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Graft 2002; 5; 58

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Polyomavirus infection is widespread, with the virus remaining in a latent form, mostly in the kidney and urinary tract, after the primary infection in childhood. BK virus and JC virus are two major human-specific polyomaviruses. With impairment in cell-mediated immunity, the virus can be reactivated, resulting in cellular damage. This can be discovered by detecting decoy cells in urine. DNA detection techniques are more sensitive in demonstrating viral reactivation. Over the past three decades, the process of polyomavirus reactivation and its importance in disease states among organ transplant recipients have been increasingly recognized. Among bone marrow transplant recipients, both autologous and allogeneic, BK viral reactivation occurs in about 50% to 60% of the patients. In this review, the authors present the data supporting the association of late-onset hemorrhagic cystitis (HC) and BK virus activity. Although these studies are very suggestive, the causal relationship has not yet been proven. In nonrenal solid organ recipients, the prevalence and clinical significance of BK viral reactivation have not been extensively studied. Recent reports have shown that this process is not uncommon among recipients of heart and pancreas-alone transplants. The cytopathic effects of the virus in the native kidneys of a pancreas-alone recipient were recently demonstrated.

Introduction

Polyomavirus (PV) infection is ubiquitous, with the virus remaining in a latent form, mostly in the kidney and urinary tract.[1,2] This infection is usually asymptomatic, but with impairment in the cellular immune system, the virus can reactivate and lead to tissue damage.[1,2] Since the discovery of these viruses, several studies have demonstrated in recipients of bone marrow and solid organ transplants that PV reactivation can be associated with disease in the urinary tract and kidneys. This article reviews the published data on the importance of this virus in patients after bone marrow transplant (BMT) and those with nonrenal solid organ transplants.

Viral Reactivation in Bone Marrow Transplant Recipients

Polyomaviruses are small (30-45 nm), nonenveloped viruses of the *Papovaviridae* family, with circular, 5.3-kilobase pair, double-stranded DNA.[1,3] These viruses are species specific; the two that infect human species, BKV and JCV, have 75% sequence homology.[4] There are also reports that another member of this subfamily, simian virus 40 (SV40), which has about 70% sequence homology to BKV and JCV, also affects humans.[5,6] BKV was first discovered in 1971 from the urine of a kidney transplant recipient, who had developed ureteral stenosis 4 months after transplantation.[3,5] JCV was also isolated in the same year from the brain tissue of a patient with Hodgkin's disease who developed progressive multifocal leukoencephalopathy (PML).[3,5] Subsequent seroepidemiologic studies revealed that primary infection with these ubiquitous viruses occurs during childhood in 60% to 100% of general population.[2,4] The virus is believed to be acquired through the respiratory or oral route.[2] There is evidence that transplacental and probably sexual transmission may also happen.[2] The primary infection is usually asymptomatic.[2,4] It is believed that during viremia of the primary infection, the virus seeds the urinary system, the lymphocytes,

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DOI: 10.1177/1522162802238458

and brain and remains in a latent form.[1,3,7] Dolei and coworkers,[8] however, have suggested that the lymphocytes are not the site of persistence of the virus; rather, they are a site of recent infection or reactivation. During latency, the viral genome either remains episomal or integrates randomly into the cell genome.[2]

Any form of impairment in cell-mediated immunity has been associated with reactivation of the virus.[1,2] This reactivation can be detected as cytopathic changes in the uroepithelial cells by the presence of infected cells with characteristic intranuclear inclusion bodies (decoy cells) in the urine.[9] Molecular techniques, including polymerase chain reaction (PCR), that detect viral DNA are more sensitive in detecting reactivation compared to the cytological methods.[2,9]

With cytological methods, PV viruria has been demonstrated in 0.3% of nonimmunosuppressed patients who had presented with urinary symptoms and in 3.2% of pregnant women, especially those in third trimester.[1] Viral reactivation has also been associated with diabetes mellitus and different malignancies treated with chemotherapy.[2] Among patients with HIV disease, PV reactivation has been demonstrated in 31% to 56% of the cases.[10,11] Extensive experience over the past two decades has shown the prevalence and importance of PV reactivation in patients with bone marrow and solid organ transplantation.

O'Reilly et al.[12] studied 45 recipients of BMT. They detected BKV in the urine of 13 (29%) of these patients at days 6 to 48 after transplantation. They also reported an association between BK viruria and transient hepatic dysfunction among their BMT recipients.

Arthur and colleagues[13] studied urine samples of 53 patients after BMT for the presence of BKV by ELISA and DNA hybridization assays. Excretion of BKV in urine was demonstrated in 47.2% of the recipients. BK viruria began as early as the first week and as late as 17 weeks after BMT. The duration of viral shedding in the urine varied from 1 to 119 days. The results also suggested that BK viruria was the result of reactivation of the latent virus. The study revealed a strong association between BKV excretion in the urine and occurrence of hemorrhagic cystitis lasting more than 7 days: 64% of those with viruria versus 15% of seropositive recipients without viruria. Although reactivation of BKV was more common in recipients of allogeneic marrow compared to those who received syngeneic or autologous marrow, this difference did not reach statistical significance. However, long-lasting cystitis was observed in 50% of allogeneic recipients but in only 6.7% of autologous or syngeneic recipients ($p < 0.01$). The authors suggested for the first time that reactivation of BK virus, brought up by immunosuppressive agents, had an etiologic role in the occurrence of long-lasting hemorrhagic cystitis in BMT recipients. In a subsequent report on 55 BMT recipients, this group reported 87% seropositivity for BK virus at the time of transplantation[14] and showed evidence that among BKV-seropositive recipients, the risk of reactivation and continuing viruria was higher in those with high antibody titers (> 1:2000). The mean time of onset of viruria was 33 days after BMT, and the mean duration of excretion of the virus in urine was 22 days. Unlike the previous report, the authors did not observe any significant hepatic dysfunction during the period of continuous BK viruria.

Apperley et al.[15] reported 8 patients after BMT with excretion of BK virus in the urine, detected by viral culture and electron microscopy. Three of these cases had hemorrhagic cystitis that started 38 to 149 days after BMT and persisted from 38 to 171 days. The authors suggested a causative role for BKV in post-BMT hemorrhagic cystitis. All of these recipients were seropositive for BK virus at the time of transplantation.

In a study of 15 patients who underwent BMT, Cottler-Fox et al.[16] found evidence of PV by urine cytology in 60% of the recipients, starting on days 7 to 26. The positive cytology persisted until day 100 posttransplant in 3 of the cases. Four of the patients had gross and 11 had microscopic hematuria. Among the former group, 2 had viruria. Gross hematuria began 1 week prior to the detection of the virus in the urine; in 1 patient, urinary viral excretion persisted for several weeks after cessation of hematuria. Among the patients with microscopic hematuria, 7 had PV in the urine, 5 after hematuria had resolved. Because of these findings, the authors suggested that PV viruria and hematuria may be synchronous but they are unrelated.

Chan and coworkers[17] studied urine samples of 84 patients after BMT, using electron microscopy (EM) and PCR. They discovered BKV in 51.2% of the cases, of which 32.6% were also excreting JCV in the urine. The majority of patients with PV viruria did not have any urinary symptoms, but they had a significantly higher incidence of microscopic hematuria (34.9%) compared to those without (4.9%). The authors concluded that PV probably contributes to urinary tract disease in some of the BMT recipients.

Bedi et al.[18] studied 95 consecutive BMT patients for evidence of BK virus excretion in the urine by PCR. BK virus was found in at least one urine specimen in 52.6% of the recipients; 40% had persistent viruria. Viral excretion began 2 to 15 weeks after transplantation. Prior to transplantation, all of the recipients with BK viruria were seropositive, and 3 had BKV shedding in the urine. The incidence of BK viruria was independent of the marrow source (allogeneic vs. autologous). Fifty percent of the patients with persistent BK viruria developed hemorrhagic cystitis, whereas none of those without viruria experienced this complication. This study showed that virtually every case of HC that occurred, despite uroprophylaxis with mesna or forced diuresis, was associated with BK viruria. Because HC associated with BK virus was often delayed until several weeks following BMT (at the time of hematologic recovery and discontinuation of immunosuppressive therapy) and because of the infrequent occurrence of this complication in continuously immunosuppressed patients such as renal allograft recipients with BKV infection, the authors suggested that development of HC associated with BK viral reactivation may require immunocompetent T lymphocytes.

Azzi et al.[19] studied 52 unselected BMT recipients for evidence of HC and BK viruria by DNA detection methods. Seven cases (12.7%) had HC, and BKV DNA was detected in at least 1 urine sample in 52.7% of these patients. In 2 of the 29 cases with viruria, BKV serology was negative at the time of transplantation, which could have been due to low sensitivity of the serologic assays. The incidence of viruria did not depend on the source of the marrow (i.e., autologous vs. allogeneic) or the use of busulphan as a part of conditioning regimens. The length of viral shedding varied from 1 week to 2 months. BK viruria was invariably demonstrated before the onset and during the episodes of HC. In 2 cases that were studied, even after the disappearance of the clinical disease, viral DNA was detected in the urine. This group also reported BK virus shedding in the urine of 77% of BMT recipients without HC.

To better assess the association of BKV reactivation with HC, Azzi and colleagues[20] compared the amount of BKV genome copies in the urine of 17 BMT patients with HC, 20 BMT recipients without HC, and 62 immunocompetent individuals. BKV urinary shedding was evident in 87% of the BMT patients with HC, in 60% of BMT recipients without HC, and 40% of the immunocompetent individuals. Urinary concentration of the BKV DNA was significantly higher in BMT recipients with HC compared to those without HC. In all immunocompetent individuals with asymptomatic BKV reactivation, a minimal amount of viral DNA was detected. The analysis of viruria in a few patients suggested that the onset of HC coincides with a burst of viral replication, which persists at high levels during the episode and then slowly decreases after the resolution of the clinical event.

Bogdanovic et al.[21] followed 11 allogeneic and 5 autologous BMT recipients to detect the presence of BKV and JCV DNA in urine, plasma, and peripheral blood leukocytes (PBLs). Three allogeneic BMT recipients developed HC. Ten of 11 allogeneic patients, including those with HC, and 4 of 5 autologous recipients were found to have BK viruria. BKV DNA was detected in PBLs in 1 patient with HC. Among BMT patients without HC, PV DNA was detected in PBLs and/or plasma in 3 cases. Thus, the authors confirmed a high frequency of PV viruria, with a predominance of BKV, among both autologous and allogeneic BMT recipients, but they could not correlate this finding with the occurrence of HC.

Childs and coworkers[22] studied 56 recipients of T lymphocyte–depleted BMT from human leukocyte antigen (HLA)–identical siblings. Nine patients developed HC between days 15 and 362 after transplantation. Polyomavirus infection was observed in 4 of these cases by urine cytology. The authors hypothesized that removal of virus-specific T cells at the time of T cell depletion increases the risk of latent viral reactivation, which can lead to development of HC.

In a study of 50 consecutive BMT recipients and 40 healthy individuals for evidence of BKV in urine and plasma by PCR, Leung et al.[23] observed gross hematuria in 6 patients, starting 29 to 72 days after BMT, and microscopic hematuria in 14 patients with onset on days 1 to 25. Conventional PCR for BKV in the urinary sediments was positive in all 50 cases, whereas all plasma specimens were negative. In 40% of the healthy controls, the result was weakly positive in the urine. By quantitative PCR, the authors demonstrated that the peak viruria and the total amount of viral excretion in the urine were significantly higher in patients with HC compared to those without. Interestingly, the healthy controls had levels of BK viruria comparable to those of BMT recipients without HC. There was no detectable BK viremia in any of the patients after transplantation. Logistic regression analysis revealed that BK viruria had a significant association with the occurrence of HC. These investigators also looked for the presence of BKV in biopsies of the bladder wall in patients with high-grade hematuria. Immunohistochemical staining for BKV large T antigen was negative in all specimens. So, Leung et al. suggested that after BMT, intense immunosuppression leads to BKV reactivation. When the viral replication exceeds a certain level, cytopathic effects of BKV result in hematuria. In some patients, immunologic response to viral activity leads to more intense cellular damage and thereby more severe hematuria.

Peinemann et al.[24] reported an incidence of 7.7% of late-onset HC among 117 pediatric BMT recipients. Hemorrhagic cystitis occurred 24 to 50 days after transplantation, and its duration varied from 1 to 7 weeks. BKV was detected by DNA hybridization and PCR in the urine of 7 patients with HC. Viral particles could be demonstrated by EM in 6 patients. The serologic studies were consistent with viral reactivation in at least 6 cases; primary BKV infection during the treatment could not be excluded in 1 patient. The authors suggested that alteration in bladder mucosa by pretransplant conditioning sets the stage for the development of late-onset HC by reactivation of BKV.

In a study of 62 patients who developed clinical signs of cystitis after BMT, PV was detected in the urine by transmission EM in 56% of the cases; 94% of them had HC.[25] Among PV-negative patients, 96% had HC, but they tended to have milder clinical symptoms. The authors concluded that there is no causative link between PV viruria and HC, and there is no association between PV infection and outcome of BMT.

Priftakis and colleagues[26] studied 25 BMT patients with BK viruria to determine a more specific marker that predicts the development of HC in those with BK viruria. Sixteen of these patients had HC. The authors found that a mutation in the transcription factor Sp1 binding site in the noncoding control region of the BKV genome was present in 43% of the patients with HC but in none of those without HC. The biological significance of this mutation is unclear, but they hypothesized that these point mutations possibly increase the binding capacity of the transcription factor Sp1, which leads to enhanced viral replication. Previously, the preliminary results of a study on the variability of the BK viral genome by Azzi et al.[19,20] did not support the speculation that different strains of BKV are involved in causing asymptomatic infection or HC.

Akiyama and coworkers[27] studied 282 BMT recipients, 45 of whom had developed HC, for evidence of adenovirus and PV activity. On the basis of the results of PCR screening of the urine samples from 45 patients, they suggested that increased PV viral shedding is secondary to HC and reported a strong correlation between adenoviruria and post-BMT HC.

Renal parenchymal involvement due to BKV reactivation has not yet been reported in any of the case series published after BMT. Renal dysfunction with BKV-associated HC is attributed to obstructive nephropathy secondary to clot formation in the bladder. Iwamoto et al.[28] reported a 17-year-old male with myelodysplastic syndrome who underwent allogeneic BMT. BKV viruria was detected on day –1 and persisted thereafter. The patient developed HC, followed by a febrile illness and acute renal failure with anuria. BKV DNA was detected in the urine specimens by PCR but not in the plasma. His course was complicated by hepatic veno-occlusive disease, and he subsequently died of multiorgan failure on day 83 post-BMT. On the basis of clinical reasoning, the authors suspected that

BKV-associated renal failure was the most likely diagnosis in this case, but they did not provide any histological evidence.

Late-onset hemorrhagic cystitis after BMT, mostly associated with BKV viruria, is usually self-limited and resolves spontaneously but may persist for several weeks. Supportive therapy, including hyperhydration and bladder irrigation as needed, is generally advised. Most of the available antiviral agents do not have significant activity against polyomaviruses in vitro.[29] There have been few case reports suggesting the beneficial effects of two antiviral agents, vidarabine and cidofovir, in patients with BKV-associated HC after BMT.

Chapman et al.[30] reported their experience with a 23-year-old man who developed HC on day 44 after BMT. Three days later, PV particles were detected in the urine by EM and identified as BKV by culturing. In addition to supportive therapy, the patient was given a 5-day course of vidarabine. Two days after the treatment started, the symptoms improved and disappeared within 7 days. On day 16 after vidarabine was started, no virus could be detected by EM.

Kawakami and colleagues[31] reported on a patient who developed dysuria and microscopic hematuria on day 69 after BMT that were associated with PV viruria. Vidarabine was started, and within 5 days, the viruria could not be detected by cytology and EM. When viruria and HC recurred within a few days, vidarabine was readministered, with prompt response.

In another case of a 48-year-old male with cytomegalovirus (CMV) antigenemia on day 60 post-BMT (reported by Vianelli et al.[32]), HC started on day 66, which led to bilateral hydronephrosis. EM for PV in urine was negative. Subsequently, investigations on urine specimens with PCR revealed the presence of BKV. A vidarabine course was administered, with symptomatic improvement within a week. This therapy was repeated twice because of recurrent HC.

Held and colleagues[33] reported the successful use of cidofovir in a patient who had HC with BKV viruria and concomitant CMV reactivation. The patient, a 54-year-old man with BMT, developed severe gross hematuria and dysuria on day 42. After detection of BKV in the urine, three doses of cidofovir were administered on days 47, 54, and 67. The number of virus copies started to decline on day 54 and reduced exponentially thereafter. Shortly afterward, his hematuria started to improve; on day 80, HC resolved.

In a more recent report, Gonzalez-Fraile et al.[34] described an 18-year-old BMT recipient who developed severe HC and BKV viruria 45 days after transplantation. Urinary symptoms did not improve with palliative measures, but after 2 weeks of cidofovir treatment, clinical response was evident.

The review of published data clearly shows that reactivation of latent BKV is common in BMT recipients, both allogeneic and autologous; up to 60% to 100% of patients have evidence of viruria by urine cytology or DNA detection techniques in larger series. Hemorrhagic cystitis occurs in up to 50% to 64% of these patients with viral reactivation, and in those with HC, viruria can be demonstrated in as many as 56% to 80% of the cases. Although the wealth of the evidence shows a strong association between BKV viruria and late-onset HC in recipients of BMT (and the data are very suggestive of a causal relationship between viral reactivation and the occurrence of HC), it still needs to be proven.

Viral Reactivation in Nonrenal Solid Organ Transplant Recipients

Reactivation of PV in renal transplant recipients, manifested as the presence of virus-infected decoy cells in the urine, has been well known since the first case was reported with ureteral stenosis. Since 1995, the role of BKV in inducing allograft nephropathy has been increasingly recognized. PV reactivation has been reported in 10% to 45% of the kidney transplant recipients; 2% to 3% of these patients develop renal parenchymal disease, manifested by tubular damage and varying degrees of interstitial inflammation.[35-37] In up to 45% of the patients with BK nephropathy, progressive virus-induced renal damage may result in graft loss.[35] The newer potent immunosuppressive agents, tacrolimus and mycophenolate mofetil, have been suggested as contributing factors in reactivating the virus, with a possible role for the microenvironment of the allograft.[36,37]

In contrast to the renal transplant setting, there are very limited data on the risk of PV reactivation in the native kidney and urinary tract in nonrenal

solid organ recipients. Masuda and coworkers[38] reported on a 20-year-old male with a history of Kawasaki disease who underwent heart transplantation and was maintained on tacrolimus, azathioprine, and steroid. Examination of urinary sediment 4 months later revealed numerous decoy cells. This finding was confirmed by immunoperoxidase staining and EM. Using in situ hybridization, BKV DNA was demonstrated in the nuclei. PV viruria had persisted even 8 months after onset. The authors did not comment on the patient's renal function.

Etienne et al.[39] studied 45 consecutive heart transplant recipients who were seen at their outpatient clinic. Urine cytology revealed dystrophic cells in 16 cases and decoy cells in only 1 patient. From the 17 urine samples studied by electron microscopy, viral particles were found only in 1 patient. Thirteen urine specimens were analyzed by PCR; PV sequences were detected in 7. Six of them were positive for BKV and 3 for JCV, and coinfection with BKV and JCV was observed in 2 cases. The authors' analysis showed that renal function among patients with evidence of PV activity was not different from the rest of the patients, and they did not receive more immunosuppressive treatments for rejection episodes compared to the general heart transplant recipients.

Haririan and colleagues[40] recently reported the first case of PV nephropathy in native kidneys of a pancreas transplant-alone (PTA) recipient. The patient was a 54-year-old male with diabetes mellitus, type 1, who underwent PTA with a baseline serum creatinine of 1.2 mg/dl. He was maintained on tacro-limus, mycophenolate mofetil, and prednisone and was treated with a course of high-dose methylprednisolone pulse for acute rejection of the graft. Nine months after transplantation, serum creatinine had increased to 2.2 mg/dl. Urine cytology revealed numerous decoy cells. Native kidney biopsy showed PV cytopathic changes in the renal tubular cells (Fig. 1).

This group also reported the results of screening 38 PTA recipients for evidence of PV viruria by urine cytology.[41] All the patients were maintained on tacrolimus, mycophenolate mofetil, and prednisone. Screening was performed 16 months (mean) after transplantation. The authors detected viruria in 4 patients. The patients with PV reactivation did not differ from the PV-negative group in regards to type of induction agent, number and severity of acute rejection episodes, and renal function, although 1 of the cases had PV nephropathy in the biopsy. The authors suggested that PV reactivation in the native kidney and urinary tract of PTA patients is not uncommon, and they supported the notion that the intensity of immunosuppressive therapy is an important risk factor for reactivation of the virus. The results of this study suggested that patients who are exposed to higher doses of tacrolimus are at higher risk of PV reactivation and viral shedding in the urine. This study clearly showed that in the absence of an allogeneic microenvironment of a renal allograft, the native kidney and urinary tract of nonrenal solid organ recipients are at risk of PV reactivation and possible virus-induced parenchymal damage.

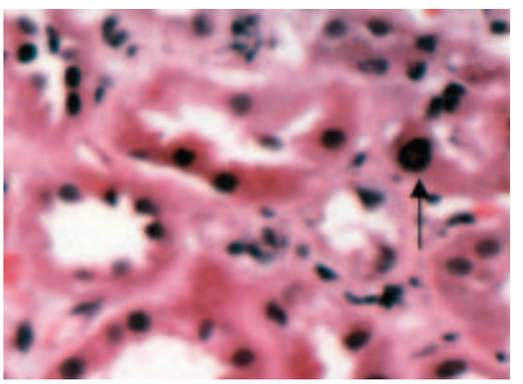

Figure 1. Hematoxylin and eosin staining of this patient's biopsy shows a tubular epithelial cell with characteristic cytopathic changes due to polyomavirus (PV) reactivation (arrow). There is minimal interstitial fibrosis. Adapted from reference 40.

Further investigation is needed to clarify the role of BKV as the cause of hemorrhagic cystitis in BMT recipients and to develop effective antiviral agents with efficacy in suppressing the viral reactivation. The importance of BKV in causing disease in the native kidneys of recipients of nonrenal solid organ grafts has just been brought to attention, and further studies are needed to characterize the extent of the disease and the therapeutic options.

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