

BKV - a Challenge for Post-Transplant Patients

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Abstract

BKV infection is widespread as early as infancy and early adolescence. The virus remains persistent at low levels in many tissues of the human body, in particular the urogenital tract. Reactivation and/or re-infection from donors in the post-transplant period may result in severe disease, including BKV-associated nephropathy and graft rejection. The aim of this study is to determine the percentage involvement of BKV in morbidity after kidney transplantation and after allogeneic stem cell transplantation. Eighty-seven studies were performed in a total of 37 post-transplant patients (out of which 59.4% were women) with a mean age of 42.2 years (SD \pm 10.6, range 26-70 years). Thirty-three patients after renal transplantation were screened for reactivation (89.2%, CI: 79.2% to 99.2%) in serum, and 4 patients (10.8%; CI: 0.8% to 20.8%) after allogeneic stem cell transplantation in urine samples when clinical evidence of haematuria was present. We used quantitative BKV PCR test kit Anatolia Geneworks, Istanbul, Turkey. We obtained a positive result in 1 patient after renal transplantation (3.03%) and in 3 patients (75%) after allogeneic stem cell transplantation and haematuria. Our data indicate that BKV is involved in morbidity after transplantation. In order to determine the most appropriate PCR sample material (serum, plasma or urine), all three should be tested simultaneously.

Keywords:

Резюме

BKV инфекцията е широко разпространена още в детска и ранна юношеска възраст. Вирусът остава да персистира в ниски нива в много тъкани на човешкия организъм, в частност урогениталния тракт. Реактивация и/или реинфекция от донора при пациенти след трансплантация на органи или тъкани може да доведе до тежко заболяване, включително BKV-асоциирана нефропатия и отхвърляне на присадката. Целта на настоящото проучване е да се определи относителния дял на участие на BKV в заболяемостта след трансплантация на бъбрек и след алогенна трансплантация на стволови клетки. Проведени са 87 изследвания на 37 пациенти след трансплантация, на средна възраст 42.2 г. (SD \pm 10.6; обхват 26-70 г.). Скринирани са 33 пациенти след трансплантация на бъбрек (89.2%; CI: 74.6%-97.0%) в клиничен материал серум/плазма и 4 пациенти след алогенна трансплантация на стволови клетки в материал урина и клинични данни за хематурия.

Приложен е PCR тест на Anatolia, Geneworks. Положителен резултат е получен при 1 пациент след бъбречна трансплантация (3.03%) и при 3 (75%) от пациентите след алогенна трансплантация на стволови клетки и хематурия. Нашите предварителни данни показват, че BKV участва в заболяемостта след трансплантация на органи или тъкани. За определяне на най-подходящия материал за изследване в PCR е необходимо едновременно приложение на теста в серум/плазма и урина.

Introduction

Polyomaviruses are ubiquitous, infecting many different mammalian species including humans. Most human polyoma-diseases are caused by JCV and BKV. BKV is a small non-enveloped double-stranded DNA virus. It is a ubiquitous virus with high seroprevalence in the general population (Knowles *et al.*,

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2003). BKV infection is usually acquired in early childhood. Transmission occurs typically via oral and respiratory routes. Following primary infection, the virus remains latent in the host in different sites, particularly the kidneys, uroepithelial cells and lymphocytes. Reactivation from latency may occur in normal subjects with asymptomatic viraemia in about 5%, while it can be associated with nephropathy in kidney transplant recipients (Dolei *et al.*, 2000; Reploeg *et al.*, 2001; Costa *et al.*, 2012). Under the circumstances of severe immunosuppression, BKV can cause pneumonitis, hepatitis, retinitis, and meningoencephalitis (Bressollette-Bodin *et al.*, 2005; Dropulic *et al.*, 2008). Hemorrhagic cystitis is seen in 25–60% of bone marrow transplant patients, usually 2 weeks after transplantation (Bressollette-Bodin *et al.*, 2005). Up to 80% of renal transplant recipients have BK viraemia, and 5%–10% progress to BKV nephropathy (BKVN) (Hirsch *et al.*, 2002). Given that polyomavirus is widely latent in the kidney, kidney transplantation (KT) is believed to be an important mode of infection in patients with end-stage kidney disease. Graft loss rate has been reported to be as high as 30%–50% following the diagnosis of BKVN (Sood *et al.*, 2012; Hirsch *et al.*, 2013). RT-PCR is the method of choice to detect viral replication in urine and blood, for diagnosis and prognosis of BKVN (Dall *et al.*, 2008, Van Din *et al.*, 2017) and screening is recommended every 3 months in the first two post-transplant years or when allograft dysfunction occurs (Posdich *et al.*, 2016). The aim of present study was to determine the percentage involvement of BKV in morbidity after KT and allogeneic stem cell transplantation (aHSCT).

Material and Method:

Material

87 tests were performed in a total of 37 post-transplant recipients (out of which 59.4%

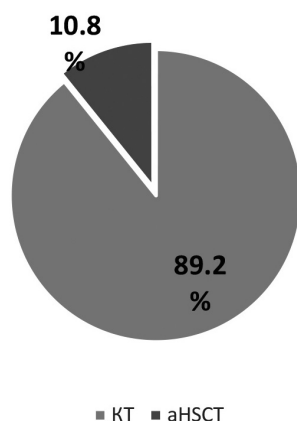


Fig. 1. Distribution of post-transplant recipients (n=37)

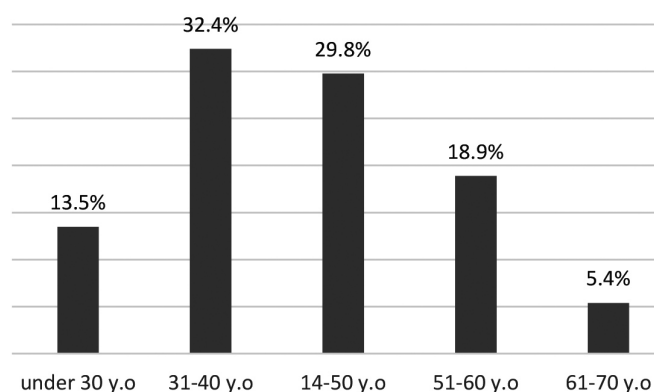


Fig. 2. Age distribution of post-transplant recipients (n=37)

were women) with a mean age of 42.2 years (SD \pm 10.6, range 26-70 years). 33 patients (89.2%, CI: 79.2% to 99.2%) after KT were screened for reactivation in serum and 4 patients (10.8%; CI: 0.8% to 20.8%) after aHSCT in urine samples when clinical evidence of haematuria was present (Fig. 1, Fig. 2).

A total of 87 studies were performed in different post-transplant periods. 28 KT recipients were monitored in more than one sample. One patient after aHSCT was tested twice (Fig. 3).

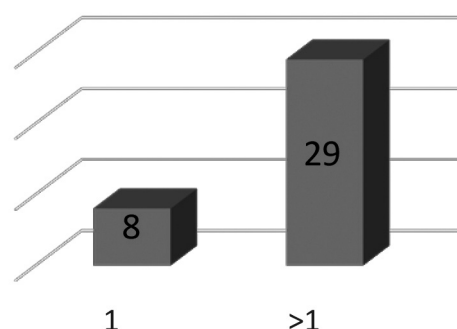


Fig. 3. Number of tests performed per patient

Method

We used quantitative BKV PCR test kit v1 of Anatolia, Geneworks, Istanbul, Turkey.

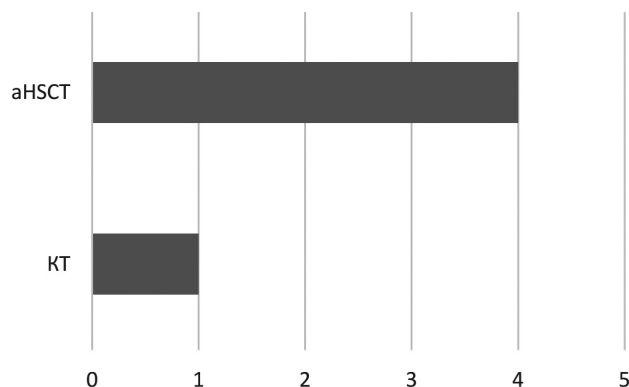
Results and Discussion

A total of five samples from four patients were positive in PCR. We obtained positive results in 1 serum sample from a patient after KT (3.03%), and in the urine samples of 3 patients (75%) after aHSCT and haematuria, where one of them was positive twice (Fig. 4, Table 1).

BKV infection is widespread in the human population. Infection is usually asymptomatic in childhood. After primary infection, the virus remains latent in many tissues and organs, mainly in the urogenital tract mucosa. Immunosuppression after transplantation leads to reactivation of the

Table 1. Summarized data for BKV PCR positive patients

Date of study	Patient	Age	Sex	Sample	Type of transplantation	Date of transplantatoin	BKV PCR (c/ml)
01.12.2015	С П П	39	female	serum	KT	27.10.2014	167 519
21.09.2018	С С Р	56	female	urine	aHSCT	03.08.2018	30 198 577 152
16.10.2018	С Х И	43	male	urine	aHSCT	12.09.2018	873 427 520
17.10.2018	Д В Д	41	female	urine	aHSCT	19.09.2018	168 423 344
03.12.2018	С Х И	43	male	urine	aHSCT	12.09.2018	16 024 406

**Fig. 4.** Number of BKV PCR positive results by type of transplantation

latent BKV infection and may cause rejection of the grafted organ or tissue. In a study of 441 organ transplant recipients in Europe 24 days after transplantation, the detected BKV-seroprevalence was 97%. In addition, there was a significant increase in antibody reactivity after the onset of immunosuppression (Antonsson *et al.*, 2013). Viral reactivation during immunosuppression causes cytopathic changes in the uroepithelium and subsequently increases the viral load in the urine. Nucleic acid amplification testing of blood and urine is the main diagnostic and prognostic test for BKV infection. Data show that BKV viruria higher than 107 c/ml and plasma BKV viremia of 104 c/ml are reported to be typical in patients with BKV nephropathy (Ferreira-Gonzalez *et al.*, 2007). BKV disease is a common complication after aHSCT. Hemorrhagic cystitis is seen in 25–60% of bone marrow transplant patients, usually 2 weeks after transplantation according to the literature (Bressollette-Bodin *et al.*, 2005). According to other authors, BKV was detected in urine in 51.4% of patients 100 days after aHSCT, but only 19.1% of them developed hemorrhagic cystitis (Posdzych *et al.*, 2015).

According to our data, 3 (75%) of the 4 patients after aHSCT developed BKV-associated hemorrhagic cystitis about 1 month after transplantation (Table 1). In our study, the viral load in the urine of these patients was high and ranged from log 7.2 to log 10.5.

Our data from the screening program of 33 kidney transplant recipients for BKV viremia after KT showed a positive result in one (3.03%) patient about 1 year after the transplantation. We do not have baseline data on the BKV seroprevalence of the patients studied. Real time PCR results do not show reactivation and viremia in most of them. A limitation of the study is that urine test was not performed for these patients.

In conclusion, BKV is more frequently involved in the morbidity of patients after aHSCT, who undergo more severe immunosuppression as a rule. BKV plays a role in morbidity after KT and aHSCT, but for more accurate determination of the proportion, a more frequent follow-up of the recipients is required simultaneously in both clinical materials - urine and serum/plasma.

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