Effect of Transient BK Viremia and Viruria on Long-term Renal Allograft Survival and Function

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ABSTRACT

Introduction. The purpose of this study is to present the five-year survival and function of the renal allograft of recipients who were diagnosed with BK viremia and viruria during the first year after renal transplantation.

Patients and Methods. BK virus was studied in 32 new renal allograft recipients, from the first postoperative day until 18 months after the transplantation. Real-time polymerase chain reaction was used to detect and quantitate BK viral load in serum and urine samples.

Results. Qualitative analysis with PCR for the DNA of BK virus showed 31 (31/228, 14%) positive serum samples originating from 20 (20/32, 62%) renal allograft recipients and 57 (57/228, 25%) positive urine samples originating from 23 (23/32, 72%) recipients. During the follow up period of 5 years, renal allograft function remained stable (eGFR 18th month: 53.9 $\pm$ 23.9 mL/min/1.73 m^2 and eGFR 5th year: 52.6 $\pm$ 20.6 mL/min/1.73 m^2). Comparison of recipients that presented with either BK viremia or viruria with a group that did not present viral reactivation did not reveal a statistically significant difference in eGFR. Furthermore, recipients with significantly high viral load in serum or urine did not present renal allograft dysfunction.

Conclusion. BK virus is potentially pathogenic in renal allograft recipients. It is certain that there is a reactivation of the virus in a high percentage of transplanted patients mostly in the first year after the surgery, without however a negative effect of the transient viremia and viruria in renal allograft function.

BKV belongs to the family of Polyomaviridae and it is present in human populations worldwide. It infects young children and 70%–90% of the adults are found seropositive [1]. In renal transplant recipients, BKV reactivation occurs in tubular epithelial cells of the donor kidney which is then amplified in the urothelial cell layer. Progression of BKV infection to polyomavirus associated nephropathy (PyVAN) leads to graft loss in up to 60% of affected patients. Viremia is believed to be a precursor to PyVAN with BK viremia preceding nephropathy by 1 to 12 weeks [2]. The onset of PyVAN occurs at a mean period of 9 to 12 months after transplantation; however, some cases have been reported as early as 7 days after transplantation. There has been a notable rise in the incidence of BK virus among kidney transplant recipients in recent years. Therefore, it is recommended to periodically assess urine and/or serum samples for BK virus activation by cytology and/or molecular biology especially during the first year after the transplantation [3]. The purpose of this study is to present the five-year renal allograft survival and function of recipients who were diagnosed with BK viremia and viruria during the first year after renal transplantation.

PATIENTS AND METHODS

BK virus was studied in 32 patients over 18 years old that underwent successful kidney transplantation in the Transplant Unit of Evangelismos General Hospital of Athens from the first postoperative day until 18 months after the transplantation. The study did not

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include patients seropositive for Hepatitis B (HBV), C (HCV) or ή HIV positive patients. Informed consent was obtained from all patients prior to their participation to the study. Renal transplant recipients were followed for a period of 5 years post-renal transplantation.

Real-time polymerase chain reaction (PCR) was used to detect the BK virus and quantify the viral load in serum and urine samples. The samples were collected on the first day after the transplantation that the patient restored diuresis and on the 1st, 3rd, 6th, 9th, 12th, 15th and 18th month thereafter. Estimated glomerular filtration rate (eGFR, MDRD 4 variables) was used for monitoring renal allograft function. Presumptive polyomavirus BK-associated nephropathy (PyVAN) was defined as BK viral load in plasma above 10000 copies/mL or BK viral load in urine above 10^7 copies/mL.

All recipients received induction therapy with monoclonal antibody against receptor of interleukin-2 before surgery and triple maintenance immunosuppression regimen including calcineurin inhibitor (cyclosporine, N:19 or tacrolimus, N:13), mycophenolate mofetil (2 g/day for patients treated with cyclosporine and 1 g/day for patients treated with tacrolimus) and corticosteroids (500 mg of methylprednisolone (MP) intravenously (IV) during reperfusion, 250 mg MP IV the first postoperative tapered to 20 mg prednisolone per os (po) by day 5 and further slow tapering to 5 mg prednisolone po by the third month).

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD). Student's t-test or paired t-test was applied for continuous variables. A standard level of P below .05 indicated statistical significance.

RESULTS

Tabulated demographic characteristics are presented in Table 1 and in more detail elsewhere along with results of BK viruria and viremia [4]. Briefly, qualitative analysis with PCR for BK virus showed 31 (31/228, 13.6%) positive serum samples originating from 20 (20/32, 62%) renal allograft recipients (20/32, 62.5%) and 57 (57/228, 25%) positive urine samples originating from 23 recipients (23/32, 71.9%). Quantification of positive samples in serum and urine showed a wide variation of the viral load. In three serum samples from equal number of recipients BK viral load was more than 10000 copies/mL, while in seven urine samples from five patients viral load was measured more than 10^7 copies/mL.

Table 1. Demographic Characteristics

Donor Source (living:deceased donor)	8:24
Donor Age (years) median (range)	59 (24–73)
Donor Gender (male:female)	13:19
Recipient Age (years) median (range)	48.5 (22–76)
Recipient Gender (male:female)	23:9
Time on dialysis (months) median (range)	41.9 (1–101)
HLA mismatches (mean ± SD)	3.19 ± 0.99
Panel Reactive Antibodies	<5%
Cold ischemia time (deceased donors) hours (mean ± SD)	19.8 ± 4.3
Episodes of Biopsy Proven Acute Rejection	none
Cyclosporine C2 levels (mean ± SD)	795.7 ± 126.7
Tacrolimus C0 levels (mean ± SD)	8.1 ± 3.3

Abbreviations: HLA, Human Leukocyte Antigens; SD, standard deviation.

Renal Allograft and Recipient Survival

From a total of 32 transplanted patients studied during the first 5 years, four patients died due to cardiovascular events with a functioning renal allograft. Recipient survival rate was 87.5%. With regard to allograft survival, four patients developed chronic allograft dysfunction with biopsy proven chronic allograft nephropathy (two cases) and interstitial fibrosis and tubular atrophy (two cases), overall renal allograft survival rate 87.5% (excluding those who died with functional renal graft). Allograft failure was attributed to noncompliance to immunosuppressive therapy and probably calcineurin toxicity. No graft was lost due to PyVAN.

Renal Allograft Function Following Detection of BK Viremia and Viruria

In the study population, renal graft function remained stable during the five years of follow up (eGFR 18^{th} month: 53.9 ± 23.9 mL/min/1.73 m^2 and eGFR 5^{th} year: 52.6 ± 20.6 mL/min/1.73 m^2, $P = .788$). Subsequently renal transplant recipients were divided in two groups based on the presence of BK viremia or viruria (viral load >1000 copies/mL in serum or urine samples). Figure 1 shows sequential eGFR measurements based on identification of BK viremia and viruria. Comparative analysis did not reveal significant difference in eGFR between groups.

In more detail, six patients were identified with very high viral load in plasma or in urine that could have been diagnosed with "presumptive PyVAN." Presumptive PyVAN resolved after decreasing immunosuppression by reducing in half the dose of mycophenolate mofetil with complete clearance of BK virus both in plasma and urine. Renal function remained stable without any sign of allograft dysfunction during the period of five years follow up. Sequential eGFR for recipients with presumptive PyVAN the first, third and fifth year post renal transplantation was 1.21 ± 0.13 mg/dL, 1.12 ± 0.42 mg/dL and 1.23 ± 0.23 mg/dL, respectively.

DISCUSSION

PyVAN shows a 3% to 10% prevalence among cases of kidney transplantation frequently resulting in permanent renal dysfunction or allograft loss. Noninvasive diagnosis of PyVAN relies upon screening for decoy cells in urine, which are epithelial cells with enlarged nuclei and large basophilic ground-glass intranuclear viral inclusions that is a simple and an inexpensive tool [5]. PCR based assays is perhaps the most commonly used assay in the clinic and BK DNA viral loads in urine or/and plasma are diagnostic of PyVAN. Some believe that BK viremia represents a significant tissue damage confirming the renal parenchymal involvement [6]. Plasma-PCR is found to be superior to urine-PCR or urine cytology in specificity and