

BK virus infection in a renal transplant Saudi child

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ABSTRACT

BK human polyomavirus (BKV) causes an asymptomatic primary infection in children, but later, establishes latency mainly in the urinary tract. Virus-host interactions influencing persistence and pathogenicity are not well-understood. We present here a 12-year-old Saudi boy, who had renal transplant in Egypt. Seven months later, he was admitted to our Pediatric Nephrology Unit as a case of renal impairment. He developed BKV infection, diagnosed and successfully managed in our hospital. This case demonstrates the expanding clinical importance of BKV in a post renal transplant patient. This virus can be detected in transitional cells in the urine (decoy cells) using cytology. Testing for BKV deoxyribonucleic acid in urine and blood is an early detection assay, and can be used as a screening test in the early stages. The early reduction of immunosuppression can improve the prognosis. No specific antiviral treatment has been established yet. This is the first report of detecting BK virus in a Saudi post-transplant child in urine and blood specimens by using polymerase chain reaction.

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nephropathy and allograft dysfunction in renal transplant recipients.¹⁻³ Organ biopsy and traditional methods such as, virus isolation does not provide a timely diagnosis. Electron microscopy, immunohistochemical analysis,^{1,4} and polymerase chain reactions (PCR) testing are gaining acceptance as more rapid, effective diagnostic methods.⁵⁻⁷ Routine post-transplant screening for BK viremia and viruria prior to the occurrence of infection dilemma and the reduction in immunosuppressive therapy for subjects with viremia appears to be attractive future approaches.^{7,8}

We describe the case of a 12-year-old male Saudi patient, who was admitted to our Pediatric Nephrology Unit with renal impairment. He subsequently developed BKV infection, diagnosed and managed in our hospital.

Case Report. A 12-year-old male who had a history of congenital chloride losing diarrhea and recurrent dehydration, as a result of these, he developed chronic renal failure and he needed hemodialysis. He had renal transplant on the 3rd of September 2004 in Egypt. He was followed in our Pediatric Nephrology Clinic on the following immunosuppressive drugs: Mycophenolate (500 mg orally, twice a day), FK506 (2 mg orally, twice a day) Prednisolone (15 mg orally, one tablet per day). In March 28, 2005, he was admitted to our hospital with a diagnosis of renal impairment. At the time of acute renal impairment rejection of the renal transplant was suspected, further investigations were instituted. Clinical examinations showed that he was afebrile, blood pressure was 110/80, heart rate was 80/min, with Cushing's features. His chest was clinically clear, cardiovascular system S1+S2+0, the abdomen was distended, but there was no ascites or organomegaly. The kidney graft was not tender. His initial investigation showed normal hemoglobin in 14.6 g/dl (11.3 - 15.0 g/dl), and high white blood cell in 16.2 (4.0 -12.0 10⁹/L), with neutrophil in 14.0 (1.1 - 7.2 10⁹/L), high platelet count of 461 (150 -450 10⁹/L), with normal liver function tests. His initial serum Creatinine was 202 umol/L (30-70 umol/L) and his serum urea was 39.4 mmol/L (2.1-7.1 mmol/L), sodium 136 (136-145 mmol/L), potassium 3.5 (3.1-5.1 mmol/L), with low chloride 82 (98-107 mmol/L). On admission, the management plan was to complete the renal biopsy, pulse Methylprednisolone was administered for 3 days, and examination of the urine and blood for Polyoma viruses. The renal biopsy was carried out on the second day of admission and showed mild chronic

The BK virus (BKV) is a human polyomavirus. The BKV has been linked to the development of hemorrhagic cystitis, urethral stenosis, and

interstitial nephritis, fibrosis, and nephrocalcinosis. His blood and urine were sent to Bioscientia: Institut für Laboruntersuchungen, Ingelheim GmbH, Germany for Polyoma virus PCR deoxyribonucleic acid (DNA). The test on the blood was negative for JC virus and highly positive for BK virus, while on the urine, the tests were negative for JC virus and highly positive for BK virus. Ultrasound of transplanted kidney displayed a normal resistive index of transplanted renal artery (Figures 1 and 2). On April 12, 2005, collation of the results showed the following: high creatinine level in serum, renal biopsy result: suggested no rejection, and high level of polyoma virus in blood and urine. Consequently, the Mycophenolate was stopped and the dose of FK506 was decreased to 1.5 mg (orally) twice a day. The creatinine level closely followed decreased immunosuppressive therapy, which gradually resulted in reduction to 75.8 $\mu\text{mol/L}$ (30-70 $\mu\text{mol/L}$) on the 5th May 2005 (Figure 3). He was later discharged home feeling well, and was given follow-up appointments.

Discussion. The BKV is a distinct human polyomavirus, belonging to the genus of Polyomavirus. It is a DNA tumor virus, non-enveloped with a closed, circular 5 kb double DNA-stranded genome of 5300 bp.¹ The other members of the Polyoma genus are JC virus and SV-40, that cause disease in humans and animals. "Polyoma" is derived from the Greek roots poly-, meaning many or much, and '-oma', meaning tumors. The BKV isolates have been classified into 4 subtypes (I-IV) by using either serological or genotyping methods for detection. The human polyomaviruses were first isolated in 1971. They were named BK after the initials of the patient, in which they were first discovered. The BK virus was isolated from the urine of a renal transplant patient who developed ureteral stenosis postoperatively.¹ Polyomaviruses are highly species-specific and have probably co-evolved with their natural hosts. Approximately 80% of adults in the United States have antibodies to the BKV.^{1,2} Peak seroprevalence is in early childhood. By the age of 3 or 4 years, 50% of children have antibodies to BK virus and by age 10, 100% have seroconverted. Increasing prevalence has been correlated with newer immunosuppressive agents, and the decline in acute rejection rates in recent years.¹ The exact cause of the increasing prevalence of this virus remains poorly understood. Most of primary infections are asymptomatic or minimally symptomatic. Common symptoms of primary infection are fever and non-specific upper respiratory infection. Following a primary infection via the respiratory tract in childhood, these viruses are diffused in the blood using the B-lymphocytes during their latent stage in the urogenital tract.^{2,3} Transmission of the virus remains

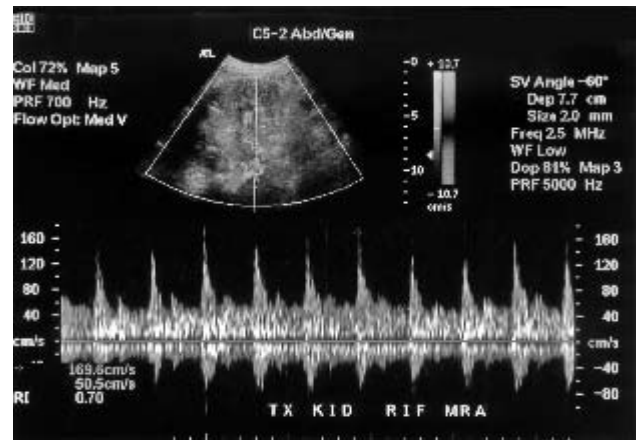


Figure 1 - Ultrasound of transplanted kidney; extra parenchymal with resistive index = 0.7 of transplanted renal artery, which is normal.

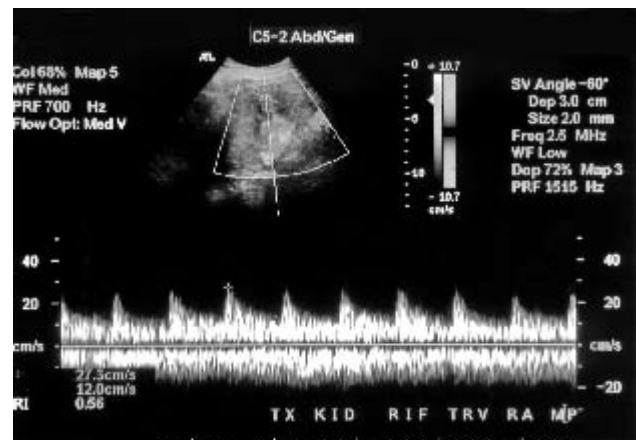


Figure 2 - Ultrasound of transplanted kidney; intra parenchymal with resistive index = 0.56 of transplanted renal artery, which is normal.

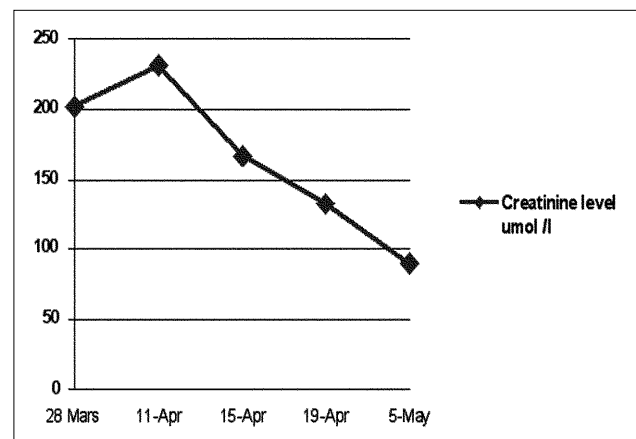


Figure 3 - The graph of sequential monitoring of creatinine level (normal range = 30-70 $\mu\text{mol/L}$) before and after decrease of immunosuppressive therapy.

unclear, however, is thought to occur by exposure of body fluids or transplacental passage.² Some authors have suggested that the natural mode of transmission of this virus is via the respiratory secretions, although gastrointestinal route has also been implicated.^{1,2,9} Polyomaviruses are often present in the stool samples from hospitalized children. These findings suggest that fecal-oral transmission of BKV may play a role in the ubiquity of the virus.¹⁰ It appears that the virus is transmitted from human to human and no known animal reservoir has been identified.³ Primary and reactivation infections have been seen in renal transplant recipients.^{2,5} Knowledge of these risk factors helps the clinician to identify subgroups of patients who might need to be more carefully monitored for polyomavirus reactivation. Urinary shedding of BKV is increased in immunocompromising conditions. The BKV disease is associated with hemorrhagic and non-hemorrhagic cystitis, ureteric stenosis and tubulointerstitial nephritis and allograft function loss.^{1,2,9} The incidence of infection is approximately 5%.³ Most infections occur within the first 3 months after the transplant; however, infections occurring greater than 2 years after transplantation have been reported.^{2,5} In our case, the infection occurred 7 months after the transplant with both viremia and viruria. Overt clinical disease from polyomavirus infection is rare, and is clearly linked to the degree of immunosuppression.^{1,5} A BKV nephropathy, is a clinical condition in renal transplant recipients, in which extensive BKV multiplication in the tubular epithelium results in loss of allograft function.^{3,9} The disease occurs in 2–3% of renal transplant recipients and is correlated with the shedding of many virus-infected epithelial cells in the urine,⁴ and with the presence of BKV DNA in the serum.^{5,6} Whenever an episode of renal dysfunction occurs in a renal transplant recipient, a polyomavirus infection such as, BK should be ruled out as the cause by performing appropriate tests. A BK viremia can be seen in patients with a wide variety of immunodeficiencies, but appears most often in renal and bone marrow transplant patients. Viremia reflects a later phase of disease and typically not seen without concomitant viruria. The clinical manifestation varies from the asymptomatic state of viremia to clinical renal dysfunction as in our case. The diagnosis of this infection is based on the combination of the presence of urinary decoy cells, virus in the urine/blood, and typical renal histological findings of interstitial nephritis.^{4,5,6} These features were present in the case reported here. Over the last decade, urine cytology is technically the simplest method to monitor polyomavirus infection after transplantation. Testing for BKV DNA in urine

and serum is a noninvasive early detection assay and monitoring tool.⁶ Serial measurement of viral loads by quantitative PCR is a useful tool in monitoring the course of BKV infection and the results should be interpreted in conjunction with the clinical picture and biopsy findings.⁶⁻⁸

The management of BKV disease in renal transplant recipients is not yet defined clearly and still evolving. Currently, reducing the dose of immunosuppressive therapy has been the best approach in treating BKV in transplant recipients.^{5,7,8} This was our own experience in this case. The effective and safe antiviral chemotherapy against BKV is desirable, and reported experience with antiviral management is only beginning to be explored over the last 4-5 years. A recent study successfully treated BKV interstitial nephritis patients with a cidofovir.¹¹ The study suggested that cidofovir may be useful in treating a subgroup of patients with BKV infection, as it showed to result in prolonged graft survival and stabilization of graft function.^{7,11} In another recent study, intravenous immunoglobulins was found to be a useful adjunct to the reduction in immunosuppression for the treatment of BK nephropathy.¹² Another recent study, found the administration of leflunomide at immunosuppressive doses as part of a moderate dose calcineurin-inhibitor-based, immunosuppressive scheme was associated with the eradication of BKV and improvement in renal graft function.¹³

In conclusion, whenever an episode of renal dysfunction occurs in immunosuppressed patients, a polyomavirus infection such as, BKV and JCV should be suspected as the cause. A positive screening result should be confirmed microbiologically and assess by quantitative assays (such as, BKV, DNA, or RNA load in plasma or urine).^{4,6,7} The PCR technique is a valid diagnostic tool to detect viral presence in urine and its systemic diffusion. Reducing the dose of immunosuppressive therapy is currently the best approach in treating BKV in transplant recipients.^{5,7,8} Further studies are needed to identify clinical and biological correlates of BKV infection in renal transplantation.

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