Decreased Viral Load and Symptoms of Polyomavirus-Associated Chronic Interstitial Cystitis after Intravesical Cidofovir Treatment

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Interstitial cystitis causes disabling bladder pain and is usually diagnosed in the absence of infection. We describe a patient with interstitial cystitis who had high urinary levels of polyomavirus that decreased dramatically after initiation of intravesical cidofovir treatment; the patient also showed substantial improvement in symptoms. Another patient had milder symptoms of cystitis and intermittent polyomavirus shedding. Polyomaviruses, particularly BK virus, may cause some cases of interstitial cystitis.

Chronic interstitial cystitis (IC) is a prevalent disorder distinguished by protracted, disabling bladder pain with characteristic cystoscopic features. IC and painful bladder syndrome, of which IC is a subset, are currently diagnosed only in the absence of infection. A number of potentially pathogenetic mechanisms have been suggested for IC, including altered bladder epithelial expression of HLA class I and II antigens and altered integrity of the glycosaminoglycan layer [1]. These changes may result in increased permeability of the urothelium, which allows urinary solutes to penetrate and irritate stromal nerves and muscles. The role of reactivation of latent infection with the ubiquitous polyomaviruses in the causation of chronic interstitial nephritis has yet not been described. The polyomaviruses BK virus (BKV) and JC virus (JCV) are ubiquitous urinary tract colonizers in early life, but they rarely cause disease in immunocompetent individuals [2].

Polyomaviruses are excreted intermittently in the urine in healthy, asymptomatic adults. BKV can be a urinary pathogen, causing renal transplant nephropathy [2] and acute hemorrhagic IC in patients with hematological malignancies [3]. Two cases of acute cystitis with urinary excretion of BKV occurring in immunocompetent children have been described [4, 5]. Furthermore, BKV excretion has been associated with transitional cell carcinoma of the bladder.

We have analyzed urinary polyomavirus shedding in hosts without severely compromised immune systems and with painful bladder syndrome. Two patients with cystoscopic appearances typical of IC were found to have persistent polyomavirus urinary infection through urinary cytological testing. One patient with very high urinary loads of polyomavirus and severe, persistent symptoms received successful treatment of this debilitating condition with local instillation of cidofovir.

A 60-year-old white man who was relatively immunocompromised as a result of polyglandular autoimmune syndrome, manifested by type I diabetes, vitiligo, and pernicious anemia, was assessed because of a 4-year history of frequent and urgent urination, strangury, and nocturia. Deferral of urination was associated with pain that prompted the need to void hourly, day and night. There was no history of hematuria. The patient had no other history of immunocompromising illness or therapy. There was no evidence of HIV infection or CD4 lymphopenia. Transurethral resection of the prostate did not alleviate the urinary symptoms. The cystoscopic appearance of the bladder was indicative of classic IC with ulceration, glomerulation, contact bleeding, and decreased bladder capacity. There was no evidence of transitional cell carcinoma of the bladder. Results of bladder histological analysis were consistent with follicular cystitis. The bladder tissue was examined retrospectively using PCR for BKV DNA and immunostaining for the simian virus 40 “large T” antigen; results of both examinations were negative. BKV and JCV DNA was quantified using real-time 5'-nuclease PCR assay with a probe and primers designed to be specific to the coding region of the large T antigen. Results of repeated urinary cytological analysis and quantitative PCR for polyomavirus DNA during a 10-month period showed evidence of polyomavirus infection, with urinary viral loads >10^5 copies/mL. Results of PCR of blood for BKV DNA were repeatedly negative. Empirical treatments with ciprofloxacin for 3 months and leflunomide for 1 month were both ineffective at reducing the symptoms of cystitis. Blood levels of leflunomide were in the therapeutic range before cessation of treatment.

A trial of intravesical cidofovir (375 mg weekly) was begun
5 weeks after the cessation of leflunomide treatment, because the IC symptoms continued unabated. With intravesical cidofovir treatment, there was considerable improvement in the symptoms. After 2 doses of cidofovir, the patient had decreased frequency of nocturia and was able to void every 2.5 h. This improvement was sustained for 8 months after the third dose of cidofovir. There was a 5 log_{10} decrease in BKV load and a 3.5 log_{10} decrease in JCV load, which was mostly sustained for >8 months (figure 1). At that time, the patient continued to have normalization of voided volumes and resolution of frequent and urgent urination and dysuria.

The second patient was a 48-year-old Chinese woman with hypertension who presented with a 10-year history of urinary symptoms. She had migrated to Australia 4 years before the onset of urinary symptoms. She initially had macroscopic hematuria and then, after a period of 3 years, developed chronic frequent and urgent urination with incomplete voiding. Results of investigations for bacterial and parasitic urinary infections were negative. At the peak of symptoms, the patient had 6 episodes of nocturia per night. Cystoscopy was performed after 6 years of these symptoms, and its findings revealed IC. Bladder histopathological analysis showed cystitis cystica. Again, retrospective examination of bladder tissue by immunohistochemistry and PCR showed no evidence of polyomavirus infection. Urinary polyomavirus levels fluctuated between viral loads of 5 x 10^3 copies/mL and undetectable loads. The only treatment given for potential polyomavirus cystitis was a 2-month course of norfloxacin treatment, which did not produce any improvement in symptoms. During 2 years of follow-up, the patient’s urinary symptoms fluctuated, but there was a trend toward improvement, such that the nocturia decreased to 1–2 times per night and the overall frequency of voiding decreased. With the low and intermittent level of urinary polyomavirus shedding, it was decided that no additional intervention was necessary.

To our knowledge, polyomavirus-induced classic IC has not previously been described. IC is a clinical entity in evolution, and the exact cause is unknown, although results of previous extensive microbiological studies have been negative. Distinct from the diffuse entity of painful bladder syndrome, the condition of the first patient had all the cystoscopic features of IC. With this study, we have identified a potential link between BKV and IC, showing a marked correlation between improvement in symptoms and cidofovir treatment–induced decrease in urinary BKV load in a patient. The clinical and virological improvements seen after intravesical cidofovir treatment were maintained for a prolonged period. Given the latency inherent in BKV infection, symptoms may recur. The presence of other urinary pathogens was unlikely, given the absence of severe immunodeficiency, the negative results of microbiological analysis, and the receipt of broad-spectrum antimicrobial therapy.

**Figure 1.** Urinary polyomavirus viral load and cytopathological analysis of samples from patient 1 in response to treatment with leflunomide (Lef.) and intravesical cidofovir (Cidof.). Results of cytopathological analysis are given as positive (+), negative (−), or indeterminate (?). BKV, BK virus; JCV, JC virus.

Urinary cytopathological analysis was used to rule out other viral infections, such as adenovirus infection. The prolonged course of ciprofloxacin treatment, although intended to be therapy for polyomavirus cystitis, would have been appropriate to treat infection with noncultivatable urinary pathogens that are more typically associated with urethritis, such as infection with *Chlamydia trachomatis* or *Mycoplasma* species. The other described patient had significantly lower urinary BKV loads (10^3 copies/mL), and BKV DNA was often undetectable. This patient’s symptoms trended toward resolution. These 2 patients may represent a spectrum of BKV-associated IC.

Our contention that BKV, not JCV, is the responsible pathogen is based on the occurrence of hemorrhagic cystitis and other renal tract diseases due to BKV in immunocompromised hosts. Additionally, substantially more healthy individuals shed JCV asymptomatically in the urine, compared with BKV. It is possible, however, that either BKV or JCV is occasionally pathogenic in immunocompetent hosts. We have not been able to show direct pathological evidence of BKV infection of bladder tissue, but the samples tested had been stored for >4 years in paraffin. Although PCR should be more sensitive than cytopathological analysis, the real-time PCR assay used was not validated for detection of BKV in tissue.

Serological evidence of BKV is found in 85% of adults [2]. Latent infections of the renal tubular epithelial and urothelial cells occur. Rates of urinary polyomavirus shedding may increase to >60% with pregnancy, older age, or immune dysfunction [6]. BKV viruria occurs at low but significant rates in all age groups, at one-half the incidence of JCV viruria [7]. Urinary JCV excretion appears to be continuous, whereas BKV is excreted intermittently [6].

Treatment outcomes of urinary tract polyomavirus disease in immunocompromised patients are inadequate because the available antiviral drugs have limited activity against BKV. Interestingly, fluoroquinolones appear to have anti-BKV activity. The immunomodulator leflunomide demonstrates substantial in vitro antiviral activity and has been used effectively to treat
BKV-associated nephropathy in renal transplant recipients [8]. The benefits seen in patients treated with leflunomide may be the result of a relative reduction in immunosuppression that occurs when this agent is substituted for calcineurin inhibitors.

Cidofovir is an antiviral that shows anti-BKV activity in vitro, albeit less than that of leflunomide. [9] Successful treatment of hemorrhagic cystitis due to BKV in bone marrow transplant recipients with use of low-dose intravenous cidofovir has been reported [10].

Single case reports of successful intravesical cidofovir treatment of hemorrhagic cystitis due to BKV [11] and adenovirus [12] in bone marrow transplant recipients reveal the benefit of this therapeutic approach. Our study indicates that local instillation of cidofovir was apparently effective in decreasing viral loads of BKV and JCV. Intravesical cidofovir treatment was well tolerated, with no observed adverse effects. The high urinary levels of BKV (viral load, 10^8 copies/mL) seen in a bone marrow transplant recipient with hemorrhagic cystitis [11] were also seen in our patient with IC treated with cidofovir. Intravesical instillation may be dually beneficial in the treatment of bladder infection, by increasing the local concentration of the drug and avoiding renal toxicity. Further work is required to better define the role of polyomaviruses in IC pathogenesis. Real-time studies will have the highest likelihood of demonstrating direct infection of the bladder. If additional evidence accumulates that shows BKV to be a cause of IC, further investigation of intravesical cidofovir treatment appears to be warranted.

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References