

Reactivation of BKV and AdV infections during post-transplant immunosuppressive therapy

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Abstract

Introduction. Viral infections are an important problem in transplantology. Infections in recipients may develop as a result of the original infection or reactivation of a latent infection. Many viruses have the ability to enter into a latent state without symptoms. The most common groups of viruses causing infections in patients after transplantations are herpesviruses, hepatotropic viruses, retroviruses, adenoviruses and polioviruses.

Objectives. The aim of the presented study is to analyze the incidence of infections caused by BKV and AdV in a group of patients after kidney and bone marrow transplant.

Material and methods. The study group consisted of 13 patients after bone marrow transplantation and a group of 10 patients after kidney transplantation. DNA was isolated from urine and serum and analysed with PCR auto-nested reaction. The amplification products were separated in agarose gel.

Results. A positive result for AdV was recorded in 7 patients after bone marrow transplant and 5 patients after renal transplant. BK virus was detected in the urine of 13 patients, and in the blood sample of 5 patients.

Discussion. Reactivation of a virus during immunosuppression is a frequent cause of graft rejection. In addition, in patients with impaired immune system, mixed infections with various types of viruses are becoming a serious problem. This study confirm that infections with BKV and AdV viruses are a major problem in the field of transplantation.

Conclusion. BKV and AdV are common causes of infections affecting patients after renal and bone marrow transplantation. BKV infections are often accompanied by human adenovirus infection. Adenovirus infections are a more common cause of infection in bone marrow transplant patients than in patients after renal transplantation.

Key words

Adenovirus, BK virus, immunosuppression, transplantation, bone marrow, kidney

INTRODUCTION

Opportunistic infections, which may lead to serious, irreversible dysfunctions, rejection of the transplanted organ, and in severe cases, even to the patient's death, are an important problem in transplantology. Immunosuppression inhibits one of the basic mechanisms of antiviral defence – cytotoxic T. lymphocytes. This enhances viral proliferation, possible reactivation of latent infections and rapid spread of the disease. Infections in recipients may develop as a result of the original infection (during the first contact with the pathogen) or as an outcome of the reactivation of a latent infection. Many viruses have the ability to enter into a latent state without symptoms. However, under the influence of certain factors, most commonly immunity decrease, reactivation of the virus can appear. There are three basic stages of post-transplant infections: the early stage (up to one month after transplantation), which includes infections caused by the surgery itself; the intermediate period (2 – 6 months after transplantation), where primary infections with viruses such as CMV, HHV-6, EBV, AdV, BKV, bacteria, fungi and infusoria occur, and the late period (more than half a year after transplantation), where common infection for the recipients include those most common in the general

population, such as infections caused by the influenza virus, parainfluenza, RSV or urinary tract infection.

Most common post-transplant viral infections. The most common groups of viruses causing infections in patients after transplantations are herpesviruses, hepatotropic viruses, retroviruses, adenoviruses and polioviruses [1].

Adenovirus. The majority of the patients become infected by at least one serotype of AdV before turning fifteen. There exists a connection between the frequency of isolating various types of viruses and the patient's age (newborns type: 1, 2, 3, 5, 6, 7; older children 3, 7; adults: 3, 4, 7, sometimes 14). In patients after transplantations the adenoviral infection rate varied from 5% – 47% [2].

Polyomavirus. the most common of these viruses is the BKV virus. Approximately 60–90% of the world population is infected with it and its reactivation occurs in 23–57% of renal recipients. 1–10% of the recipients suffer from nephropathy leading to irreversible damage to the grafted kidney [3].

Characteristics of AdV. AdV belongs to the genus *Mastadenovirus*, of the family *Adenoviridae*. It is a type of virus that infects only mammals, unlike the other type of virus from this family, i.e. *Aviadenovirus* which infects bird.

Currently, there are 52 known serotypes of AdV, which have been divided into 6 subgenera, labeled A – F, and contained in each subgroup are several types of virus. The criterion for this division is the sequence of nucleotides in the DNA [4].

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Adenovirus virion is composed of a single molecule of double-stranded DNA constituting 12–17% of the virus. The capsid is icosahedral in shape and composed of 252 capsomeres (240 hexons and 12 pentons). Each penton has a projecting protein fibre with a terminal knob 10–37 nm in length, depending on the type of virus. Virions do not have a lipid shell, and are approximately 80 nm in diameter. Virions of adenoviruses exhibit stability in terms of pH (6–9). Fat solvents and small chlorine concentration do not influence the virus. Adenoviruses retain their viability in the temperature between -25° and -70° for about 2 months; however, after being heated to 56° for 10 minutes they become inactivated [5].

Adenovirus infections are frequent and constitute up to approximately 13% of all human viral infections [6]. Adenoviruses are one of the most frequent causes of diarrheas in paediatric patients and affect mainly infants and children up to 2 years of age. In older age, the human body produces antibodies against the so-called intestinal adenoviruses, AdV 40 and 41 [7]. In adults, gastrointestinal infections are usually mild and self-limiting. In infants, the infection is slightly more severe than in older children, also concomitant infections of the throat and the respiratory tract are more common in infants and cover 80% of cases, whereas in older children – 31%. Another condition caused by the AdV is tonsillitis.

The only criterion allowing for the differentiation between viral and bacterial tonsillitis is age. Infections caused by AdV affect children below 3 years of age, while bacterial infections occur between the ages of 5 and 17 [6]. Among the most common ophthalmic infections are conjunctivitis and keratitis. In the case of keratitis, after few days from infection, point-changes appear on the eye's surface; however, they do not require treatment and disappear within couple of weeks [8]. Adenoviruses, mainly type 11, are also responsible for haemorrhagic cystitis in children. This disease is more common in boys, and its symptoms include bloody urine, frequent urination, fever, burning pain in the abdomen and painful urinary urgency [9]. Neurological complications caused by adenoviruses are rare, but very dangerous due to the high risk of death. The disease most commonly affects newborns and immunocompromised people.

Characteristic of BKV. The BK virus belongs to the *Polyomaviridae* family and the *Polyomavirus* genus. Currently, there are 5 known human polyomaviruses: BKV, JCV, WUV, KIV and MCV. There are 4 subtypes of BKV, labeled I – IV, including 4 sub-groups within the subtype I (a, b1, b2, c) [10].

The genome of the BK virus consists of a single-stranded, circular DNA molecule with a length of 5'153 bp. The genetic material is enclosed in an icosahedral capsid, approximately 45 nm in diameter. The capsid of the polyomaviruses is composed of 3 proteins: VP1, VP2 and VP3, which are made up of 72 capsomeres, grouped into 12 pentamers and 60 hexamers [10].

Polyomavirus infections are very common although it is estimated that 70–90% of the adult population has antibodies against BK and JC virus. These infections, usually occurs in early childhood and are asymptomatic. They do not pose a threat in immunocompetent individuals; however, in patients with reduced immunity, particularly after kidney and bone marrow transplantation, they are the cause of

serious infections [11]. Modes of BKV transmission have not been fully recognized, although it is believed that the viruses are transmitted through respiratory droplets, the faecal-oral route, after exposure to infected blood, including organ transplants, and through the placenta [12]. As a result of childhood infections, the viruses penetrate the tissue where they undergo latency. The main location of the BKV virus latency is considered to be the urinary tract. After application of immunosuppressive therapy, which lowers the body's resistance, BK virus and other polyomavirus, are reactivated. They may cause respiratory infections (mainly KIV and WUV), interstitial nephritis in transplant recipients (BKV), haemorrhagic cystitis after bone marrow or kidney transplantation, and progressive multifocal leukoencephalopathy (JCV) [10].

Aim of the study. The aim of the study was to analyze the incidence of infections caused by BKV and AdV in a group of patients after kidney and bone marrow transplant. The relationship between BKV infection and the incidence of AdV infection was also analyzed.

MATERIALS AND METHOD

Characteristic of the population and the research material.

The study group consisted of 13 patients after bone marrow transplantation (11 children and 2 adults) treated in the Independent Public Clinical Hospital No. 4. in Lublin (PSK4), and in the Children's Clinical Hospital (DSK), both in Lublin, south-eastern Poland, as well as a group of 10 patients after kidney transplantation from PSK4.

The research material consisted of 23 urine and serum samples obtained from 23 patients infected with the BK virus. The material was stored in sterile test tubes and frozen at -23°C until analysis.

Isolation of viral DNA from urine sample. Conducted using the Viral DNA Kit (QIAGEN), in accordance with the standard procedure provided by the manufacturer.

Isolation of viral DNA from serum. Conducted using DNA Blood Mini-Kit (QIAGEN), in accordance with the standard procedure provided by the manufacturer.

PCR auto-nested. A method for increasing sensitivity based on performing 2 successive reactions, out and in. The products obtained in the 'out' reaction are the matrix for the 'in' reactions. 1 µl of the product is transferred from the 'out' reaction to the 'in' reaction (the volume designated for the isolate should be refilled with water, the other ingredients and the profile of the reaction without change).

The out PCR reaction BKV/AdV. The volume for one sample equaled 20 µl (water for PCR – 7 µl; 10x bufor PCR – 2 µl; Bufor Q – 4 µl; MgCl₂ – 0.6 µl; dNTPs – 0.4 µl; primer PEP 1 / AZH 1 – 0.5 µl; primer PEP 2 / AZH 4R – 0.5 µl; *Taq Hot Start* polymerase – 0.1 µl). After stirring it was divided into 15 µl and 5 µl of DNA isolate was added respectively to each. Primer sequence for BKV: **PEP 1** – 5' AGT CTT TAG GGT CTT CTA CC 3'; **PEP 2** – 5' GGT GCC AAC CTA TGG AAC AG 3'. Primer sequence for AdV: **AZH 1** – 5' GCC GAG AAG GGC GTG CGC AGG TA 3'; **AZH 4R** – 5' ATG ACT TTT

GAG GTG GAT CCC ATG GA 3'. Amplification was conducted in a thermocycler in the conditions described in Table 1. Size of the PCR products of the 'out' reaction: BKV-176 bp, AdV-150 bp.

Tables 1. BKV/AdV PCR thermocycler conditions.

Temperature	Time (amount of cycles)
95°C	15 minutes
94°C	1 minute (35 cycles)
55°C	1 minute (35 cycles)
72°C	1 minute (35 cycles)
72°C	5 minutes

Restriction. To distinguish BK from JC virus it is necessary to conduct a restriction enzyme digestion with FokI BKV-specific, as a result of which, after electrophoresis under an UV lamp, it will be possible to observe 2 bands for BKV and 1 for JCV.

Mix 10 µl of the product of reaction, 16 µl water, 1–2 µl of the FokI enzyme and 2 µl of 10 x buffer Tango. Incubate at 55°C for 15 hours; then at 80°C for 20 minutes to inactivate the enzyme and detect in agarose gel.

Detection. Amplification products are separated in a 2% agarose gel at 96V for about 20–30 minutes. In the case of BKV, 2 DNA bands with sizes of 120 bp and 56 bp, and for JCV 1 band with a size of 176 bp is observed under UV light.

RESULTS

Occurrence of AdV in patients after bone marrow transplant. The study group consisted of 13 participants. A positive result for AdV was recorded in 7 of them (53.8%) and a negative in 6 (46.2%) (Fig. 1).

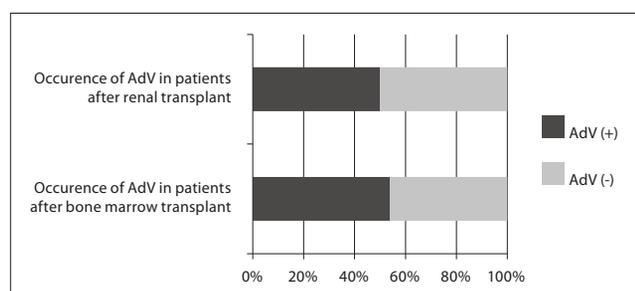


Figure 1. Percentage analysis of AdV occurrence in patients after bone marrow and renal transplant

Occurrence of AdV in patients after a renal transplant. The study group consisted of 10 participants. A positive result for AdV was recorded in half of them (50%) (Fig. 1).

Analysis of the presence of BKV and AdV in the urine and blood samples of patients after bone marrow transplantation. The presence of adenovirus was found in the urine of 7 patients (53.8%) and in the blood of one patient (7.7%). BK virus was detected in the urine of 13 patients (100%), and in the blood sample of 5 patients (38.5%) (Fig. 2, Tab. 2).

Table 2. Results of BKV/AdV DNA in patients after bone marrow transplant

BKV/AdV DNA	Number of patients	
	BKV	AdV
Urine+ / blood +	5 (38.5%)	1 (7.7%)
Urine + / blood -	8 (61.5%)	6 (46.2%)
Urine - / blood +	0 (0%)	0 (0%)
Urine - / blood -	0 (0%)	6 (46.2%)

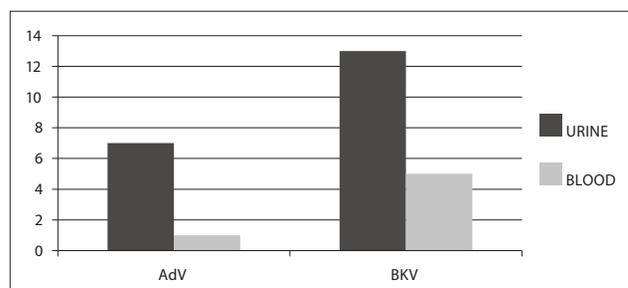


Figure 2. Analysis of viruria and viremia levels caused by AdV and BKV in patients after bone marrow transplant

Analysis of BKV and AdV presence in urine and blood samples in patients after renal transplant. The presence of adenoviruses was found in the urine of 5 patients (50%) and in blood samples of 2 (20%). BKV was found in the urine of all of the patients (100%) and in the blood of 1 (10%) (Fig. 3, Tab. 3).

Table 3. Results of BKV/AdV DNA in patients after renal transplant.

BKV/AdV DNA	Number of patients	
	BKV	AdV
Urine+ / blood +	1 (10%)	2 (20%)
Urine + / blood -	9 (90%)	3 (30%)
Urine - / blood +	0 (0%)	0 (0%)
Urine - / blood -	0 (0%)	5 (50%)

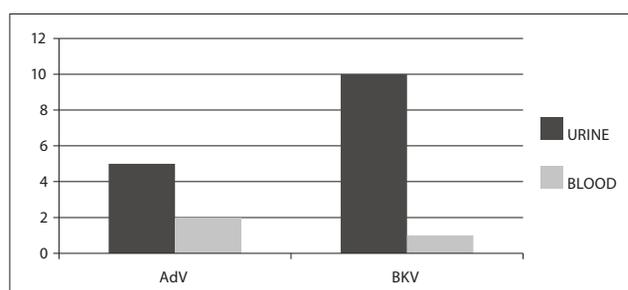


Figure 3. Analysis of viruria and viremia levels caused by AdV and BKV in patients after a renal transplant

The course of AdV and BKV infections in patients after bone marrow transplant. BKV was present in the urine throughout the period of testing in all the patients. In 5 of the 6 patients, BKV infection was accompanied by adenovirus infection, manifested by the presence of AdV DNA in urine or blood. 1 patient had a full-blown infection where BKV and AdV were present in both urine and blood samples (Tab. 4).

Table 4. Course of AdV and BKV infection in patients after bone marrow transplant.

	Date of the study	BKV		AdV	
		BLOOD	URINE	BLOOD	URINE
Patient 1	21.04.2009	-	+	-	-
	28.04.2009	+	+	-	+
	05.05.2009	+	+	-	-
	12.05.2009	-	+	-	-
	19.05.2009	-	+	-	-
Patient 2	04.06.2009	-	+	+	-
	12.06.2009	-	+	-	-
	17.06.2009	+	+	-	-
	23.06.2009	+	+	-	-
	17.07.2009	+	+	+	-
Patient 3	22.10.2009	+	+	+	+
	27.10.2009	-	+	-	-
Patient 4	19.11.2010	-	+	-	-
	19.12.2010	-	+	-	-
Patient 5	21.12.2010	-	+	-	-
	30.12.2010	-	+	-	+
Patient 6	20.01.2011	+	+	-	-
	25.01.2011	+	+	-	-
	02.03.2011	-	+	-	+
	16.03.2011	-	+	-	+

DISCUSSION

Because of the continuous development in the field of transplantation, both that of solid organs as well as hematopoietic cells, and the immunosuppression associated with it, viral infections may occur more frequently and with more severe symptoms. In addition, in patients with impaired immune system, mixed infections with various types of viruses are becoming a serious problem. Reactivation of a virus during immunosuppression is a frequent cause of graft rejection. That is why an effective viral diagnosis and undertaking quick treatment of such infections is crucial [6].

The incidence of adenovirus infections in transplant patients has increased significantly in recent years. This may be due to several reasons: greater awareness of the pathogenicity of the virus, intensified immunosuppressive therapy, more sensitive diagnostic methods and systematic control. AdV infections ranges from 5% – 47%, depending on the age of the patient, type of diagnostic method, and the analyzed sample [2]. Mortality among patients ranges from 10% to as much as 80%. Children fall sick more often than adults because they are more susceptible to primary infection or reactivation of latent infections. A larger amount of AdV DNA was detected in the tonsils of children under 9 years of age than in older ones. It is believed that the more frequent reactivation of adenoviral infection is caused by abandoning the once standard practice of tonsillectomy in young children [13]. Higher mortality due to AdV infection has been reported in patients after transplantation from unrelated donors, patients with acute lymphocytopenia after antilymphocyte globulin therapy and in cases of graft-versus-host disease [2].

Clinical symptoms in patients who are infected with adenovirus include infections of the upper and lower respiratory tract, interstitial pneumonia, hepatitis, diseases of the genitourinary system, such as haemorrhagic cystitis or inflammation of the kidneys, and digestive system diseases, such as haemorrhagic colitis. AdV in patients after bone

marrow transplantation is typically detected within 100 days of transplantation [2]. The disease can be either located within a single organ or disseminated throughout the body. Regular blood tests are now widely used in AdV infection prevention in patients after transplantation, particularly in children. The virus can be detected in the blood from 2 – 3 weeks before the development of clinical symptoms, which allows for rapid implementation of treatment [14]. Various serotypes of adenoviruses are isolated from patients, most often these are viruses belonging to the A, B and C subgenus. Patients with mixed infections exhibit a longer period of virus excretion than patients infected with only 1 serotype [2].

Patients after transplantation, especially bone marrow transplantation, are particularly vulnerable to infections of the respiratory tract which can even prove fatal. Adenovirus infections in children are detected, on average, in less than 30 days after transplantation, and in adults even less than 90 days, and detected in approximately 14% of patients [15]. Risk factors conducive to adenovirus infection include: graft-versus-host disease, herpes virus infection and isolating adenoviruses from various clinical specimens. Mortality resulting from AdV infection reaches up to 50%, despite the use of antiviral therapy [16].

Adenovirus infections are a frequent cause of diseases in renal transplant recipients. In most patients, the infection is manifested by haemorrhagic cystitis present with fever, haematuria and soreness during micturition. In a study conducted by Watcharananan et al., nearly 2/3 of patients showed severe dysfunction of the transplanted organ. Average time of onset of the infection is 5 weeks after transplantation [17].

According to various studies, the estimated frequency of AdV infection in patients after HSCT ranges from 3% – 47% [18]. In the study conducted by Bil-Lula et al., adenoviral infection concerned up to 44.8% of patients after transplantation of hematopoietic stem cells.

AdV DNA was detected in 55.8% of urine samples and in 1.9% of serum samples, and 28.8% of patients showed disseminated infection, where the presence of AdV was detected in both urine and blood. The presented study also demonstrated that AdV infection is often accompanied by the BKV infection. The authors of the presented study also argue that BKV and AdV infection occur most commonly as co-infections [18].

BK virus is a major etiologic factor in interstitial nephritis in patients who have undergone renal transplant [10]. The reactivation of the BK virus affects 10–60% of patients after renal transplantation. As demonstrated in the literature, nephropathy associated with BKV reactivation occurs in 8% of recipients, causing transplant rejection in up to 50% of cases [19].

BK virus reactivation is an important cause for developing various symptoms in patients after renal transplantation. This seemingly insignificant infection during immunosuppression is a major contributory factor to the loss of the transplanted organ. The symptoms of infection can be detected in more than 80% of adults. Anti-BKV antibodies are detected in 73% of renal allograft recipients. It has not been established whether the infections caused by the BK virus in transplant recipients result from the reactivation of persistent infection, or whether the recipients are infected with the virus derived from the donor [20].

The main locations where the virus becomes latent, are renal tubular epithelial cells and the urinary tract, as well as lymphoid cells or brain tissue. BKV reactivation occurs in people with

weakened immune systems, resulting from immunosuppressive therapy after transplantation. Other factors contributing to infection may include: pregnancy, chemotherapy, HIV infection, uncontrolled diabetes, the use of cytotoxic drugs, the presence of anti-BKV antibodies in the donor organ, mismatch of the donor's and recipient's HLA tissue types, and the age and gender of the patient (older, male) [21].

Clinical manifestations of BK virus infection usually include interstitial nephritis, ureteral stenosis and haemorrhagic cystitis. BKV can cause graft dysfunction, it is estimated that the BK nephropathy occurs in 2–5% of recipients, and is the cause of organ rejection in 45% of cases. The disease may begin within 4 months after kidney transplantation and continue until graft failure, with an average diagnosis time of 9.5 months [21]. At its earliest, nephropathy was diagnosed as early as the 6th day, the latest 6 years after transplantation [22].

In the past few years, in renal transplant patients, the incidence of BKV caused nephropathy has increased. This is probably caused by the increase in the amount of transplantation procedures, as well as more effective diagnostic methods. Until recently, BKV nephropathy was misdiagnosed as acute transplant rejection, which resulted in improper treatment, intensification of the disease, and ultimately graft loss. Interstitial nephritis can continue for months without giving visible symptoms. The final diagnosis is confirmed by a renal biopsy in order to detect morphological changes caused by viral replication. Sometimes, the biopsy can give a false negative result due to the focal nature of the disease. The development of the disease can be observed using the initial detection of the virus in urine, then blood, and finally in the kidneys of the patient. BK nephropathy is detected in approximately 8% of patients after kidney transplantation, resulting in graft loss in 50% of cases within 2–3 years [19]. In a study conducted by Sung et al., viraemia was detected in 18.8% (12/64) and viruria in 28.1% (18/64) of patients after renal transplant [23].

Haemorrhagic cystitis (HC) is a very common complication in renal transplant recipients and allogeneic haematopoietic stem cell transplantation (HSCT). The disease occurs in 5–40% of patients after HSCT [24]. However, in 50–100% of recipients, BK viruria is detected; thus, the mere presence of the virus in the urine is insufficient to cause the disease [25]. Risk factors favouring the development of haemorrhagic cystitis include: acute form of graft-versus-host disease, a specific mutation of BKV, the type of immunosuppressive drugs used, and BK virus subtype, and a graft obtained from an unrelated donor. Haemorrhagic cystitis in patients after haematopoietic cell transplantation usually develops late in the post-translational period. However, HC can develop even a few days after transplantation. In the studies conducted by Erard et al., in 33% of recipients of allogeneic haematopoietic cell transplantation in whom BKV viraemia was detected, the development of HC occurred in 43% of the cases, an average of 9 days after transplantation [10].

In the presented study, BK virus infection occurred in 100% of the cases, whereas AdV infection concerned 52.2% of all patients. These studies confirm that infections with these viruses are a major problem in the field of transplantation.

CONCLUSIONS

BKV and AdV are common causes of infections affecting patients after renal and bone marrow transplantation. BKV

infections are often accompanied by human adenovirus infection. Adenovirus infections are a more common cause of infection in bone marrow transplant patients than in patients after renal transplantation. BKV DNA and AdV are more frequently isolated from urine samples than blood samples.

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