Polyomavirus Allograft Nephropathy: Parenchymal and Extraparenchymal Manifestations

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Viral infections are a leading cause of posttransplant morbidity and mortality. Polyomavirus, represented by one its members, the BK virus (BKV), causes asymptomatic latent infection in the human host. Reactivation of this virus during periods of immune suppression has been associated with nephropathy and vasculopathy. The authors describe two cases of BKV allograft nephropathy, stressing the different and quite unpredictable presentation and response to therapy. One patient presented with acute rejection, BKV tubulointerstitial nephritis, and eventual renal allograft failure despite reduction of immunosuppression and antiviral therapy. The second patient presented with viral allograft nephropathy followed by obstructive allograft ureteropathy. Placement of ureteral stent in addition to a reduction of immunosuppressive agents resulted in recovery of allograft function.

ABBREVIATIONS:

BKV	BK virus
MMF	Mycophenolate mofetil
IVIG	Intravenous immunoglobulin
HLA	Human leukocyte antigen
CMV	Cytomegalovirus
MHC	Major histocompatibility
PCR	Polymerase chain reaction

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Introduction

A recently recognized cause of morbidity and mortality in the posttransplant period is the polyoma family of viruses, especially one of its members, the BK virus (BKV). BKV is a nonenveloped DNA virus, ubiquitous in the environment, that induces a pleomorphic disease in humans from asymptomatic viruria to allograft loss in solid organ transplant recipients.[1] BKV infection after kidney transplantation is most often asymptomatic but may present with pyuria, interstitial nephritis, ureteral stenosis, and, in cases of bone marrow transplantation, hemorrhagic cystitis.[2] Although various immunosuppressive regimens may be incriminated in some cases, the degree of immunosuppression has been thought to represent an even more important risk factor for the development of manifestations of this infection.[3] Currently, there is no proven antiviral therapy for posttransplant BKV infection. Decreasing immunosuppression and use of certain antiviral agents may allow clearance of virus by the host defense system.[4,5] We discuss two cases of polyomavirus-associated allograft nephropathy to illustrate the need for a high index of suspicion in transplant recipients.

Case History 1

A 60-year-old Hispanic male developed end-stage renal disease secondary to diabetic nephropathy. In December 2000, he received a living related (one haplotype human leukocyte antigen [HLA] match) kidney transplantation. Good graft function was noted immediately, as documented also by renal scan on the first postoperative day. He received 5 days of Thymoglobulin® (Sangstat Medical Corporation, NJ), 1 to 1.5 mg/kg/day (dose was adjusted based on absolute and/or percent CD-3 lymphocyte counts), and maintenance immunosuppression consisted of tacrolimus (maintaining 12-h trough levels of 10–15 ng/ml), mycophenolate mofetil (MMF: 1000 mg bid), and prednisone. On this regimen, his serum creatinine reached a baseline concentration of 1.5 mg/dl. Approximately 12 months posttransplant, during a routine follow-up visit, his serum creatinine was found to be 2.1 mg/dl. The patient's clinical course is depicted in

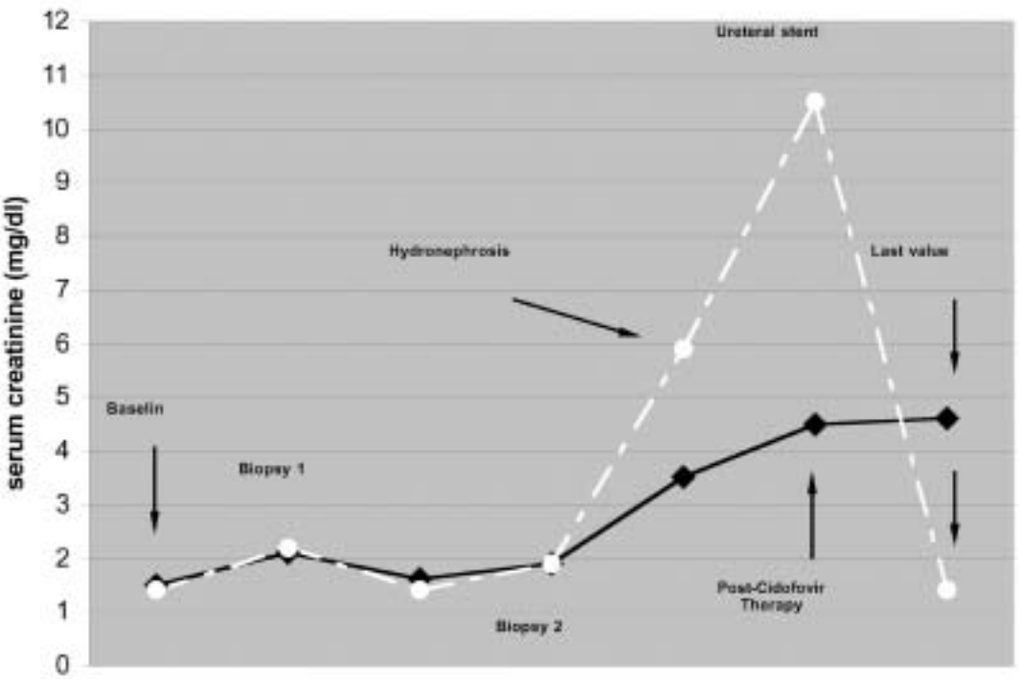

Figure 1. Serum creatinine (mg/dl) in 2 patients with polyomavirus allograft nephropathy. Case 1 is symbolized by filled diamonds, whereas case 2 is symbolized by filled circles. After initial baseline creatinine values, case 1 (♦) underwent the first biopsy and therapy for acute allograft rejection (biopsy 1), followed by a second biopsy (biopsy 2), which revealed viral inclusions. The next creatinine value is shown at completion of cidofovir therapy and the last at the time of initiation of dialysis. Case 2 (●) underwent the first biopsy (biopsy 1) and was found to have possible tacrolimus toxicity. The second biopsy (biopsy 2) was performed for elevated creatinine, and viral inclusions were identified. Serum creatinine continued to rise, and hydronephrosis was diagnosed. After ureteral stent placement, serum creatinine returned to normal.

Figure 1 (symbol ♦). He denied any systemic complaints, and physical examination was unremarkable. A percutaneous renal allograft biopsy revealed mild acute allograft rejection (Banff class IA),[6] and there was no evidence of viral inclusion bodies. Treatment with methylprednisolone led to stabilization of serum creatinine. However, over the ensuing 3 months, the renal allograft function deteriorated, and he developed nephrotic range proteinuria (5.5 grams/24 h). A repeat allograft biopsy revealed the presence of prominent interstitial infiltrates and virus inclusions in the tubular epithelium (Fig. 2). Immunohistochemical staining with polyoma antibody was positive. His serum was positive for polyomavirus by polymerase chain reaction, and urine cytology specimen showed several "decoy cells" (Fig. 3). Serologic studies for cytomegalovirus were negative. The MMF dose was reduced to 500 mg bid, and tacrolimus was dosed to maintain a 12-h trough level between 5 and 10 ng/ml. He received intravenous gamma globulin (IVIG), 400 mg/kg/d (5% Polygam®, American Red Cross, Washington D.C.), for 5 days. However, his serum creatinine continued to rise, serum remained positive for polyomavirus, and "decoy cells" persisted in urine. At this point (4 weeks after last dose of IVIG), after adequate parenteral hydration, the patient was administered cidofovir (60 mg; 0.7 mg/kg intravenously). He received two more treatments with cidofovir (85 mg; 1 mg/kg) at 15-day intervals. Despite therapy, he developed further deterioration in renal function, his urine continued to be positive for polyoma virus, and the patient required initiation of dialysis almost 2 years after transplantation (approximately 6 months after diagnosis of polyomavirus infection).

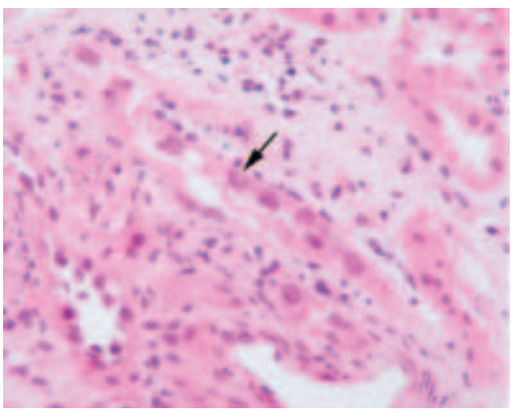

Figure 2. Histopathology of renal allograft tissue from case 1 showing renal tubule lined by degenerating epithelial cells infected with polyomavirus. Typical lightly basophilic intranuclear inclusions can be appreciated (arrow) (hematoxylin and eosin 200×).

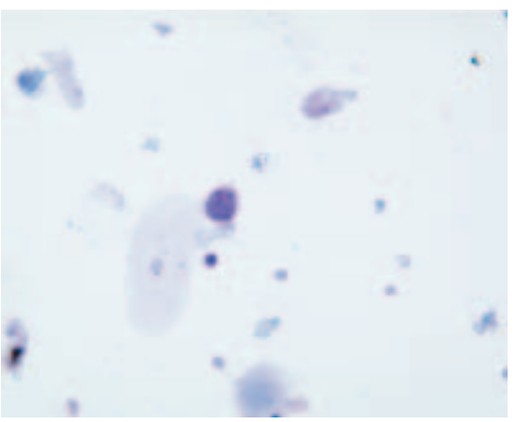

Figure 3. Urine cytology from case 1 showing "decoy cell" (polyomavirus-infected urothelial cell) in the center of the photomicrograph field. Note the rounded nucleus with smudgy, glassy intranuclear inclusion and margination of nuclear chromatin (Papanicolaou stain, 400×).

Case History 2

A 36-year-old Caucasian female was diagnosed with diffuse proliferative lupus nephritis. Despite cyclophosphamide and steroid therapy, her renal function declined, and she reached end-stage renal failure. Two years later, she received a cadaveric renal transplant (zero HLA A, B, DR mismatch). The postoperative course was complicated by severe acute tubular necrosis, and she received induction therapy with Thymoglobulin® (Sangstat Medical Corporation, NJ), 1 to 1.5 mg/kg/day (dose was adjusted based on absolute and/or percent CD-3 lymphocyte counts), for 5 days. Maintenance immunosuppression was initiated with tacrolimus (12-h trough level between 5–10 ng/ml), MMF (1000 mg bid), and prednisone. MMF was discontinued due to persistent diarrhea and neutropenia, and sirolimus was added to the immunosuppressive regimen (maintaining 24-h trough levels from 5–10 ng/ml). One month posttransplant, she developed a rise in serum creatinine, and the allograft biopsy revealed no evidence of acute rejection or viral inclusion bodies. The patient's clinical course is depicted in Figure 1 (symbol •). A slight decrease in tacrolimus and initiation of therapy with a calcium channel blocker led to a return of the serum creatinine concentration to baseline values. Approximately 6 months later, a repeat allograft biopsy was performed when her serum creatinine concentration increased from a baseline of 1.4 to 1.9 mg/dl. Histopathology again revealed the absence of acute rejection, but this time it was significant for viral inclusions. At that hospital admission, a nonobstructive hydronephrosis was noted. Her serum was positive for cytomegalovirus (CMV) antigen (pp65 antigen). Virologic studies for polyomavirus were not performed. Sirolimus was discontinued, and the patient was started on oral ganciclovir (dose adjusted for renal function). After 21 days, while receiving oral ganciclovir, her serum creatinine continued to rise. A repeat biopsy demonstrated diffuse tubulointerstitial infiltrate with basophilic intranuclear inclusions consistent with polyoma virus infection. Immunohistochemical staining with polyoma antibody was positive. Her serum was positive for polyomavirus by polymerase chain reaction, and "decoy cells" were also identified in her urine cytology specimen. In addition, an ultrasonogram revealed worsening hydronephrosis, secondary to distal ureteral stenosis (Fig. 4A). The patient underwent ureteral stent placement with expected gradual resolution of the hydronephrosis (Fig. 4B) and gradual improvement in allograft function. At 26 months posttransplant, her serum creatinine concentration stabilized at 1.4 mg/dl (Fig. 1), and currently she is maintained on tacrolimus (12-h

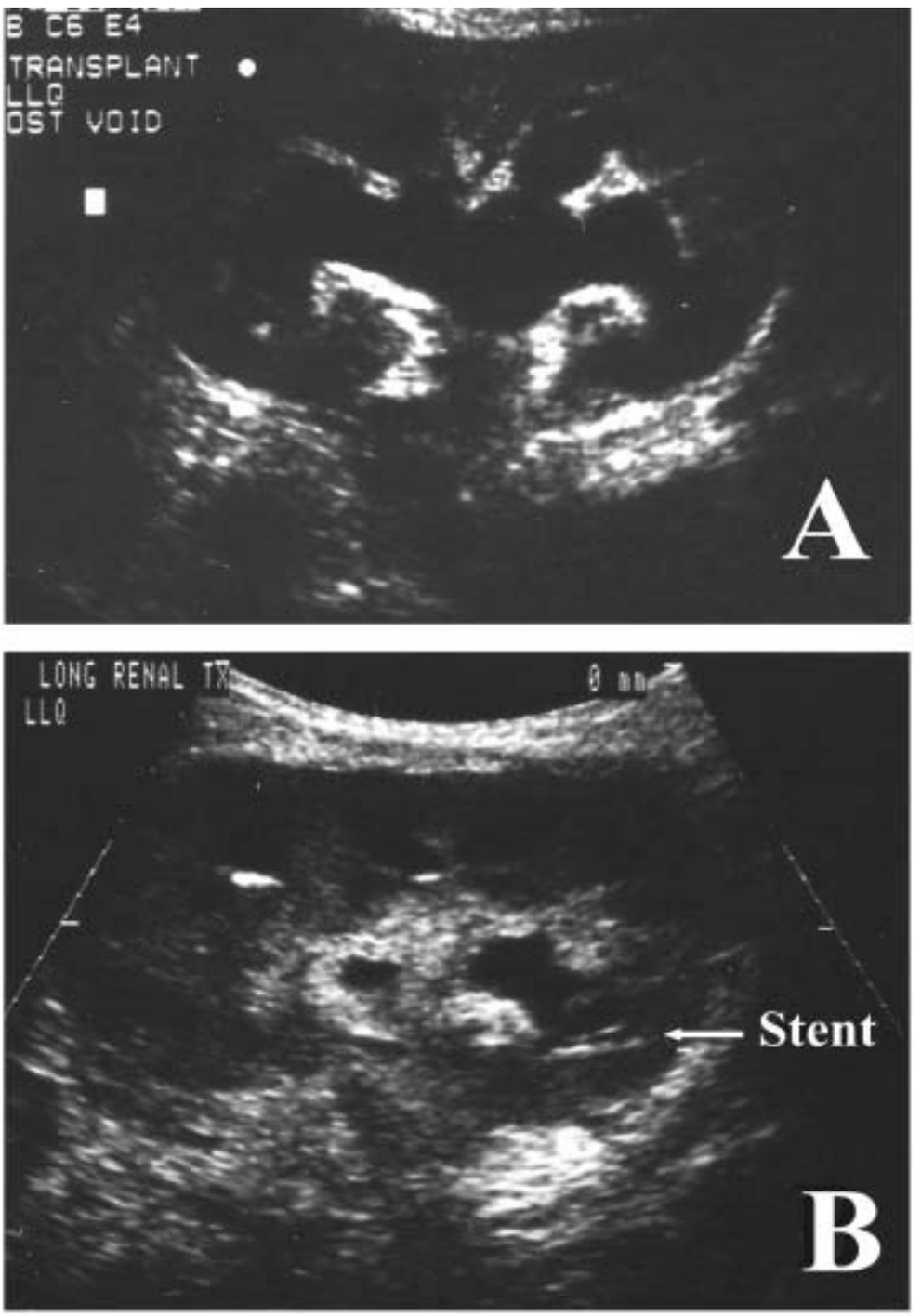

Figure 4. Extra-parenchymal complication in a patient (case 2) with posttransplant polyomavirus infection. Ultrasonogram of renal allograft reveals marked hydronephrosis in (A) and resolution after stent placement in (B).

trough level < 5 ng/ml) and prednisone. Follow-up urine cytology and a virologic study on polyomavirus were not performed.

Discussion

As previously reported in the literature,[1] rejection episodes may render the renal epithelium susceptible to BKV replication. Our first case illustrates just that, in as much as the BKV allograft nephropathy was diagnosed after an episode of acute rejection. Whether BKV was involved from the outset is unclear. One possible explanation for this sequence of events is the fact that rejection therapy is a risk factor for the development of polyomavirus nephropathy.[7] Because primary infection with polyoma virus occurs in childhood,[8] the majority of the kidneys harbor the virus at the time of transplantation. In conditions of immunosuppression, humans are at risk for reactivation of the virus, occasionally with grave consequences.[9] The mechanisms are incompletely understood, but it is believed that overexpression of major histocompatibility (MHC) class II antigens takes place.[10]

An expanding body of evidence suggests the need to study the presence and persistence of polyomavirus in renal tissue from the time of engraftment to determine if allograft dysfunction, if noticed afterwards, is due to primary infection (virus originating from the donor) or reactivation (invasion of allograft by recipient's preexistent polyomavirus).[11-16] The polyomavirus may be elusive and, at times, identified after several episodes of drug-resistant rejection.[1] In both our patients, the viral inclusions were seen at the second biopsy. It is therefore tempting to speculate that systematic testing for polyomavirus at the time of transplantation, with follow-up as dictated by the clinical status of each patient, may help diagnose and treat this infection early, without exposing the recipient to additional unnecessary immunosuppression. A difference can be made between the two members of this *Polyomaviridae* family (BK and JC),[17] which are most commonly associated with renal allograft nephropathy,[18] by using polymerase chain reaction (PCR) with specific probes.[19]

Much has been reported in the literature with respect to the relationship between the immunosuppression regimen and polyomavirus allograft nephropathy, and there is enough evidence to suggest that the combination of tacrolimus-MMF-prednisone is more likely to be associated with this infectious complication.[2,3] Both our patients were initially receiving this drug combination—hence the need for higher suspicion and possibly testing for polyoma nephropathy under these circumstances.

In addition to parenchymal disease, our second patient exhibited a known extraparenchymal complication of polyomavirus infection—ureteral stenosis.[20] Our patient experienced this complication soon after being diagnosed with viral allograft nephropathy, despite reduction in immunosuppression. Therefore, it is important to investigate the possibility of nonparenchymal complications (i.e., ureteral stenosis or ulcerations, hemorrhagic cystitis, etc.),[20,21] even after successful treatment of parenchymal disease.

One could argue that the disease might be more severe if parenchymal alterations are associated with nonparenchymal processes. The fact that she did not receive additional immunosuppression (quite the contrary, she underwent a reduction), coupled with oral ganciclovir therapy, facilitated a good outcome, despite the impressive ureteral stenosis. It is unclear if the removal of sirolimus from the immunosuppressive regimen allowed for complete recovery of renal function after placement of the ureteral stent.

In terms of therapy, recent studies point toward cidofovir as a first-line antiviral agent.[22] However, one has to be cautious in these conditions because cidofovir can induce activation of cytomegalovirus.[23] Monitoring of BK viral load can be performed with PCR, and it is an adjuvant in assessing the response to therapy.

In conclusion, we want to stress the importance of recognizing the polyomavirus infection early because it can present with parenchymal alterations as well as extraparenchymal pathology. When additional immunosuppression is anticipated for the treatment of allograft rejection, one should attempt to determine the BK viral load in order to minimize the stimulation of viral replication that can be seen in those cases. Even if therapy becomes standardized, patient-to-patient variability remains a reason for continuous monitoring because the outcome can differ from case to case, as illustrated by our patients.

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