Case Report

Bladder Carcinoma Associated with BK Virus in a Renal Allograft Recipient

Abstract

Bladder carcinoma is a relatively rare carcinoma reported in renal allograft recipients. While many oncogenic viruses have been implicated as causative factors for certain malignancies, questions have been raised about possible role of BK virus in pathogenesis of urothelial cancers. In this report, we have described a patient who developed BK virus nephropathy followed 3 years later by bladder carcinoma. Interestingly, while the tumor tissue demonstrated BK virus, the adjacent normal urothelium was stained negative for BK virus. Considering the viral potential to inhibit tumor suppressors and its differential localization within tumor tissue, it is possible that the virus contributes to tumorigenesis.

Keywords: *BK virus nephropathy, bladder malignancy, polyomavirus, renal allograft recipient, urothelial carcinoma*

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Introduction

Renal transplant recipients are at risk from opportunistic infections and occasionally their oncologic manifestations. We report on a renal allograft recipient developing a high-grade urothelial carcinoma with BK virus (BKV) nephropathy 2 years before the detection of the malignancy. BKV was demonstrated in urine, blood, and tumor tissue, suggesting a strong association and possible oncogenicity.

Case Report

A 59-year-old female, with end-stage renal disease from hypertension with no prior history of nonsteroidal anti-inflammatory drug intake, received living-related kidney transplantation from her maternal cousin in May 2012. She received induction therapy with three doses of thymoglobulin at 0.9 mg/kg and tacrolimus, mycophenolate mofetil along with prednisolone. She received cytomegalovirus prophylaxis with valganciclovir for 3 months and trimethoprim-sulfamethoxazole for 1 year. The initial 2 years were uneventful except for an episode of diarrhea in March 2014 when serum creatinine peaked to 2.34 mg/dl. Investigations for diarrhea were inconclusive. She received parenteral fluids and antibiotics and recovered with serum creatinine of 1.42 mg/dl. In August 2014, when creatinine increased to 2.1 mg/dl, urine examination revealed trace proteinuria, 1–5 red cells, and some epithelial cells per high-power field and renal histology showed the presence of ground glass intranuclear inclusions within the lining of tubular epithelial cells along with a moderately dense lymphoplasmacytic infiltrate in the interstitium [Figures 1 and 2]. Immunohistochemistry revealed SV-40 antigen in tubular epithelial cells. BKV DNA was identified in the serum – 2,784,000 copies/ml (Artus BKV RG PCR Kit: QIAGEN GmbH, Germany). In view of BKV nephropathy, mycophenolate mofetil was changed to azathioprine 50 mg once daily, and dose of tacrolimus was reduced targeting a trough <4.0 ng/ml. Prednisolone was continued at the dose of 5 mg/day. Her serum creatinine ranged from 1.6 to 1.9 mg/dl on follow-up.

In October 2017, she developed pain and hematuria on micturition with clots. She reported loss of appetite and a 4 kg weight loss over 3 months. Examination of urine under high power revealed numerous red cells; decoy cells were not identified with Papanicolaou stains. Ultrasonography revealed two irregular mass lesions – in

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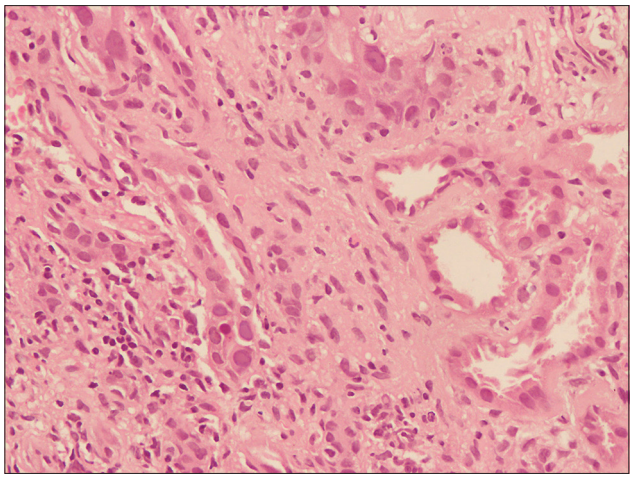

Figure 1: Kidney biopsy: Hematoxylin and eosin stain - ground-glass intranuclear inclusions in tubular epithelial cells

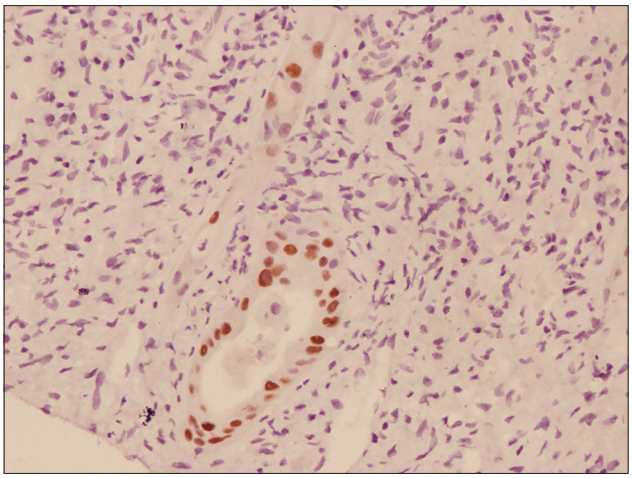

Figure 2: Kidney biopsy: Immunohistochemistry showing SV40 positivity in tubular epithelial cells

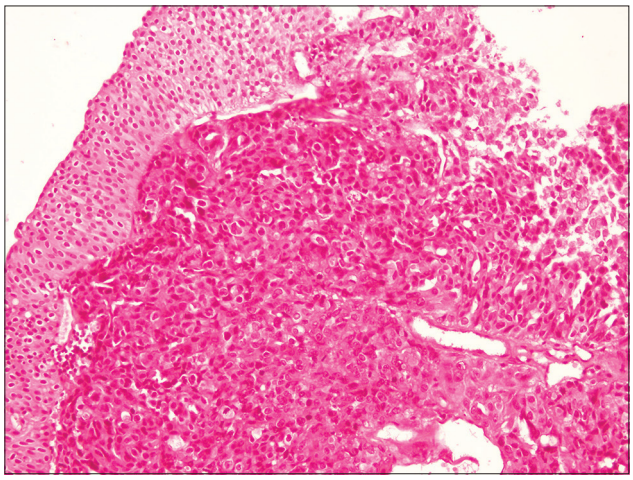

Figure 3: Bladder biopsy: Mucosa with extensive ulceration and necrosis; nests and cords of atypical cells, with moderate nuclear atypia and increased mitosis

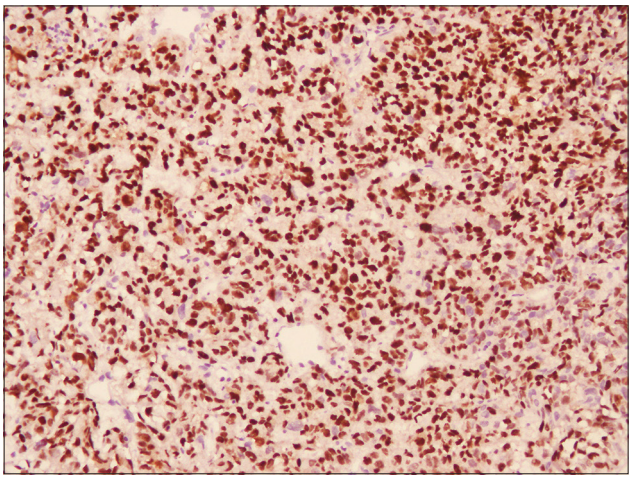

Figure 4: Bladder biopsy: Immunohistochemistry demonstrating tumor areas stained positive for GATA-3

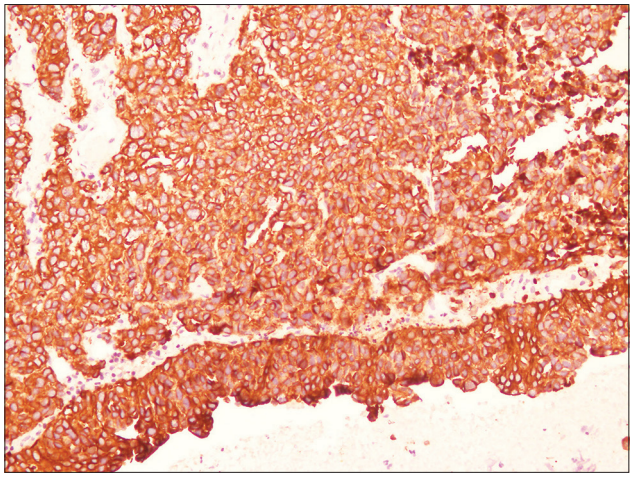

Figure 5: Bladder biopsy: Immunohistochemistry demonstrating tumor cells stained positive for CK-7

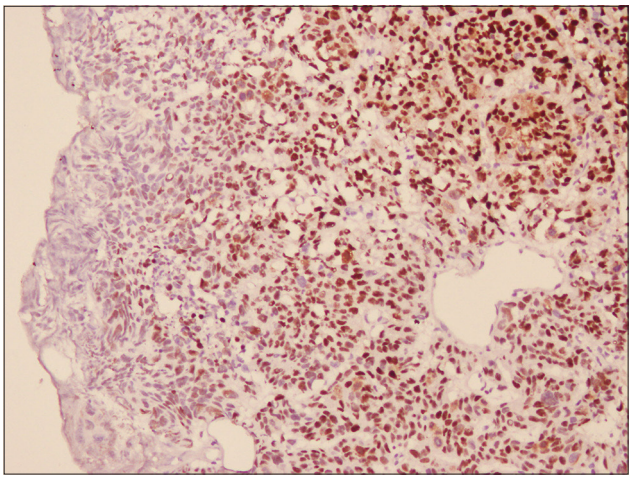

Figure 6: Bladder biopsy: Immunohistochemistry demonstrating tumor cells positive for SV-40; however, adjacent normal urothelium is negative for SV-40

Table 1: Case reports with BK virus demonstrated in urothelial malignancy

Authors	Number of patients	Type of transplant	Induction	Maintenance	Detection of BKVN	Maintenance immunosuppression used after DX of BKVN	Interval between BKVN and CA bladder	Comments
Roberts *et al*., 2008[4]	10	Kidney	Not specified	Not specified	Not specified	Not specified	Not specified	
Emerson *et al*., 2008[5]	1	Kidney	ATG	Tac MMF steroids	Yes	Sirolimus only		Graft nephrectomy done 3 years later in view of persistent BK viremia. Graft pathology revealed intraepithelial neoplasia within tubules
Hill *et al*., 2009[6]	1	Kidney	Not specified	Tac MMF steroids	Yes	CysA/AZA/steroids	About 2 years	
Fernández Rivera *et al*., 2010[7]	1	Kidney-pancreas	ATG (1.25 mg/kg × 5 doses)	Sirolimus MMF steroids	Yes	Sirolimus/steroids	Not specified	Tac to sirolimus in first-month posttransplant in view of hyperglycemia and unrevealing pancreas biopsy
Galed-Placed and Valbuena-Ruvira, 2011[8]	1	Kidney + pancreas	Not specified	Tac/MMF/steroids	Yes	Not specified	About 2 years	
Pino *et al*., 2013[9]	1	Kidney	Not specified	Tac/MMF/steroids	Yes	Not specified	5 years	
Alexiev *et al*., 2013[10]	1	Kidney-pancreas	Not specified	Not specified	Transplantectomy	Not specified		
Alexiev *et al*., 2013[10]	1	Kidney	Not specified	Not specified	Kidney BX negative for BKVN	Not specified		
Yin *et al*., 2015[11]	1	Kidney	Not specified	CysA/MMF/steroids	No	Not specified		Same dose of immunosuppression postcystectomy
Salvatore *et al*., 2016[12]	1	Kidney	Not specified	Tac/MMF/steroids	Yes	Not specified	5 years	
Yan *et al*., 2016[13]	13	Kidney	Variable	Variable	Variable	Variable	Variable	31% of all urothelial CA were positive for Tag, and >50% of invasive urothelial CA were positive for Tag

BKVN: BK virus nephropathy, MMF: Mycophenolate mofetil, Tac: Tacrolimus, AZA: Azathioprine, CysA: Cyclosporine A, CA: Carcinoma, ATG: Antithymocyte globulin, Tag: T antigen

the anterior and lateral walls of bladder, respectively. Cystoscopic bladder biopsy showed a high-grade papillary urothelial carcinoma. Immunohistochemistry confirmed positivity for CK7 and GATA-3 and focal positivity for uroplakin [Figures 3-5]. Tumor cells stained positive for SV-40 [Figure 6]. Interestingly, at this time, serum polymerase chain reaction for BKV DNA revealed just 340 copies/ml. Magnetic resonance imaging (MRI) showed deposits encasing the distal right ureter, abutting the vaginal vault along with evidence of adherence to the small bowel loops. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan revealed FDG avid uptake lesions seen on MRI with no evidence of metastasis.

In view of patient's frailty and locally invasive disease, she was treated with 54 Gy of three-dimensional conformal

radiation therapy fractionated to 1.8 Gy per session, 5 days weekly for 6 weeks. Tacrolimus was switched to everolimus, while prednisolone was continued. A second FDG-PET showed modest reduction in uptake compared to previous scans with no evidence of distant metastases. The serum creatinine remains around 2.3 mg/dl at the last follow-up.

Discussion

The BKV (BK polyomavirus [BKV]) was first isolated in 1971, by Gardner *et al*., after inoculation of Vero cells with urine samples from a 39-year-old Sudanese renal allograft recipient with the initials B. K.[1] Primary infection by BKV is usually in apparent and occasionally be accompanied by a mild respiratory illness or urinary tract symptoms. During the primary infection, when mild respiratory or urinary symptoms may manifest, viremia occurs when latency in organs is established. Immunological impairment leads to reactivation. Virus isolation and Southern blot hybridization analysis have established that kidney is the main site of BKV latency in healthy individuals.[2] However, BKV has also been detected in the liver, stomach, lungs, parathyroid glands, tonsils, and lymph nodes. Transmission may occur via oral, respiratory, or transplacental routes.

The BKV genome is a closed, circular 5 KB double-stranded DNA molecule that replicates bidirectionally from a unique origin. The early genes encode the large tumor antigen (TAg), the small tumor antigens (tAg), and the truncated TAg that are expressed by alternatively spliced mRNAs soon after infection of the host cell.[1] The main property of Tag in relation to transformation and oncogenicity is its ability to bind and block the functions of tumor suppressor proteins p53 and pRB family.[2]

McCabe demonstrated that in the cells lacking retinoblastoma gene, DNA methyltransferase 1 (DNMT1) is activated, which in turn is associated with tumor suppressor gene hypermethylation culminating in tumorigenesis. The same group demonstrated that DNMT1 is strongly activated by BKV Tag.[3]

Many cases of high-grade urothelial carcinoma occurring in patients with prior BKV nephropathy have been described demonstrating the occurrence; duration between the events ranging from a few months to as long as 5 years [Table 1]. In many of these cases, the nature of induction and maintenance immunosuppression is unclear.

In this patient, thymoglobulin was used at a lower dose and duration, and the other immunosuppressants too, dosed at a standard range. BK viremia was far lower at the time the malignancy was detected. A declining viremia which may be seen following reduction of immunosuppression may not be predictive of reduction of risk of malignancy in all cases. A protocolized monitoring for BK viremia while reducing the risk of BK nephropathy may avert downstream oncogenicity as well when early reduction in immunosuppression is attempted to thwart viral replication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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