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BK nephropathy in pediatric hematopoietic stem cell transplant recipients

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Abstract

BK nephropathy is a known cause of renal insufficiency in kidney transplant recipients. Activation of the polyoma virus may also occur in the native kidneys of non-renal allograft recipients. BK nephropathy has only been reported in a few patients after hematopoietic stem cell transplantation (HCT), most being adult patients, and the single reported pediatric case had evidence of hemorrhagic cystitis. The response to anti-viral therapy also seems to differ widely. Here, we describe two cases of BK nephropathy in the native kidneys of HCT recipients exposed to high levels of immunosuppression due to graft-versus-host-disease. Neither of our patients had any evidence of hemorrhagic cystitis. We present definitive renal pathology and detailed chronological evidence of the rising serum creatinine with simultaneous serum and urine BK PCR titers. In one of our cases, anti-viral therapy did not seem beneficial as documented by continued renal dysfunction and serum/urine BK PCR titers. Based on our report, intense immunosuppression in pediatric HCT recipients seems to be involved in the activation of BK virus and BK nephropathy should be suspected even in the absence of hematuria in HCT recipients with unexplained renal dysfunction.

Keywords

Hematopoietic stem cell transplantation; immunosuppression; renal insufficiency; viral infection

Introduction

BK virus, a polyoma virus, occurs in normal hosts of all ages (1). The virus remains latent in the kidney and urinary tract causing no renal impairment and is activated following immunosuppression. Latent infection is marked by urinary shedding of BK virus which may be associated with detection of BK virus in the serum. BK nephropathy is best diagnosed by renal biopsy confirming the presence of BK virus in the kidney. In renal transplant patients, impaired allograft function and ureteric ulceration have been reported (2). BK virus induced nephropathy may affect up to 10% of renal allograft recipients (3).

Recipients of hematopoietic stem cell transplant (HCT) represent another category of immunosuppressed patients at risk for urinary complications of BK virus infection. The most commonly reported manifestation of BK virus infection following HCT is hemorrhagic cystitis (4). Acute kidney injury (AKI) has been reported in HCT patients as a complication of BK virus infection (5,6), secondary to urinary tract obstruction by clots in the setting of hemorrhagic cystitis (7). Shapiro et al. described polyomavirus nephropathy in a 14 year old recipient of an unrelated cord blood transplant (CBT) with hemorrhagic cystitis (8). We describe two pediatric cases of biopsy proven BK nephropathy in HCT recipients who presented with renal failure without any signs of hemorrhagic cystitis.

Case One

A 10 year old boy presented with an increase in his serum creatinine to 1.5 mg/dL three years after an unrelated cord blood transplant (CBT) for treatment of chronic myelogenous leukemia (CML). He was treated for CML lymphoid blast crisis at 7 years of age with plasmapheresis for leucocytosis and hemodialysis for hyperkalemia. Cytogenetic analysis demonstrated Philadelphia chromosome confirming CML. He failed initial induction therapy with Daunomycin, vincristine, prednisone and L-Asparaginase, but went into remission with ifosfamide, etoposide and imatinib mesylate. Following a second course of ifosfamide and etoposide, he was prepared for 5/6 matched CBT with cranial and total body irradiation for 4 days, and cyclophosphamide 60 mg/kg/day for 2 days. He was transplanted 1 year after initial presentation. His graft-versus-host-disease (GVHD) prophylaxis consisted of horse anti-thymocyte globulin, methylprednisolone, and cyclosporine. His post-transplant course was complicated by numerous viral (including adenovirus) and bacterial infections as well as hypothyroidism, chronic adrenal insufficiency and growth hormone deficiency. On day 100 post-transplant, the patient developed severe chronic GVHD which required more aggressive immunosuppression, including prednisone, mycophenolate mofetil (MMF), tacrolimus, infliximab (3 doses) and extra-corporeal photopheresis (ECP) weekly which was weaned to monthly over several weeks. His hypertension began 75 days post-transplant and was initially managed with clonidine, labetalol and amlodipine and gradually reduced over the first year to just amlodipine until 3 years post-transplant when enalapril was started. Two months after the addition of enalapril, the serum creatinine started to rise. At the time of renal consultation, he was on rifabutin and gatifloxacin for treatment of an atypical mycobacterium infection, steroids 0.5 mg/kg every other day, MMF, tacrolimus, clarithromycin, gemfibrozil and omeprazole.

Because of his rising serum creatinine level, the enalapril and clarithromycin were empirically stopped followed by tacrolimus. The serum creatinine continued to rise over the next 2 months to 3 mg/dL. The patient denied dysuria, gross hematuria or flank pain. There was no history suggestive of volume depletion or recent non-steroidal anti-inflammatory drug use. Physical examination was not contributory. Initial diagnostic evaluation included a urinalysis which was negative for protein and blood with an absence of cells or casts, normal serum electrolytes and therapeutic tacrolimus levels (3–7.5 ng/ml). Laboratory investigations revealed BK viruria and viremia. BK viruria had begun 2 days after his HCT and persisted with a gradual increase in the polymerase chain reaction (PCR) in urine from 230,000 copies/mL (2 days post-transplant) to a maximum of 460,000,000 copies/ml with simultaneous plasma BK PCR of 110,000 copies/ml at 36 months post-HCT. His serum creatinine level at this time was 2.6 mg/dL [See Figure 1]. Urinalysis prior to biopsy and after was consistently negative for blood. Serum cytomegalovirus and Epstein-Barr virus PCRs were negative. The patient underwent a percutaneous kidney biopsy that included predominantly medullary tissue. Five of eight glomeruli were globally sclerotic. There was extensive ongoing tubular epithelial necrosis with patchy interstitial lymphocytic inflammation, edema and fibrosis associated with tubular atrophy. Many tubular lining cells

were enlarged, hyperchromatic and contained nuclear viral inclusions characteristic of Polyoma virus and was confirmed by a positive immunohistochemical staining with antibodies to SV40 T antigen (Figure 2a & 2b). At time of diagnosis of BK nephropathy, the patient's immunosuppression included steroids 0.5 mg/kg every other day, MMF, tacrolimus and monthly ECP.

Antiviral therapy with cidofovir 0.5 mg/kg/dose weekly for a total of 4 doses was initiated less than 1 week after confirmation of BK virus-induced nephropathy with simultaneous blood urea nitrogen of 67 mg/dL and serum creatinine level of 3.2 mg/dL. One week following the final cidofovir infusion, serum creatinine peaked at 3.5 mg/dL with unchanged BK viral load. One month after cidofovir was stopped; a 2 week course of ciprofloxacin was initiated. BK viruria persisted although levels began to decrease. Six months following the last dose of ciprofloxacin, plasma BK PCR was undetectable and has remained so to date [See Figure 1]. The patient's serum creatinine level gradually declined and is currently 1.7 mg/dL 5.5 years post-HCT. Although initial computed tomography scans and ultrasounds demonstrated normal kidneys, 3 months after the elevation of the serum creatinine level and 3 years after the CBT, there was mild pelviectasis. Three months later he developed multiple bilateral sub-centimeter cortical cysts with an interval decrease in size of both hypoechoic kidneys. Last renal ultrasound 5 years after HCT continued to show new cyst formation with lack of interval growth in either kidney.

Case Two

A 13 year old boy was referred to the nephrology clinic for evaluation of renal insufficiency, hypertension and edema 16 months following a HCT for Fanconi's anemia. Baseline ultrasound of the kidneys on diagnosis of Fanconi's anemia was normal except for a right pelvic kidney; 24 hour creatinine clearance was 133 ml/1.73 m²/minute. Initially, the patient's blood cell counts remained fairly stable but gradually he became dependent upon blood and platelet transfusions. Thus, 2.5 years after diagnosis, the patient underwent a non-myeloablative unrelated peripheral blood stem cell transplant. His post transplant course was complicated by hypogammaglobulinemia requiring intravenous immunoglobulin infusions, adrenal insufficiency, numerous episodes of Gram-positive bacteremia, and pulmonary aspergillosis. Hyperacute GVHD involving the skin and GI tract was diagnosed 10 days post-HCT. The patient was treated with 2 mg/kg prednisone, MMF and tacrolimus (levels of 4 to 10 ng/ml). A steroid taper was unsuccessful and eventually intra-oral psoralen ultraviolet A radiation (PUVA) was initiated. Four months post-HCT, he commenced ECP every other week for 3 months and then monthly with a steroid taper until it was stopped 1.5 years post-transplant. MMF was stopped three months later due to positive HHV6. Almost 2 years post-HCT, the patient was treated with Rituximab for warm auto-antibody induced Evans syndrome (low haptoglobin and increased LDH) which caused the patient to once again be transfusion dependent. The patient had chronic hypertension early in his post-transplant course which was managed with amlodipine and enalapril and then clonidine and losartan.

At the time of transplant, the serum creatinine level was 0.4 to 0.5 mg/dL. Eight months later, his serum creatinine level increased to 0.8–1 mg/dL. He received therapy with amphotericin and caspofungin for six months due to invasive fungal disease, with concomitant increases in serum creatinine which persisted after cessation of both drugs. One and a half years after HCT, the serum creatinine rose to 1.5 mg/dL and continued to rise to 2.3 mg/dL, 2 years post-HCT. The patient underwent a diagnostic renal biopsy which demonstrated classic findings of BK nephropathy including severe tubulo-interstitial disease with extensive ongoing tubular epithelial necrosis, protein and cellular casts, moderately intense lymphocytic inflammation that focally formed nodules and moderate interstitial

fibrosis with tubular atrophy. Viral inclusions were widespread and numerous tubular epithelial cells were positive by immunoperoxidase method for SV40 T antigen (Figure 3a, b & c). Eleven of twelve glomeruli were normal in appearance; one was globally sclerotic. Renal vasculature was unremarkable. At time of diagnostic biopsy, the patient's immunosuppression included prednisone 0.4 mg/kg daily as per a taper schedule, tacrolimus, beclomethasone and budenoside.

BK virus was first detected at 9 months post-HCT with BK PCR of 1.5 million copies/ml in urine. Serum BK PCR fluctuated over next 18 months with concurrent serum creatinine of 0.9 mg/dL. One and a half years after transplant, his serum BK PCR rose dramatically to 220,000 copies/ml followed 1 month later by an elevation in serum creatinine to 1.4 mg/dL. Over the next 6 months, his serum BK PCR remained between 18,000 to 210,000 and his serum creatinine level gradually increased to 2.3 mg/dL [See figure 2]. The patient began cidofovir 0.25mg/kg/week but within days of first dose, serum creatinine level increased to 2.9 mg/dL and so after the 2nd dose, therapy was stopped. The patient was counseled regarding dialysis options but declined all therapy and died a few weeks later.

Discussion

A greater number of childhood hematological, metabolic and autoimmune diseases are now being treated with HCT (9). With new immunosuppressive drugs and more aggressive GVHD management, patients are surviving longer. However complications from infections are a significant cause of morbidity and mortality. BK virus is a known cause of nephropathy in renal transplant patients(10) and can lead to loss of the allograft. Diagnostic renal pathology in renal transplant patients with BK nephropathy include intranuclear polyomavirus inclusion bodies in tubular epithelial and glomerular parietal cells, epithelial cell necrosis and acute tubular injury with varying degrees of inflammatory cell infiltrates, tubular atrophy and fibrosis (11). Viral inclusions are identified with antibodies to the SV40 large T antigen, or by direct visualization with electron microscopy of the virus in infected tubular epithelial cells(10,11). Here we report two cases of BK nephropathy in pediatric HCT patients. Similar renal pathology was identified in both patients including characteristic viral inclusions by routine stains and confirmation by immunohistochemistry. These cases suggest that BK virus infection poses a similar risk to the HCT pediatric population as the renal transplant patients.

Previous reports link hemorrhagic cystitis and BK virus infection in HCT recipients with secondary renal injury from urinary tract obstruction (4,7). Neither of our patients had evidence of hematuria or hemorrhagic cystitis throughout their clinical course. An acute rise in serum creatinine prompted the renal biopsy in both patients. Biopsy results suggest that BK virus infection is not limited to hemorrhagic cystitis in the HCT population but can be a cause of acute and chronic kidney disease. Thus, BK nephropathy should be excluded in HCT recipients on aggressive immunosuppression for GVHD with an elevated serum creatinine, and BK viruria/viremia even in the absence of hematuria or symptoms of hemorrhagic cystitis.

In our review of the literature, BK nephropathy in an adult HCT recipient without overt hemorrhagic cystitis was described as early as 2003. However, BK PCR in the serum was not evaluated and the authors only report the presence of BK virus in the urine with no record of quantity (12). There is a report of an adult HCT recipient with classic BK nephropathy without hemorrhagic cystitis (13). However this report described an unusual circumstance of an adult with recurrent Non-Hodgkin's lymphoma with hydronephrosis requiring a retrograde ureteral stent placement (13).

Based on the recommendations in the literature for the renal transplant population, we suggest screening HCT patients for BK virus (14). BK nephropathy is accompanied or preceded by BK viremia and viruria (15). BK virus DNA in urine precedes BK viremia by 7 weeks making the urinary PCR potentially a more appropriate screening test (15). But it is an expensive test and benign urinary shedding is a known phenomenon in healthy individuals as well as immunocompromised hosts (1). Therefore, detection of BK virus in the serum would be beneficial in assessing the need for early intervention to curtail the progression of subclinical BK virus activation before overt clinical disease is evident (14).

The definitive diagnosis of BK nephropathy requires a biopsy. The literature reports different thresholds of viremia or viruria that correlate with clinical disease. Thus a renal biopsy may not be indicated in all patients with a markedly elevated serum BK PCR (10,16,17). However, in patients who develop an elevation of serum creatinine with no alternate obvious etiology, clinical suspicion for BK nephropathy should be high and a biopsy considered prior to initiation of therapy. Both of the patients reported here underwent renal biopsies shortly after elevation in serum creatinine was detected and a conclusive diagnosis was made. Historically in renal transplant recipients, earlier detection of BK nephropathy prior to renal damage has reduced the rate of progression to irreversible renal allograft failure from >60% to 10–30% (16). Whether cidofovir and other anti-viral agents or reduction of immunosuppression is responsible for this trend is unclear (3,16) but these data support potential advantages to earlier diagnosis even in the HCT recipients. However, given the lack of clearly defined therapy, the benefit of early diagnosis is not known. (17).

Cidofovir and ciprofloxacin have been shown to eliminate BK virus in murine models as well as select studies in vivo (18,19). However, the decision to initiate cidofovir is difficult since the drug itself can cause irreversible tubular atrophy and fibrosis. In Case 1, only months after the cessation of all therapy (cidofovir and then ciprofloxacin) was the BK virus finally undetectable making it inconclusive if the medications contributed to the viral clearance or more likely whether it was the reduction in immunosuppression. However, in the cases reported by Limaye et al., one adult HCT patient had clearance of BK viremia following low-dose cidofovir (13) although other reports negate this experience (12). In addition our first patient developed BK nephropathy while receiving gatifloxacin therapy for a mycobacterial infection. Perhaps he had a BK viral strain that was quinolone resistant and perhaps ciprofloxacin did not contribute at all to viral clearance. Testing for viral sensitivity may be useful in such circumstances. Ultrasound evaluations in patient 1 now demonstrate lack of kidney growth and numerous renal cysts suggesting chronic irreversible renal damage likely secondary to BK nephropathy; however we cannot exclude other factors as causing or impacting cyst formation. It seems likely that the patient will eventually progress to end stage renal disease and require long term dialysis or a renal transplant. Thus it is unclear whether earlier therapy would have altered the rate of progression of our patient's chronic kidney disease. In patient 2, therapy with low dose cidofovir was followed by an acute deterioration of renal function and therapy was prematurely stopped.

We emphasize that vigilance for BK nephropathy is required in this stratum of immunosuppressed pediatric patients even in the absence of hemorrhagic cystitis. Prospective controlled trials of therapeutic agents against BK virus are currently in progress in renal transplant patients and the findings may be applicable to HCT recipients as well.

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Figure 1a

Figure 1b

Figure 1.

Figure 2.

Figure 3.