Fatal Cardiovascular Collapse Due to BK Virus Infection of Capillary Endothelial Cells in a Renal Transplant Recipient: A Novel Clinical Syndrome

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Fatal Cardiovascular Collapse Due to BK Virus Infection of Capillary Endothelial Cells in a Renal Transplant Recipient: A Novel Clinical Syndrome

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BK virus (BKV) is an increasingly recognized cause of acute renal allograft dysfunction. The most common manifestations of BKV infection in renal transplant patients include asymptomatic viral shedding in the urine, renal allograft dysfunction, and ureteral stenosis. This is the first report of BKV infection causing systemic endothelial cell injury with capillary leak, cardiovascular collapse, multiorgan failure, and death. The authors alert clinicians to this as a possible emerging infection in the setting of more potent immunosuppression regimens among renal transplant patients.

Case Report

A 52-year-old man with type 1 diabetes mellitus complicated by end-stage renal disease underwent a cadaveric renal transplant in February 1999 after 2 years of hemodialysis. Within 2 weeks of his transplant, he experienced an episode of acute renal failure. Histological analysis of the renal allograft biopsy revealed an intense interstitial nephritis without tubulitis. The patient was treated for possible rejection and/or cyclosporine (Sandimmune) toxicity with a 1-week course of OKT3 (Muromonab-CD3) and subsequent conversion from cyclosporine to tacrolimus (Prograf). His renal function improved and stabilized to a serum creatinine level of 1.6 mg/dl. His immunosuppressive regimen consisted of prednisone 10 mg po qd, mycophenolate mofetil (Cellcept) 500 mg po tid, and tacrolimus (Prograf) 3 mg po bid. Prior to transplant, the patient had negative tests for human immunodeficiency virus (HIV) and hepatitis B and C. He was cytomegalovirus (CMV) IgG positive and was treated for 3 months with oral ganciclovir 500 mg po tid. He was discharged to home on simvastatin (Zocor) 20 mg qd for hyperlipidemia.

In early September 1999, he developed bilateral lower extremity weakness. This progressed to difficulty walking over the next 7 to 10 days. Concomitantly, he noticed gradual onset dyspnea on exertion and bilateral upper extremity edema. He denied any fevers, chills, headache, nausea, vomiting, abdominal pain, change in bowel habits, or urinary symptoms. He presented to an outside hospital, where he was found to have a serum creatine kinase (CPK) level of 339 mIU/dl. His simvastatin was discontinued, and he was transferred to our hospital with a diagnosis of statin-induced myositis. His other medications included trimethoprim/sulfamethoxazole (Bactrim) SS qd, furosemide (Lasix), amlodipine (Norvasc), atenolol (Tenormin), aspirin, insulin, and vitamin E.

On admission, he appeared fatigued with shallow breathing. He was afebrile with blood pressure 110/40 mmHg, respiratory rate 22/min, and oxygen saturation of 95% on room air. There was no scleral icterus or lymphadenopathy. His lungs were clear and heart sounds distant without murmur. There was no abdominal organomegaly, and the kidney allograft was nontender. His extremities

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showed diffuse edema, and the biceps were tender. There were no rashes. His neurological exam showed normal mentation, cranial nerve, and cerebellar testing. Strength was decreased proximally (3/5) more than distally (4/5) in four extremities, consistent with generalized myopathy. Deep-tendon reflexes were normal, and the plantar responses were flexor bilaterally. Vibration sense was decreased distally in the lower extremities, indicating the presence of a distal symmetrical sensory polyneuropathy.

Admission blood work revealed a white blood cell count of 18,200/µl (70% neutrophils, 17% bands); hematocrit, 35.0%; platelets, 150,000/µl; international normalized ratio (INR), 1.0; and erythrocyte sedimentation rate, 41 mm/h. Serum electrolytes, liver enzymes, and amylase were normal. Other relevant blood chemistries included the following: blood urea nitrogen, 71 mg/dl; serum creatinine, 2.4 mg/dl; glucose, 263 mg/dl; CPK, 629 mIU/dl; and albumin, 2.5 mg/dl. The urinalysis revealed no proteinuria or cells.

During the first few days in hospital, the albumin dropped to 1.7 mg/dl, and worsening anasarca developed, especially in the upper extremities. Magnetic resonance imaging of the mediastinal arterial and venous systems did not show any thrombus or vascular anomalies. The CPK peaked at 1317 mIU/dl and then remained between 600 and 800 mIU/dl. His weakness progressed, and he developed bilateral biceps pain and tenderness. The white blood cell count continued to rise to 28,000/µl with a left shift. His immunosuppressive therapy was stopped except for steroids. The patient developed hypotension and mental status changes and was transferred to the intensive care unit. Serum creatinine increased to 3.4 mg/dl. A renal allograft biopsy showed mild to moderate interstitial fibrosis and tubular atrophy. Some small vessels showed myxoid intimal fibroplasia and foci suggestive of fibrinoid necrosis. There was no evidence of rejection.

A lumbar puncture was performed revealing normal opening pressure and cerebrospinal fluid (CSF) parameters. CSF cultures for bacteria, mycobacteria, fungi, and viruses were negative. The CSF Venereal Disease Research Laboratory (VDRL) test and cryptococcal antigen were negative. Serum thyroid-stimulating hormone, free T_4, and cortisol were normal. Multiple blood cultures for bacteria, fungi, and mycobacteria were negative; serum cryptococcal antigen and rapid plasma reagin (RPR) were negative; serum CMV rapid antigen testing was negative; HIV, Epstein-Barr virus, *Borrelia burgdoferi*, toxoplasma, mycoplasma, echovirus, adenovirus, and coxsackie serologies were unrevealing; and urinary legionella antigen was negative. A transthoracic echocardiogram showed normal systolic function with concentric hypertrophy and decreased filling. No pericardial effusion was present.

Shortly thereafter, he was resuscitated from an asystolic arrest and required vasopressor support. The electrocardiogram showed low voltage throughout all leads, and enzyme measurement confirmed myocardial injury. He developed episodes of rapid atrial fibrillation and atrial flutter. The INR increased to 2.9, the albumin fell to 0.9 mg/dl, and the platelet count fell to 33,000. There were no heparin-induced antibodies, and a DIC screen was negative.

Over the next 5 days, he developed worsening anasarca and hypotension. Intravascular monitoring revealed a low cardiac index with hypovolemia. Despite aggressive therapy with both crystalloids and colloids, his cardiac output and intravascular volume were difficult to maintain due to progressive systemic capillary leak. He developed acute renal allograft failure, and hemodialysis was initiated.

A deltoid muscle biopsy (Fig. 1A) showed large and atypical endothelial cells lining small blood vessels and capillaries. These cells had large nuclei with hyperchromasia and frequent intranuclear inclusions (Figure 1B). Some of the endothelial cells had undergone morphological changes consistent with apoptosis, and some small vessels were completely necrotic. The patient was started on intravenous ganciclovir (Cytovene), doxycyline, and ciprofloxacin (Cipro) to cover cytomegalovirus, ehrlichia, and rickettsia. He expired the subsequent day (hospital day 19) despite maximum support. At autopsy, similar findings were seen in blood vessels within the myocardium.

Polyomavirus was identified in the muscle biopsy using antipolyomavirus polyclonal antibody immunoperoxidase staining (Fig. 2). Electron microscopy of the muscle biopsy showed that the en-

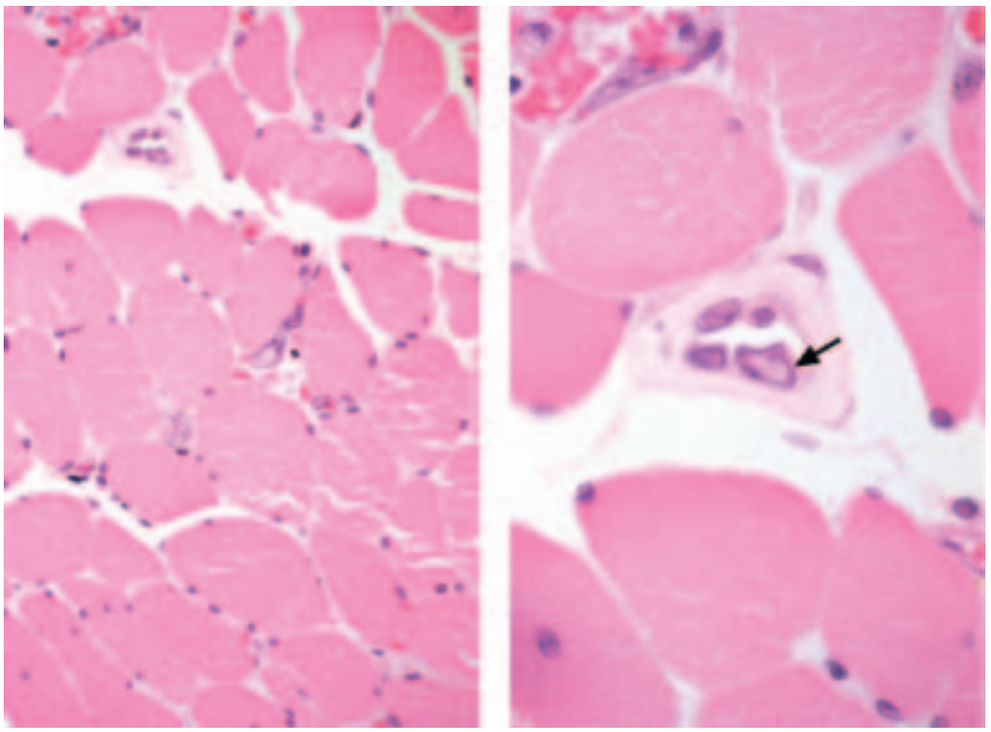

Figure 1. Left panel shows a low-power (100×) magnification of the skeletal muscle biopsy under hematoxylin and eosin staining. Remarkable is the paucity of inflammatory cells, given the prebiopsy clinical diagnosis of myositis. Righthand panel is a high-power (400×) magnification of the same sample, highlighting a muscle capillary and the atypical appearance of the endothelial cells. The arrow indicates an inclusion body within the nucleus of the endothelial cell.

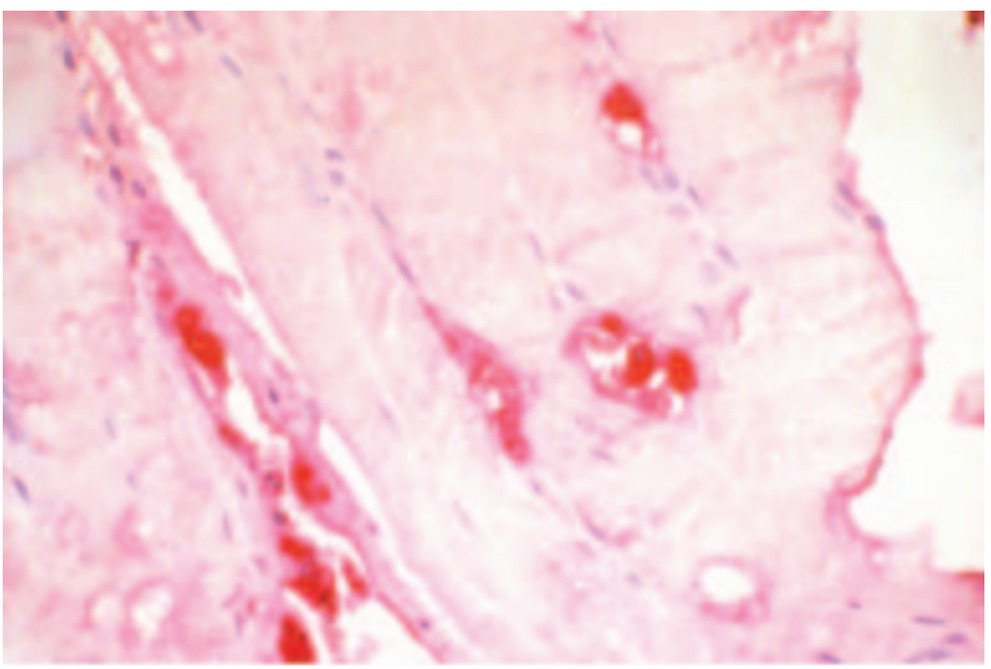

Figure 2. Immunoperoxidase staining of deltoid muscle biopsy using a polyclonal antibody against polyomavirus.

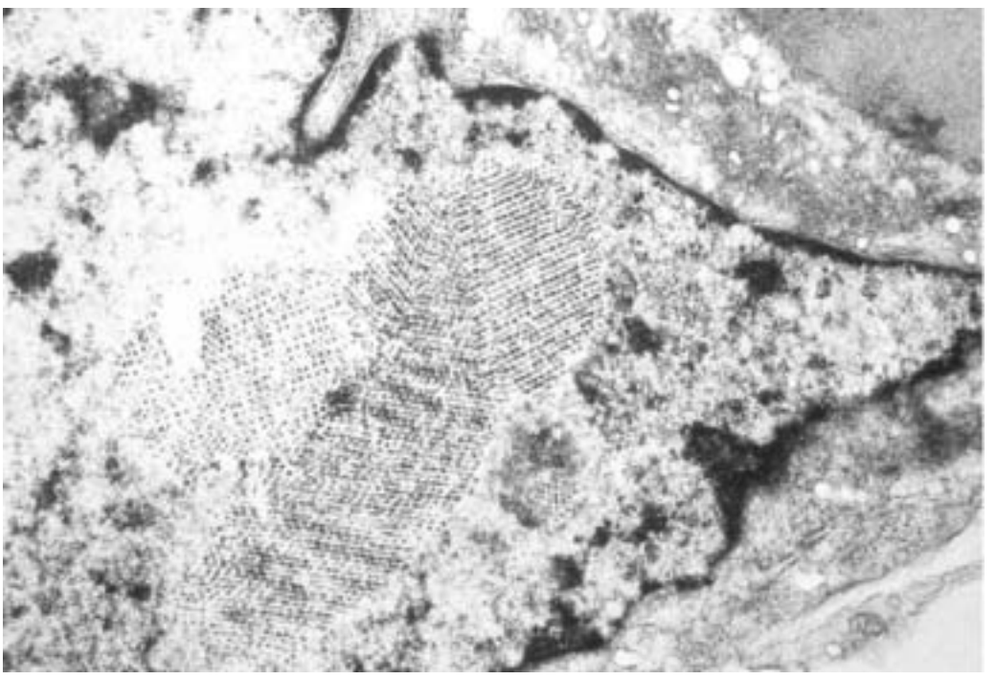

Figure 3. Electron micrograph (45,000×) demonstrating polyomavirus BK within an endothelial cell inclusion body.

dothelial cell viral inclusion particles were polyomavirus (Fig. 3). The polyomavirus was speciated to BK virus (BKV) using specific polymerase chain reaction (PCR) primers and confirmed using dot blot hybridization of the PCR amplicons. Control experiments using JC virus primers and probes were negative (data not shown).

Retrospective serologic analysis of both donor and recipient sera for previous BKV exposure demonstrated that the patient had IgG antibodies prior to transplant and developed a strong positive IgM response at the time of this illness, suggesting a reactivation of preexisting infection rather than a primary infection. The renal allograft donor was negative for both IgG and IgM antibodies (Table 1).

Discussion

We present a clinical discussion of a recently described case of BKV-induced endothelial destruction in an immunosuppressed kidney transplant patient with diabetes.[1] To our knowledge, this is the first report of the syndrome of multiorgan failure with capillary leak syndrome due to endotheliitis caused by a polyomavirus in humans.[1] Prior to this illness, the patient had received 40 mg simvastatin, in combination with a calcineurin inhibitor. The findings of an elevated CPK, muscle pain, and weakness led to some delay in diagnosis as the syndrome was initially felt to be consistent with statin-induced myositis.

Polyomaviruses are widely distributed in nature.[2] BKV was first isolated from the urine of a renal transplant patient who developed ureteral stenosis postoperatively.[3] In the United States, antibodies to BKV are acquired by 50% of children by ages 3 to 4. The antibody prevalence to BKV reaches nearly 100% by ages 10 to 11 and then declines to 70% to 80% in older groups.[2] The mode of acquisition is believed to be either via the respiratory system or the urine-oral route.[2,4,5] In view of the ubiquitous presence of BKV (and JC virus) in the urine of normal people, the lack of proven aerosolization of these viruses, or their presence in saliva, makes the urine-oral route more likely.

Various clinical syndromes attributed to polyomaviruses have been described in renal transplant recipients and other immunosuppressed hosts. BKV causes renal failure secondary to acute interstitial nephritis, distal ureteral stenosis, hemorrhagic cystitis and (less commonly) desquamative interstitial pneumonitis, upper respiratory tract disease, and meningoencephalitis.[2,4,6] The most common scenario is one of asymptomatic infection, in which the virus may be detected in the urine without evi-

Table 1 | **BKV Serologies of Patient and Renal Allograft Donor**

Serum Specimen	IgM Antibody Titer	IgG Antibody Titer
Patient pretransplant	640 (negative)	163,840 (positive)
Patient at time of illness	40,960 (positive)	163,840 (positive)
Donor	160 (negative)	2560 (negative)

Low to negative ≤ 2560; 2560 > moderately low < 10,240; 10,240 ≥ moderately high < 40,960; high ≥ 40,960.[24]

dence of disease.[4,6] The ubiquitous nature of the virus and its detection in asymptomatic patients provides diagnostic challenges to clinicians managing patients with BKV-mediated disease. Recent findings suggest that serum PCR for BKV may assist clinicians in discriminating between patients with asymptomatic infection from those with active or at high risk for developing end-organ disease.[7,8] Readers are also referred to a very recent comprehensive clinical review on BKV for a more detailed discussion.[4]

Fatal disease from BKV has been described but is rare. All the fatal reported cases occurred in immunosuppressed children. A 6-year-old with hyper-IgM syndrome died of disseminated BKV infection manifested by tubulointerstitial nephritis and pulmonary disease.[9] A 5-year-old child with Hodgkin's disease and cartilage-hair hypoplasia died of renal failure due to BKV.[10] A fatal case of BKV pneumonitis and acute respiratory distress syndrome with concomitant hemorrhagic cystitis and renal failure was reported in an 8-month-old girl following stem cell transplantation.[11] The most recent reported case was of a 14-year-old boy with acquired immunodeficiency syndrome (AIDS) who developed fulminant hepatopulmonary disease with diffuse alveolar damage and death.[12] Although details in many of these cases are lacking, the frequent lung involvement in children may suggest that these may have been primary infections rather than reactivation of latent infection.

Polyomaviruses can induce endothelial cell transformation in nude mice, resulting in tumors that are very similar in appearance to human Kaposi's sarcoma (KS).[13] Indeed, endothelial infection by BKV in humans is supported by the demonstration of BKV DNA sequences in a high fraction of KS using PCR.[13] Some authors suggest that reactivated BKV can secondarily infect KS tissue and hasten KS progression through increased cytokine and growth factor production.[13] The case we describe was unique because endothelial cell infection in this patient resulted in fulminant and fatal consequences. The polyomavirus in this patient may represent either a novel BKV strain that evolved into an endothelial cell-tropic phenotype or a novel polyomavirus antigenically related to BKV with strong tropism to endothelial cells. Preliminary evaluation by one of us suggests that this polyomavirus is BKV with unique genotypic changes (Koralnik IJ et al., unpublished data). Phenotypic studies of this virus in vitro are in progress.

It is unclear if and how the host patient and/or the donor allograft may have provided a unique milieu for this fatal disease. The fact that he was taking tacrolimus and mycophenolate mofetil probably increased the chances of BKV reactivation.[4] In hindsight, the diagnosis of acute interstitial nephritis in the early posttransplant period may have occurred secondary to undiagnosed systemic reactivation of BKV with primary infection of a previously BKV-naive renal allograft. The extensive viral replication that would have ensued after treatment with OKT3 could have provided an environment for the development of mutations in the noncoding regulatory region of the viral genome, leading to altered cell tropism.[14,15] Although these conclusions are clearly speculative, they raise potential concerns about the importance of correctly diagnosing patients with renal allograft interstitial nephritis due to BKV.

Although this case is novel in the literature, we believe that cases like it have previously occurred but have not been diagnosed. For example, a report of a fatal idiopathic capillary leak syndrome in a renal transplant patient demonstrated a clinical

course similar to our patient, but studies looking for BKV were not performed.[16] In addition, post-transplant microangiopathic syndromes may, in some cases, have a similar presentation of diffuse endothelial injury. It is very likely that several of these cases may be mediated by BKV endothelial injury. Evaluation of renal transplant patients with hemolytic uremic syndrome for BKV infection using PCR of serum may be of interest. With our report, increased awareness may reveal more cases of BKV infection reported by other clinicians. Although rare, this syndrome is fatal, and further knowledge about potential prevention could be lifesaving, especially given that there is no obvious effective treatment once disease occurs. The reduction in immunosuppressives in this patient proved to be too little, too late.

Based on the scant amounts of published data, treatment of BKV infection in renal transplant patient lies largely in reducing the level of immunosuppression.[4,17,18] In patients with HIV-induced suppression of cell-mediated immunity, treatment with highly active antiretroviral therapy remains the modality of choice in treating polyomavirus infections, although no controlled studies have validated this approach.[4] Case reports demonstrating benefits of vidarabine in BKV-mediated hemorrhagic cystitis[19] and cytarabine in JC virus–mediated progressive multifocal leukoencephalopathy[20,21] are largely anecdotal and difficult to extrapolate to renal transplant patients with allograft interstitial nephritis, especially to cases such as this. Cidofovir demonstrates in vitro activity against some polyomaviruses[22] and was used in a case report of BKV hemorrhagic cystitis.[23]

In conclusion, we report a novel case of polyomavirus infection and destruction of systemic endothelial cells resulting in muscle pain and weakness and subsequent cardiovascular collapse secondary to systemic capillary leak, multiorgan system failure, and death. The identified polyomavirus represents a novel BKV strain with endothelial cell tropism. We hope this report will alert clinicians caring for renal transplant patients to the possibility of this syndrome in compatible cases, especially those in whom myositis, microangiopathic syndromes, or systemic capillary leak is noted or suspected.

Acknowledgments

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