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BK Virus Viremia in the First Days After Bone Marrow Transplantation: A Case-Control Study

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Abstract

Background: Reactivation of BK virus (BKV), viremia is a major clinical complication in transplant recipients. There are many studies of BKV infection among tissue transplant recipients, especially renal-transplant recipients. Although the presence of BKV in patients' urine occurs frequently, the detection of BKV in the blood of transplant recipients, especially after bone marrow transplantation (BMT), is less studied.
Objectives: The aim of this study was to detect BKV in 54 blood samples of BMT recipients in the first days after transplantation.
Methods: This case-control study was performed in a university-affiliated hospital, Tehran, Iran, from October 2017 to October 2018. Blood samples were collected from 54 hematopoietic stem cell transplant recipients, and 54 healthy subjects without any tissue transplantation, and tested daily for BKV DNA using the quantitative real-time PCR technique.
Results: In this study, two patients (3.7%) developed BK viremia at a median of 10 days (range: 1 - 10 days) after BMT, while none of the control subjects was positive for BKV in blood samples. The analysis of data showed no significant difference between the case and control groups (CI: 0.986 - 1.094, $P < 0.153$).
Conclusions: Our data suggest that BKV viremia involved in active infection may not occur in the first days after BMT. This finding can affect controlling and managing BMT patients.

Keywords: BK Virus, Blood, Bone Marrow Transplantation, Hematopoietic DNA, Real-Time Polymerase Chain Reaction, Stem Cell, Transplant Recipients, Viremia

1. Background

Bone marrow transplantation (BMT) is a novel medicinal procedure for patients with certain malignancies of the bone marrow or blood, such as leukemia and multiple myeloma (1). Hematopoietic stem cell transplantation (HSCT) leads to granulocytopenia, impaired body defense system, and impaired humoral and cellular immune responses (1, 2). Therefore, in spite of its usefulness for the survival of patients with life-threatening diseases, BMT remains a potential danger with many possible outcomes such as graft-versus-host disease (GVHD) and infections (1, 2).

Viral infection, especially infection with opportunistic viruses, is a major cause of clinical complications, mortality, and morbidity following transplantation. Various pathogenic viruses can infect transplant recipients (3, 4). Among viral infections, latent infections may involve transplant recipients (5). After the primary infection, some viruses can usually establish a latent infection in tissues such as the nervous, reticuloendothelial, and lymphatic systems (5). Then, when the immune system is damaged or suppressed, such as in the cases of transplantation or infection with human immunodeficiency virus (HIV), these viruses are reactivated to cause clinical complications for their hosts (5, 6).

Several viral families, including *Herpesviridae* and *Polyomaviridae* families, are known for their ability to cause latent infections. The infection due to the reactivation of these viruses is responsible for serious clinical complications and diseases among transplant recipients (7-9). The

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BK virus is a member of the *Polyomaviridae* family, and its infection typically occurs during the early years of life (10). Primary infection with BKV leads to a disseminated infection and asymptomatic disease; therefore, the virus can be persistent in the urinary tract to act latently (11-15). The virus remains silent unless a state of immunosuppression is imposed, such as HIV infection and organ transplantation (11-13). Research has demonstrated that the reactivation of BKV is more severe than the primary BKV infection (16). BKV reactivation has been associated with a variety of clinical outcomes in transplant recipients, such as hematuria, severe BK viruria, especially in renal transplants, hemorrhagic cystitis, nephritis, and ureteral stenosis (16-19). Moreover, reactivation of BKV can be associated with significant mortality and morbidity in the tissue transplant recipients. However, the reactivated BKV infection in the blood of BMT patients has been less studied and remains controversial compared to infections from other viruses.

Considering the importance of therapeutic insights and clinical predictors used for the diagnosis of BKV-related infection, the detection of BKV can lead to the prevention of complicated clinical outcomes.

2. Objectives

We evaluated the presence of BKV in the blood samples of BMT recipients in a referral General Hospital in Iran.

3. Methods

3.1. Study Subjects

A case-control study was conducted on blood samples from 54 BMT patients and 54 immunocompetent volunteers as a healthy control group referring to the Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, from October 2017 to October 2018. Taleghani Hospital is the only referral medical center for BMT in Iran to help patients who need these types of treatments. The immune system of the patients was suppressed before BMT. Clinical data were gathered from all the BMT recipients such as the age at the time of BMT, sex, and clinical outcome (diseases). The blood samples of the patients were collected before and 5 and 10 days after BMT. This study was approved by the Ethics Committee of Medical Experimentation on Human Subjects, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethics Committee Approval Code: IR.SBMU.RETECH.REC.1396.344).

3.2. Viral Nucleic Acid Extraction

The plasma was separated from blood samples. Subsequently, the viral DNA was extracted by the High-Pure Viral Nucleic Acid Kit (Roche Life Science) according to the manufacturer's protocol. Then, the purified viral DNA was eluted in nuclease-free water and stored at -40°C until molecular assay.

3.3. Molecular Assay

For the detection of BK viremia in blood samples, the real-time PCR method was used as previously described (20).

3.4. Data Analysis

Descriptive and analytical statistics were performed using IBM SPSS Statistics Software for Windows, version 19.0 (IBM Corp., Armonk, N.Y., USA). The chi-square test was used to calculate the association between variables. The P values of less than 0.05 were considered statistically significant.

4. Results

In total, 54 BMT recipients and 54 healthy controls were evaluated in our study. The mean age of the 54 BMT patients and controls was 37.4 and 45.2 years, respectively. The group of BMT patients consisted of 18 female and 36 male patients while there were 26 women and 28 men in the control group (Table 1). Based on the results of the chi-square test, there was no significant difference in age ($P < 0.117$) and sex ($P < 0.117$) distribution between BMT recipients and the control group. Moreover, among the BMT recipients, there was no statistically significant difference in the BKV positive blood samples between different transplantation types ($P < 0.697$).

As shown in Table 2, out of 54 BMT recipients, two (3.7%) cases were positive for BK viremia, and 52 (96.3%) were negative. Both the two positive cases for BK viremia belonged to the group whose blood samples were collected 10 days post-BMT, and the type of their transplant was multiple myeloma. However, there was no significant difference in BK viremia between cases and controls (CI: 0.986 - 1.094, $P < 0.153$).

5. Discussion

BKV is not detected under normal conditions in individuals with healthy immune systems (12, 13, 16). Therefore, the presence of BKV in the blood of immunosuppressed individuals can be a good predictor of clinical complications and BKV-related disease, including nephropathy and transplant rejection (12, 13, 16). BK viremia is associated with

Table 1. Clinical Features of BMT Recipients and Controls[a]

Characteristics	BMT Group (N = 54)		Control Group (N = 54)	P Value
Age, y				0.144
Mean	41.54		45.2	
Range	2 - 68		4 - 71	
Gender				0.117
Female	18 (33.3)		26 (48.1)	
Male	36 (66.7)		28 (59.9)	
Transplant type (N = 54)	**Test negative**	**Test positive**		0.697
HD	13 (24.07)	0 (0)	-	
MM	22 (40.74)	2 (3.7)	-	
AML	9 (16.66)	0 (0)	-	
ALL	6 (11.11)	0 (0)	-	
NHD	2 (3.7)	0 (0)	-	
GC	2 (3.7)	0 (0)	-	

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplantation; GC, germ cell; HD, Hodgkin's disease; HLCs, healthy controls; MM, multiple myeloma; NHD, non-Hodgkin's disease.
[a]Values are expressed as No. (%).

Table 2. The Frequency of BK Viremia in the Blood of BMT Patients and Controls[a]

Study Groups	Test Results			P Value	OR	CI
	Positive	Negative	Total			
BMT group	2 (3.7)	52 (96.3)	54 (100)	0.153	1.038	0.986 - 1.094
Control group	0 (0)	54 (100)	54 (100)			

[a]Values are expressed as No. (%).

GVHD in hematopoietic transplant recipients (13), which reflects the role of this opportunistic virus in clinical complications post-BMT. Our results showed the frequency of BK viremia was 3.7% in BMT recipients in a time-dependent manner. In both positive cases, blood samples were collected one week post-BMT. Reactivation of opportunistic viruses such as cytomegalovirus (CMV) in the blood of transplanted individuals has been identified in the first days after hematopoietic stem cell transplantation (21, 22). In line with our study, Maggi et al. conducted a study in the period of 0 to 10 days after transplantation and found that Torquetenovirus (TTV)-causing viremia can be a predictor of CMV recurrent infection in liver and kidney transplant recipients (23). The active BKV infection has been most commonly seen in kidney transplant recipients, and a high load of BKV has been detected in the urine of kidney transplant individuals (24). However, the low incidence of BKV has been reported in the blood of other transplant recipients, including BMT recipients (10). Various studies have shown the presence of BKV in the blood and urine of kidney and BMT recipients, especially within several weeks and months post-transplantation (11-13, 16, 25). Dall and Hariharan reported BKV reactivation in 30% to 60% of nephritis developed graft failure in renal transplant recipients; however, the patient condition improved after using novel methods of detection and follow-up of BKV in the blood and urine of transplant recipients (26).

Azar et al. in a retrospective study found BKV infection in 8.5% of renal-transplant recipients during several months post-transplantation (27). In a cohort study among 203 kidney transplant recipients, 19% of the patients developed BK viremia after transplantation (28). Transplantation rejection occurred in three patients with BK viremia containing a high viral load in the blood (29). BMT recipients in the first days after transplantation are at risk of opportunistic infections because of severe immunosuppression (30). Most reports were based on studies in various durations (months to years) while BK viremia has been less studied within the first days post-BMT, with heterogeneous results. Erad et al. indicated the strong association of BK viremia with hemorrhagic cystitis in a time-dependent manner (31) and observed that 44 patients (33%) developed

BK viremia within at a median of 41 days post-BMT (range: 9 - 91 days). However, in the current study, only were two transplant recipients positive for BK viremia in less than 10 days post-BMT.

5.1. Conclusions

In summary, the results of the current study indicate that in spite of the low frequency of BK viremia in BMT patients, the chance of developing active BKV infection is weak in the first days and weeks post-BMT. However, more studies are needed with extended scales and populations to effectively predict and monitor patients in need of BMT.

Footnotes

Conflict of Interests: The authors declare that there is no conflict of interest.

Ethical Approval: The ethical code was IR.SBMU.RETECH.REC.1396.344.

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