasma load increases in the first 3-6 months after transplantation, as it happened in our patients, with a decrease after the first year posttransplantation1-3,10. This replication course has been associated with the stronger immunosuppressive therapy during the first months posttransplantation1-3,5,10. It has been described that the intensity of the immunosuppression is the main risk factor for BKV replication, more than the type of immunosuppressive drugs3. Moreover, other factors related to donor and recipient could contribute to BKV replication, such as the use of polyclonal antibodies, male receptor, HLA
pre-sensitized or HLA mismatches\(^1\). In our study, only the donor and recipient age were associated with BKV replication.

In this scenario, the reduction of immunosuppression can be a difficult task, considering that the higher prevalence of viral replication occurred during the first months posttransplantation when there is a higher risk of development of acute rejection episodes. Moreover, we must take into account that some of these patients are HLA sensitized, as in three cases of our series.

In our study, in all the cases of positive BKV PCR, immunosuppression was minimized, reducing tacrolimus dose, to obtain lower levels, and reducing or suppressing mycophenolate. A strict vigilance of renal function and HLA antibodies was maintained during the follow-up and no acute rejection episodes were diagnosed.

In respect to the efficacy of the adjuvant therapy, cidofovir with or without leflunomide was used in three patients who did not show a reduction of viral load or where a lack of improvement of renal function was observed. One patient presented the negativization of BKV viremia after one year of follow-up, the other two patients had no changes, and one of them lost his graft because of PVAN. Therefore, we share the doubts suggested by other authors about the efficacy of these antiviral agents\(^1,3\), mainly because they are used in patients that received a minimized immunosuppressive regimen. In addition, the data regarding its efficacy in prospective, randomized, controlled comparative studies are scarce\(^1,3\).

After one year of follow-up, only two patients maintained viruria and viremia and in the rest of cases viremia was negative. These good results make us consider the potential benefits of the early detection of BKV replication on graft prognosis.

In conclusion, our data show that an early diagnosis of BKV replication by an easy screening protocol has been useful to diagnose this entity. It allowed us to prevent a greater damage due to BKV on the graft and consequently improve its prognosis.

References