

Running Head: Risk Factors of BK Virus in Kidney Transplant Recipients

Investigating Risk Factors for the Development of BK Virus Infection in Kidney Transplant Recipients in Guilan Province during 2007-2015

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Abstract

Purpose: Polyomavirus nephropathy has been recognized as an important cause of silent loss of kidney transplant function in up to 50% of kidney recipients⁽¹⁾. The present study aimed to evaluate the risk factors associated with BK virus infection in kidney transplant recipients.

Materials and Methods: Clinical information, urinary Decoy cells, and blood polymerase chain reaction (PCR) tests were collected for polyomavirus infection in 223 kidney transplant recipients undergoing surgery at Razi hospital at Guilan University of Medical Sciences between 2007 and 2015. Kidney biopsies were performed in patients with BKPyV- DNAemia more than 10,000 Copies/ml or increased plasma creatinine.

Results: Among 223 patients, 116 (52%) were male. The mean age of participants was 49.57 ± 13.48 years. Out of 223 participants, 41 (18.4%) had Decoy cells in their urine, and 182 (81.6%) did not, 15 of whom (6.7%) had viral genome in their blood. Only did 3 patients out of 10 have BK Virus nephropathy in their kidney biopsy. Among risk factors, it was found that post-transplant duration ($P < 0.001$) and the use of anti-thymocyte globulin ($P = 0.001$) were the most significant risk factors for finding decoy cells in patients' urine.

Conclusions: Post-transplant time, particularly the first 6 months, was found as the most important risk factor for the reactivation of polyomavirus infection in our patients because of strong immunosuppression and use of anti-thymocyte globulin (for prophylaxis or rejection treatment). It is concluded that kidney transplant recipients should be monitored in episodically after transplantation.

Introduction (2912 words)

BK Polyomavirus (BKPyV) is a non-enveloped double- stranded DNA virus that is a member of polyoma subgroup of papova viruses, which includes JC virus and SV40^(2, 3).

Infection with BK virus is common in the general population, with an estimate of seropositivity in adults by 80%-90%^(4, 5). After resolution of primary infection, BK virus remains latent in several locations throughout the body, most notably within the genitourinary system⁽⁶⁾. During immunosuppression, the virus may become reactivated and begin to replicate^(3, 7, 8).

After the introduction of potent immunosuppressive medications in the late 1990s, BK virus viremia was reported in up to half of renal allograft recipients in the first few months^(9, 10), but only 10%-15% of patients developed viremia

⁽⁶⁾. Progression of viremia is thought to be a prerequisite for the development of BK virus nephropathy (BKVN) ⁽⁵⁾; about 3%-5% of allografts were being lost due to BKVN ⁽¹¹⁾.

Transplant kidney biopsy remains the gold standard for diagnosing BKVN ⁽¹²⁾.

There is no definite treatment for BK virus (BKV) infection including: BKV nephropathy ^(11, 12).

Studies that look for risk factors responsible for BKVN have shown inconclusive results ⁽¹¹⁾. To identify risk factors for BKPyV, we examined the patients who received kidney transplants during 2007-2015.

Materials and Methods

Patients and sample size

This is a descriptive, retrospective, cross-sectional single center study. Among 250 adult kidney Transplant (Kidney TX) patients, 223 patients who have undergone surgery in the university hospital (Razi hospital, Guilan University of Medical Sciences, Rasht, Iran) since October 2007 to September 2015, have been enrolled in this study. All the patients provided written informed consent before study entry.

Study Design

The purpose of this study was to evaluate the impact of age, gender, blood group, body mass index (BMI), length of time of kidney TX, level of serum creatinine (sCr), and glomerular filtration rate (GFR) (measured by MDRD Equation) during detection of Decoy cells, length of time on Hemodialysis (HD) before kidney TX, etiology of end stage renal disease (ESRD), duration of having a stent after kidney transplant, type of immunosuppressive drugs used for induction and maintenance therapy, Hepatitis B and C, cytomegalovirus (CMV) infection association, diabetes mellitus (DM) involvement before kidney TX, rejection prophylaxis by methyl prednisolone (MP) pulse and anti-thymocyte globulin (ATG), maintenance immunosuppressive therapy by cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus, as the risk factors associated with the advent of polyomavirus infection in kidney TX recipients .

Procedures

All the patients received MP pulse (500-1000mg/ day, for 1-3days) and ATG (1mg kg/ day, for 7 days, cumulative dose:350- 400 mg) as induction therapy in operating room and after surgery.

Maintenance immunosuppressive drugs included prednisolone (5-7.5 mg/day with breakfast), cyclosporine (trough level 100-150ng/ml), tacrolimus (trough level 5-8 ng/ml), sirolimus (trough level 6-10ng/ ml), and mycophenolate mofetil (1000- 2000 mg/day before meal). All kidney transplant recipients received living-unrelated kidney donation.

Inclusion and Exclusion Criteria

Inclusion criteria were those who have done their kidney transplantation surgery in our center and those who have a GFR more than 20 ml/min. Also, those who have had a kidney TX for less than 3 months and those with graft loss due to other etiologies were excluded from the study.

Evaluation

Evaluation began with finding decoy cells (even one cell) in urine every month at first six months post-transplant and then every other months, [Urine cytology smears stained using Papanicolaou method were evaluated for the presence of cells with intranuclear viral inclusions (decoy cells, which were counted (number per 10 high-power fields)]. The viral load of BK- JC virus DNA RT- PCR (sensitivity for detection of BK-JC virus genome is 2 copy/ μ l) was measured in blood and urine in case of an increase in plasma creatinine level (>25% baseline) or if decoy cell was seen more than 2 times in the urine cytology. All lab tests were performed in one lab.

If the sCr were normal, the dose of immunosuppressive drugs would be reduced, and the patient would be followed regularly. However, if sCr were increased or if plasma BKV (BK Virus) DNA PCR exceeded more than 10,000 copies/ml respectively, whichever happens alone or together^(13, 14), a kidney TX biopsy would be considered. Due to high costs of both BK-JC virus DNA RT-PCR measurement and kidney biopsy, some patients did not accept to do such tests because their insurance did not cover the expenses.

Statistical Analysis

All collected data were analyzed via SPSS software version 18. According to the type of variables, descriptive statistics, mean, and standard deviation (SD) were used. Since distribution of BMI values based on Kolmogorov-Smirnova and Shapiro-Wilk tests in both kidney TX groups followed a normal distribution in terms of the status of decoy cells in the urine (positive or negative), therefore, the independent T- test was used to compare the mean of BMI in the two groups. Since the duration of the transplant variable and the values of GFR in both groups do not follow the normal distribution, therefore, the non- parametric U Mann Whitney test was used to compare the mean transplantation time. Parameters would be considered significant if P- value were < .005.

Results:

223 kidney TX adult recipients have undergone kidney TX surgery from October 2007 to September 2015. 116 recipients (52%) were male, and 107(48%) were female. The youngest and oldest recipient were 17 and 79-years-old. Decoy cells were found in 41(18.3%) recipients; 15 patients (6.7%) had viral genome in their blood. The mean post transplantation time was 7 months for those with the decoy cells in the urine and an average of 12 months for those without any decoy cells, showing a significant difference between the two groups using Mann Whitney U test ($P < .001$). There was no significant relationship between the age, sex, blood groups and etiology of ESRD with BKV infection in kidney TX recipients. Kolmogorov-Smirnova test for the distribution of BMI showed that in both groups of patients with or without decoy cells in urine [(26.45±4.02) (27.11±5.02) respectively], BMI followed the normal distribution. Comparing BMI in both groups of patients by Two Independent t test showed no meaningful differences between them. There was no significant relationship between rejection and initiation of dialysis in transplant patients with finding decoy cell in urine.

There was no significant statistical difference in the average and SD of Plasma creatinine (1.38±0.65 mg/dl), and GFR with (61.09±20.97 ml/min) or without (59.86±24.85 ml/min) decoy cells in urine.

Comparing dialysis duration before transplantation in patients with or without decoy cells in urine [(12.88±11.99months), (16.91±18.75months) respectively] by Mann-Whitney U test showed no significant differences. Fisher's Exact test showed no meaningful relationship between positive urine decoy cells and infection by hepatitis B and C, CMV infections and DM. Chi-square test showed no relationship between positive urine decoy cells and corticosteroid pulse induction (1 or 3 grams) during kidney TX. Fisher's-Exact test showed a meaningful relationship between positive urine decoy cells and thymoglobulin injection 95% CI: 1.88-22.79, OR = 6.55, $P = .001$, Table 1. There was no association between the type of immunosuppressive drug regimen (tacrolimus, cyclosporine, mycophenolate mofetil, and sirolimus) and positive decoy cells in urine (Fisher's Exact test $P = .337$) Table 1.

In almost all the patients, ureteral stent was removed after nearly one month, and no ureteral stricture was found. Although nearly all the recipients and donors were HLA mismatched, this was not statistically significant for emerging of decoy cells in urine. Recipients and donors were all negative for finding "Decoy Cells" in urine before kidney transplant. Urinalysis in the patients with decoy cells in their urine was interestingly normal.

Cold ischemic time was less than 1 hour. CMV serostatus in all donors and recipients were positive just for IgG.

Discussion

The human BK polyomavirus is associated with two significant complications in transplant recipients: polyoma virus associated nephropathy (PyVAN) in 1-10% of kidney transplant recipients and polyomavirus-associated hemorrhagic cystitis (PyVHC) in 5-15% of hematopoietic stem cell transplant (HSCT) patients⁽¹⁵⁻¹⁷⁾.

Although JC virus (JCV) inhabits in the uroepithelium⁽¹⁸⁾ and during the periods of immunosuppression may be reactivated⁽¹⁹⁾, it rarely causes nephropathy⁽²⁰⁾.

After kidney transplantation, the state of immunosuppression BKV replication starts and progresses through detectable stages: Viruria, viremia and then nephropathy⁽²¹⁾. In reviewing the articles for screening BKV infection after kidney transplantation, different methods for finding BKV are provided by articles, the choice of which depends on the policy of the kidney transplant department and economic issues. These tests vary from finding decoy cells in the urine (sensitivity 100%- specificity 45%.^(2,22), to measure the BK viral load in the urine and blood^{(10,11,12, (23, 24)}. However, measuring BK viral load has a higher value (sensitivity 100%- specificity 66-90%) depending on viral load more than 10,000 copies/ml in blood.^(22, 25). Accordingly, it is chosen to find decoy cells in urine as screening test in our study, because it is less expensive and insurance covers it. Figure 1 shows “decoy cell” taken in the lab. Among 223 participants in this study, 41 (18.3%) had decoy cells in their urine, 15 of whom (6.7%) had viral genome in their blood, virus Counts was more than 10^4 copies/ml.

Only 10 patients agreed to have a kidney biopsy, of whom only 3 reported BKV Nephropathy. Although a negative kidney biopsy due to focal nature of involvement cannot rule out BKVN with 100% certainty, according to literature, diagnosis may be missed in one third of biopsies⁽²⁾.

Vera in Spain showed positive PCR in 75% of urine and 33% in plasma of kidney TX patients⁽²⁶⁾. Study by Bohl showed viral genome in the urine of 44% of patients⁽²¹⁾.

In our study, the incidence of BKV in men and women was 5.2% and 10.3% respectively, in addition the incidence of JC virus in men was 10.3%, and in women was 6.5%, and the incidence of finding BK and JC virus together in urine in men and women was 1.7%, and 2.8% respectively. In our study, there was no statistically-significant relationship between sex, BK and JC virus.

In a retrospective study of 880 kidney transplant patients by Prince et al, male sex was reported as the main risk factor for the virus⁽²⁷⁾. This finding is in contrast to our finding due to the genetic.

In our study, the average age of patients was 49.57 ± 13.48 years. There was no relationship between age and decoy cells in urine of our patients. Nevo showed similar finding⁽²⁸⁾. Ramos found that age is associated with finding BK-

JC Virus in renal transplant recipients (P .003)⁽²⁹⁾. These differences are not statistically significant. Average sCr in our patients with decoy cells in their urine was 1.38 ± 0.65 mg/dl, no significant increases were found in plasma creatinine. In our study, the incidence of CMV (IgG positive and IgM negative) was 97.6 % in those patients with decoy cells in their urine, but it was 6% in patients without decoy cells in their urine. In a study by Theodoropoulos in 2012, the incidence of CMV in BK virus negative patients was 8.5%, but in those with viruria, viremia, and those with BKVN, it was 12.4, 21.3, and 32.3%, respectively⁽³⁰⁾. These differences in findings may be related to the level of immunosuppression, type of immunosuppressive drugs, and race.

In our study, the average BMI was 26.4 ± 4 in patients with positive urine decoy cells and 27.1 ± 5 in those with negative urine decoy cells. This calculation showed no statistically meaningful relations between BMI and urine decoy cells. In some studies, BMI was considered as a risk factor. Perez showed that BMI more than 25 must be considered as a risk factor⁽³¹⁾. Obesity may predispose to infection through creation of a pro-inflammatory state with blunting of the immune response at both the humoral and cellular levels, as well as generalized tissue hypoperfusion leading to decreased tissue oxygen tension⁽³¹⁾. Increased weight may also cause inconsistencies of immunosuppressant drug levels and longer operation time, resulting in prolonged graft ischemia and delayed graft function⁽³¹⁾.

There was no association between kidney TX recipient's blood group and BKV infection. All our patients were ABO compatible, googling for it showed no results except for blood group incompatibility. No significant relationship was found between hepatitis C, B, and BK viruria. Dheir demonstrated positive relationship between BK Virus nephropathy and Hepatitis B virus positivity⁽³²⁾. Hepatitis B virus positivity was related to dialysis care and duration. The relationship between immunosuppressive drugs (cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, and antithymocyte globulin) used for our patients and urine decoy cells showed statistically significance relationship between anti-thymocyte globulin use and positive urine decoy cells 95% CI: 1.88-22.79, OR = 6.55, P = .001 (Table 1). Those patients who received anti-thymocyte globulin showed decoy cells in their urine 6.5 times more than other patients. This finding was consistent with a study by Oliver Prince⁽²⁷⁾.

Bernnan showed a positive relationship between viruria and tacrolimus (in 46% of 200 renal transplant recipients), but only 13% in those who received cyclosporine, (P .005)⁽⁹⁾. The differences between our study and Bernnan's is related to drug protocol (e.g., drug dose, genetic, and anti-thymocyte globulin) which was used for all of our patients as induction therapy and rejection treatment.

Average post-transplant duration in the patients with decoy cells in their urine was 10.90 ± 5.62 months. In the group with positive urine decoy cells, it was calculated as 7 months, and in the group with negative urine decoy cell it was 12 months, which was statistically significant ($P < .001$).

This result means that regarding intense immunosuppression during first months post kidney transplantation, most decrease in immunity would be happen at that time and can result in reactivation of latent virus. In study by Saundh, different patterns of reactivation were observed: BK viruria was detected after 3-6 months, and JC viruria was observed as early as 5 days post-transplantation⁽³³⁾. The difference in our study and Saundh was related to drug protocol.

In our study, 9 out of 223 patients had DM, 3 of whom (7.3%) had positive urine decoy cells, which was not statistically significant. This was consistent with lopez finding⁽³⁴⁾. DM was considered as a recipient risk factor for developing BKVN⁽¹⁾.

There was no relationship between kidney TX rejection and polyomavirus infection in our study, because only 4 patients had acute rejection, one of whom was JC positive. In his study, Christopher showed no relationship between transplant rejection and polyomavirus infection⁽³⁵⁾.

In our study, average GFR in patients with positive, and negative decoy cells was 61.09 ± 20.97 , 59.86 ± 24.58 ml/min respectively, that was not statistically significant. Haung also showed similar findings⁽³⁶⁾. It means that we do not have severe nephropathy to deteriorate GFR.

In our study, average duration on dialysis before kidney TX for patients with positive and negative urine decoy cells was 12.88 ± 11.99 and 16.91 ± 18.75 months, respectively, which is not statistically significant. Girmaneva et al, found that unlike the control group, patients with viruria $> 10^7$ were treated longer by dialysis and had impaired graft function one-year post transplantation. ($P < .05$)⁽³⁷⁾. Hemodialysis was considered as an immunosuppressed state⁽³⁸⁾. Ureteral stent was removed 3 to 4 weeks post transplantation, and was not statistically significant in the presence of the virus in the urine. However, Jamboti reported that ureteric stent could be associated with increased risk of BK viremia⁽¹⁾. This may be related to ureteric stenosis and urinary stagnation.

Conclusion

Polyomavirus infection is a serious threat for the life of transplanted kidney. It could occur at any time post transplantation and cause an increase in plasma creatinine level silently. Also, it may lead to irreversible tubulointerstitial changes in transplanted kidney and then loss of the graft⁽²¹⁾.

There is no definite treatment for BKV nephropathy^(25, 39).

Our study found that the first few months post kidney TX and the use of Anti-thymocyte globulin were considered as serious risk factors for polyomavirus infection.

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Declaration of conflict of interests:

The authors: Masoud Khosravi, Mahlagha Dadras, Ali Monfared, Siamak Granmaieh, Mohammad Shenagari rashti, Soheil Soltanipour, Gholamreza Mokhtari, declared that they have no conflicts of interest with respect to the research and authorship of this publication.

Authors' contributions:

Masoud Khosravi: Designed the study and provided most of the data, and wrote the manuscript.

Ali Monfared: reviewed and finalized the manuscript.

Mahlagha Dadras: collected data from clinical files and provided references.

Mohammad Shenagari: All Viral PCR tests was done under his supervision.

Siamak Granmaieh, RIP: All urine evaluation for decoy cells was done by him.

Soheil soltanipour: statistical analysis was done by him.

Gholamreza Mokhtari: all transplant surgeries at our center were performed by him.

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Soheil Soltanipour, Gholamreza Mokhtari, reviewed and approved the manuscript.

Medical Ethics Code:

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Table 1. Frequency of Finding Decoy Cells in Urine by Immunosuppressive Drugs

Drug Regimen		Urine Decoy Cells N (%)	No Urine Decoy Cells N (%)	Total	P-value
Mycophenolate mofetil + Tacrolimus		1 (0.4%)	18 (8.1%)	19(8.5%)	0.337
Mycophenolate mofetil	+	30 (13.5%)	122 (54.7%)	152 (68.2%)	
Mycophenolate mofetil + Sirolimus		7 (3.1%)	14 (6.3%)	21 (9.4%)	
Mycophenolate mofetil		0	3 (1.3%)	3 (1.3%)	
Sirolimus		0	5 (2.2%)	5 (2.2%)	
Cyclosporine		3 (1.3%)	18 (8.1%)	21 (9.4%)	
Tacrolimus		0	2 (0.9 %)	2 (0.9%)	
Total		41 (18.4%)	182 (81.6%)	223 (100%)	
Thymoglobulin therapy	+	27 (90%)	70 (57.9%)	97 (64.2%)	0.001
	-	3 (10%)	51 (42.1%)	54 (35.8%)	

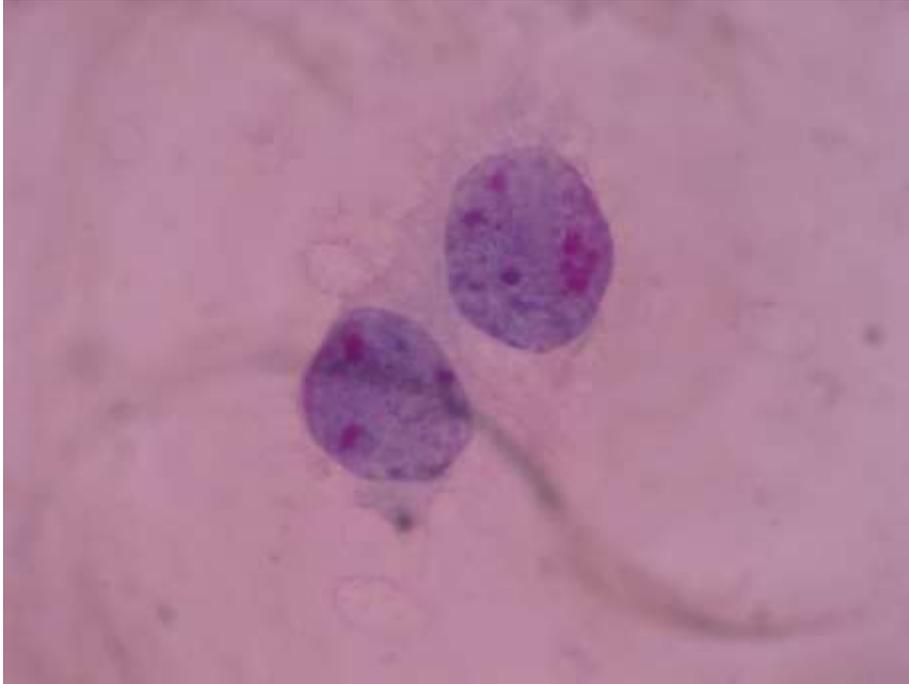


Figure 1. Decoy cells in urine (photo taken in our lab)

Accepted