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BK virus nephropathy in the native kidneys of a pediatric heart transplant recipient

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Abstract: BK virus is a human polyoma virus that may cause nephropathy in immunosuppressed patients. It is a well-recognized cause of renal allograft dysfunction and allograft loss in renal transplant recipients, but it is an infrequent cause of nephropathy outside this setting. There are a few case reports of BK virus nephropathy in the native kidneys of immunosuppressed adult patients with non-renal transplants, but so far it has not been reported in pediatric non-renal solid organ transplant recipients. We report a case of a seven-yr-old heart transplant patient who was diagnosed with BK virus nephropathy, eight months after his second heart transplant. Despite intervention, his renal dysfunction progressed to renal failure. He is currently receiving maintenance hemodialysis and awaiting renal transplantation. It is important to recognize BK virus infection as a possible cause of renal dysfunction in immunosuppressed children who are non-renal transplant recipients.

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Key words: BK virus – polyoma virus – heart transplant – nephropathy – children – viral infections

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Polyoma virus nephropathy is recognized as an important cause of allograft dysfunction and graft loss in pediatric and adult renal transplant recipients (1, 2). Nephropathy secondary to BK virus in the native kidney is uncommon. Although there are published case reports of BK virus nephropathy in the native kidneys of adults with heart (3–6), lung (7, 8), pancreas (9), and bone marrow (6, 10, 11) transplant recipients, no cases have yet been reported in pediatric heart or solid-organ transplant recipients.

We present a case report of a seven-yr-old child who developed irreversible kidney failure secondary to BK virus nephropathy, following a second heart transplantation.

Case report

A previously healthy 17-month-old African-American male presented with congestive heart failure secondary to idiopathic cardiomyopathy. Renal evaluation was normal, with blood urea nitrogen of 15.0 mg/dL, serum creatinine of 0.4 mg/dL, and a normal renal ultrasound.

At 18 months of age, he received a cardiac transplant. Post-transplant immunosuppression included induction with antithymocytic globulin 15 mg/kg for five days, and maintenance therapy with cyclosporine and azathioprine. Cyclosporine trough levels were 250–300 ng/mL initially with taper to 150–200 ng/mL over one yr. Steroids were only used for rejection. He had eight episodes (three biopsy proven) of acute rejection. All rejection episodes were treated with 4–8 doses of intravenous methylprednisolone (20 mg/kg/dose BID). Two rejection episodes were also treated with antithymocytic globulin, and one rejection episode was treated with methotrexate. Three rejection episodes were also treated with 2 g/kg of IVIG. One year after the transplant, cyclosporine was switched to tacrolimus monotherapy. Target tacrolimus levels were 10–13 ng/mL. Subsequently, with addition of mycophenolate mofetil, tacrolimus was decreased to 5–8 ng/mL. The patient developed hypertension and was treated with enalapril and clonidine

Abbreviations: IVIG, intravenous gamma globulin; eGFR, estimated glomerular filtration rate; PCR, polymerase chain reaction; CMV, cytomegalovirus.

transdermal therapeutic systems patch. His serum creatinine was 0.4 mg/dL and eGFR was 120 mL/min/1.73 m^2. Four and a half yr after transplant, the patient's immunosuppression was converted to sirolimus with low dose tacrolimus because of renal insufficiency presumed to be secondary to calcineurin inhibitors. His serum creatinine was 0.7 mg/dL, and the eGFR was 84 mL/min/1.73 m^2 as calculated by the Schwartz equation (12). Urinalysis was normal, with no proteinuria or hematuria. Testing for polyoma virus was not performed. The patient received a second heart transplant at six yr and nine months of age. Induction immunosuppression consisted of five doses of anti thymocytic globulin and methylprednisolone, with a maintenance regimen of tacrolimus and sirolimus. Tacrolimus maintenance trough levels were 6–8 ng/mL, and sirolimus levels were 6–8 ng/mL.

Prior to the second heart transplantation the patient's serum creatinine was 0.9 mg/dL and eGFR was 70 mL/min/1.73 m^2. He developed acute renal failure following transplant surgery and was hemodialyzed for three days. At discharge, his serum creatinine was 1.0 mg/dL, with an eGFR of 62 mL/min/1.73 m^2. Ten months following the second heart transplant there was acute deterioration of renal function, and the serum creatinine rose to 3.6 mg/dL (eGFR 16 mL/min/1.73 m^2). A percutaneous kidney biopsy was performed, and the patient was started on hemodialysis. Renal biopsy demonstrated fairly advanced chronic tubulointerstitial injury with a mild lymphocytic interstitial nephritis and many intranuclear inclusions typical of BK-polyoma virus infection (Fig. 1). Immunostaining for SV-40 large T antigen (antibody to which cross-reacts with BK-polyomavirus) was also positive (Fig. 1), and electron microscopy demonstrated characteristic intranuclear viral particles of about 30–40 nm in size, providing additional confirmatory evidence (Fig. 2). BK virus PCR quantitative analysis of blood was reported to demonstrate 200 000 000 copies/mL.

The patient was treated with 0.5 g/kg of IVIG. Cidofovir at 0.5 mg/kg/dose was given once, and subsequently weekly doses of cidofovir were given at 0.25 mg/kg for five additional wk. Cidofovir was discontinued because the patient had generalized malaise, muscle aches, nausea, and emesis. Nine months later because of persistent BK viremia two more weekly doses of cidofovir (0.25 mg/kg) were tried, which the patient did not tolerate. Also, immunosuppression was lowered to Prograf trough levels of 2–4 ng/mL and sirolimus levels of 6–8 ng/mL. Although there was a slow decline in blood BK virus levels by PCR, there was no improvement in kidney function, and the patient continued on maintenance hemodialysis (Table 1).

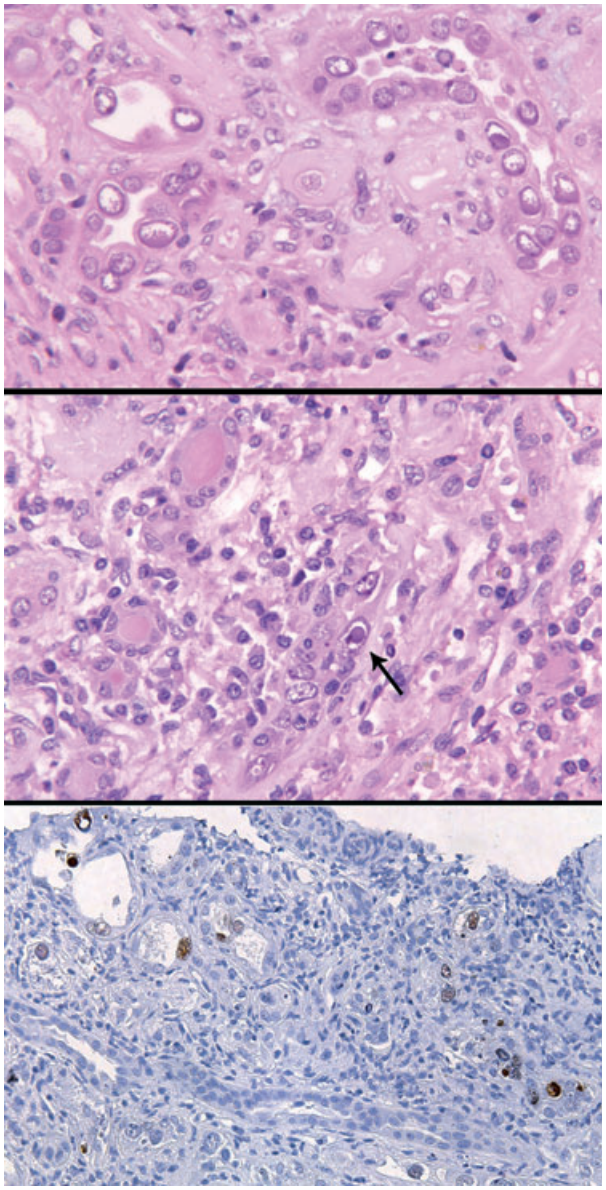

Fig. 1. Upper panel: Kidney biopsy, demonstrating margination of chromatin and "watery" intranuclear inclusions typical of BK-polyoma virus infection, within enlarged tubular epithelial cell nuclei. *Middle panel*: A more distinct intranuclear inclusion, somewhat resembling CMV, is present in one tubular cell nucleus (arrow), as can also be seen in BK virus infection. A mild interstitial nephritis is present in the background. *Lower panel*: Immunohistochemical stain for SV-40 T-antigen, demonstrating the typical reactivity in nuclei of scattered infected cells (positive nuclei are brown). (Upper and middle panels hematoxylin and eosin stain, lower panel immunoperoxidase stain).

This patient is currently 9.5 yr old and has been receiving maintenance hemodialysis for the past 2.5 yr. He has good cardiac function as measured by echocardiogram, and is receiving

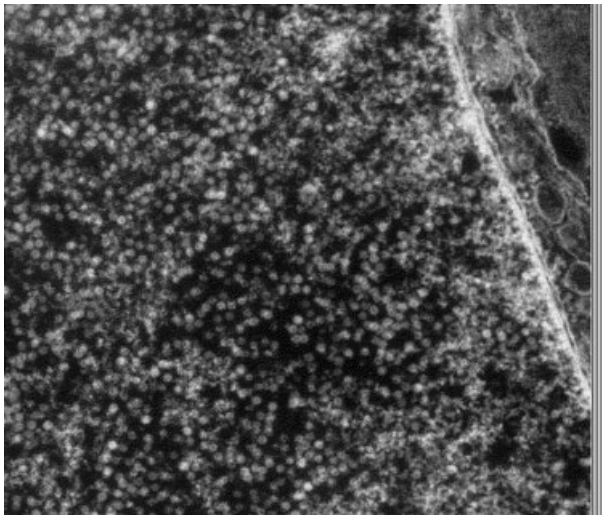

Fig. 2. High magnification electron micrograph demonstrating nuclear membrane at right, with multiple intranuclear viral particles having morphology typical of BK virus at left (original magnification × 45 000).

low dose tacrolimus (target levels = 2–4 ng/mL) and sirolimus (target levels = 5–7 ng/mL). He is currently awaiting a deceased donor renal transplantation. Two and a half yr after the diagnosis of BK virus nephropathy and lowering of immunosuppression, his blood continues to be positive for BK virus, with a recent blood BK virus PCR of 39 000 copies/mL.

Discussion

BK virus was first described in 1970, and is named after the initials of the sentinel patient. Primary infection with BK virus typically occurs in childhood, with the virus remaining latent in the bladder, renal epithelium and lymphoid cells. Polyoma virus is now well recognized as a renal pathogen in immunosuppressed pediatric and adult renal transplant recipients (1, 2).

BK virus nephropathy much less commonly occurs in the native kidneys of non-renal transplant recipients. There have been a few case reports of BK virus nephropathy in the native kidneys of adult heart (3–6), lung (7, 8), pancreas (9), and bone marrow (6, 10, 11) transplant recipients. In children, BK virus nephropathy outside the setting of renal transplantation is very uncommon. It has been reported in a 14 yr old with cord blood transplant for acute myeloid leukemia (11), and in a five yr old on chemotherapy for acute lymphoblastic leukemia (13). Our patient diagnosed with BK nephropathy at seven yr of age is to our knowledge the first pediatric heart transplant recipient reported to develop renal failure secondary to BK virus nephropathy.

Our patient presented with a decline in renal function much like that of renal transplant recipients, in whom BK virus nephropathy often presents with progressive graft dysfunction heralded by a rising serum creatinine. The diagnosis of BK nephropathy can be established by the demonstration of viral replication in blood, and by a kidney biopsy. It has been suggested that a persistent plasma BK virus load of 10 000 - copies/mL or more for more than three wk is highly suggestive of BK virus nephropathy in renal transplant recipients (2). An appropriate copy

Table 1. Clinical course and therapy

Age in yr	Event	eGFR mL/min/1.73 m^2	Immunosuppression
1½	First heart transplant	120	ATG 15 mg/kg × 5 days CSA 250–300 ng/mL initial CSA 150–200 ng/mL maintenance MMF 3–5 mcg/mL
2½	Hypertension	120	Tacrolimus 10–13 ng/mL initial 5–8 ng/mL maintenance MMF 3–5 mcg/mL Multiple episodes of rejection
6	Renal insufficiency	84	Tacrolimus 8–10 ng/mL Sirolimus 6–8 ng/mL
6¾	Second heart transplant	70	ATG 15 mg/kg × 5 days Tacrolimus 6–8 ng/mL Sirolimus 6–8 ng/mL
7½	BK virus on renal biopsy hemodialysis	16	Tacrolimus 2–4 ng/dL Sirolimus 5–7 ng/dL Cidofovir 0.25–0.5 mg/kg IVIG 0.5 g/kg
9½	Maintenance hemodialysis		Tacrolimus 2–4 ng/dL Leflunomide 10–20 mg/day IVIG 2 g/kg monthly × 3

ATG, antithymocytic globulin; CSA, cyclosporine; eGFR, estimated glomerular filtration rate; IVIG, intravenous gamma globulin; MMF, mycophenolate mofetil.

number threshold has not been established for non-renal transplant recipients.

The definitive diagnosis of BK virus nephropathy requires a renal biopsy. The typical lesion is a patchy interstitial nephritis with characteristic intranuclear viral inclusions that most typically either have a watery or finely granular appearance, but can be more distinct with a perinuclear halo somewhat resembling CMV. The interstitial nephritis can mimic acute cellular rejection if the viral inclusions are not recognized. Immunohistochemical staining for SV40 (large T antigen) can be helpful in confirming the diagnosis, as this antibody cross-reacts with the BK polyoma virus. If infected cells are present in the portion of the biopsy for electron microscopy, intranuclear viral particles approximately 40 nm in size can be demonstrated (14). Our patient had both, high PCR copy counts and biopsy confirmation of BK virus nephropathy.

The incidence of BK nephropathy appears to correlate with the degree and duration of immunosuppression. Our patient was immunosuppressed from 17 months of age. More importantly he had also received multiple doses of antirejection therapy with his failing first heart transplant, and increased immunosuppression (antithymocytic globulin induction) with his second heart transplant.

Our patient's progression to renal failure was no doubt facilitated by (i) his substantial lifetime immunosuppression burden, which may have contributed to development of a more severe nephropathy, (ii) continued immunosuppression necessary to avoid cardiac allograft rejection, and (iii) his substantial substrate of underlying chronic kidney disease as a result of multiple renal insults, including episodes of poor cardiac function, and calcineurin inhibitor toxicity. These factors limited his renal reserve, such that the injury due to BK virus had a proportionately greater effect than on a normal kidney. Since this patient was immunosuppressed from 18 months of age, it is likely that he had a primary BK virus infection during his prolonged course of immunosuppression, although a reactivation of BK virus that the patient acquired before his first cardiac transplant is also a possibility. The persistent decline in kidney function and the very high BK virus PCR copy count would be consistent with a prolonged duration of BK virus nephropathy.

This patient is currently on hemodialysis, awaiting a deceased donor renal transplant. He continues to have high levels of BK viral replication and with ongoing BK viremia, the question arises as to when he should undergo kidney transplantation. Kidney transplant in the face of persistent viremia may place him at higher risk for BK nephropathy in the transplant kidney and subsequent graft loss. In the renal transplant recipients, it is recommended that re-transplantation for graft failure due to BK virus nephropathy is performed when there is no evidence of active BK virus replication. The role of nephrectomy of the infected graft prior to retransplantation in patients with BK viremia is unclear (15). Success with allograft nephrectomy at the time of re-transplantation has also been reported during active BK nephropathy (16). The primary therapeutic intervention for BK nephropathy is careful lowering of immunosuppression early in the course of BK nephropathy. Additional therapy may include use of quinolones, leflunomide, cidofovir, and IVIG (17). In our patient we plan to use leflunomide, with repeated doses of IVIG, and consider native nephrectomy prior to renal transplant if BK viremia persists.

Should recipients of all transplants be monitored for BK viremia? In a study of 173 kidneys and 24 hearts and 37 liver transplants, Puliyanda et al. reported BK viremia in 7/173 (4%) patients with kidney transplant, 1/37 (2.7%) with liver transplant, and 0/24 heart transplant recipients. Six out of seven renal transplant recipients in this series had BK virus DNA $> 2 \times 10^5$ copies/mL, while the liver transplant recipient had low titers. Four out of the six renal transplant biopsies showed typical features of BK virus nephropathy. The study suggests that the risk for BK virus nephropathy to be highest in renal transplant recipients and very low in recipients of non-renal solid organ transplants (18). Other authours have reported BK viuria in 15–26.5%, and BK viremia in 0–12% of adult recipients of solid organ transplants (19–21), In a study of children aged 1–18 yr, BK virus was detected in urine samples of 19 of 38 (50%) renal transplant recipients, and one of seven (14%) patients with renal disease on immunosuppression. In the same pediatric series, 8/38 (21%) renal transplant recipients and 2/42 (4%) non-transplant renal patients had plasma samples positive for BK virus by PCR (22). It is unclear why BK virus nephropathy appears to occur relatively frequently following renal transplant but only rarely in native kidneys of non-renal transplants. Some have suggested that renal tubular injury during the process of renal transplantation or during allograft rejection may activate or otherwise facilitate polyoma virus infection, leading to nephropathy. Pendese et al. (23) have suggested that a second, organ-specific hit such as kidney inflammation, kidney ischemia, or donor-recipient human leukocyte antigen mismatch is

necessary for the development of active nephropathy. This may in part explain the greater frequency of BK virus nephropathy in kidney transplant recipients compared to other solid organ transplants.

Renal dysfunction in the cardiac transplant recipient traditionally has been attributed to use of calcineurin inhibitors and other nephrotoxic drugs, as well as repeated episodes of renal hypoperfusion during cardiac allograft dysfunction. Also, the native kidneys in some patients have been subjected to prolonged ischemia or poor perfusion prior to cardiac transplantation. Prior to 2005 when this case presented, we were not aggressive in performing a kidney biopsy or obtaining BK virus PCR testing in cardiac transplant recipients with slowly rising serum creatinine. We biopsied this patient primarily because he had an acute unexplained rise in serum creatinine. A higher level of physician suspicion and more frequent testing may yet show that BK virus nephropathy rates in the native kidneys in immunosuppressed patients are higher than currently reported. Clinicians should have a high index of suspicion, and consider BK nephropathy of the native kidneys, in the differential diagnosis of patients with rising serum creatinine in all pediatric transplants, and perhaps all immunosuppressed children.

In conclusion, BK virus nephropathy can occur in the native kidneys of pediatric non-renal transplant recipients. We have changed our clinical approach so that all pediatric non-renal transplant patients and immunosuppressed patients with rising serum creatinine are tested for BK virus by PCR, and a renal biopsy performed when indicated. These patients may benefit from early detection and careful modification of their immunosuppressive regimens, with the intent of avoiding irreversible renal damage. However, significant reduction in immunosuppressants may not always be possible in some transplant recipients particularly those in whom the consequences of non-renal graft loss are of more critical importance than maintaining renal function.

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