

Case Report

Association of bladder adenocarcinoma and BK virus infection in a pancreatico-renal transplant recipient

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Abstract

Viral infection has been related to post-transplantation tumour development, particularly Epstein–Barr virus, human papillomavirus, hepatitis B and C viruses, and herpes virus 8. Recently, BK virus (BKV) has emerged as an important cause of tumour formation in solid organ transplant recipients. BKV oncogenic potential relates to the ability to inactivate the functions of tumour suppression proteins p53 and pRB family, and induction of chromosomal aberrations. We report a case of urinary bladder adenocarcinoma in a pancreatico-renal transplant recipient which was diagnosed 2 years after BKV infection. Immunohistochemical staining for SV-40 was positive in neoplastic cells but negative in non-neoplastic cells.

Keywords: BK virus; kidney transplantation; renal transplantation; urinary bladder neoplasms

Introduction

Polyomavirus BK has been classified in the *Polyomaviridae* family, which includes JC virus, simian virus 40 and monkey polyomavirus [1]. In renal or pancreatico-renal transplant recipients, BK virus (BKV) infection may lead to deterioration of renal function and irreversible graft failure [2]. Although BKV is a well-known cause of allograft nephropathy in recipients of kidney transplants, the occurrence of BK nephropathy in native kidneys of recipients of non-renal transplants has also been documented [3]. Optimal treatment for BKV nephropathy has not been established; however, early diagnosis based on prospective screening of BK viraemia and BK viraemia [4] and reduction of immunosuppressive therapy remains an important approach [5].

BKV has emerged as an important cause of tumour formation, more frequently renourinary tract tumours, in solid organ transplant recipients [6]. The mechanism by which BKV induces post-transplantation tumour develop-

ment is not fully understood. BKV expresses a viral oncogene, the large T-antigen (Tag) that inactivates p53 and the pocket protein family, including pRB. It has recently been demonstrated that the BKV Tag activates the DNA methyltransferase 1 gene—DNMT1. DNMT1 is associated with tumourigenesis through tumour suppressor gene hypermethylation [7,8].

We here report the case of a pancreatico-renal transplant recipient who, 2 years after graft failure due to BKV nephropathy and under haemodialysis treatment, developed a urinary bladder adenocarcinoma. Immunohistochemical staining for SV-40 was positive in neoplastic cells but negative in non-neoplastic cells.

Case report

A 38-year-old woman, with a 16-year history of diabetes mellitus, underwent a simultaneous pancreas–kidney transplantation from a blood group and human leucocyte antigen (HLA) A2- and HLA A8-compatible cadaveric donor on 11 September 2001. The procedure was uneventful, and immediate graft function was excellent. The immunosuppressive regimen included timoglobulin (five doses of 1.25 mg/kg/day), tacrolimus (0.2 mg/kg/day in two divided doses), mycophenolate mofetil (2 g/day) and prednisone with a decreasing dosing schedule until 5 mg daily at 6 months. She received 3-month anti-cytomegalovirus (CMV) prophylaxis with oral ganciclovir because of CMV+ donor/CMV– recipient, as well as cotrimoxazole and itraconazole for 6 months according to the protocol of our hospital, and low-molecular-weight heparin during the first 2 weeks followed by acetylsalicylic acid 150 mg/day.

The patient was discharged from the hospital on Day 23 after transplantation, with a serum creatinine concentration of 1.2 mg/dL, blood glucose of 83 mg/dL, amylase 50 mg/dL and lipase 35 mg/dL. One month after transplantation, the patient presented hyperglycaemia that required insulin therapy. Pancreatic sonography and an ultrasound-guided biopsy of the pancreas were unrevealing; tacrolimus was

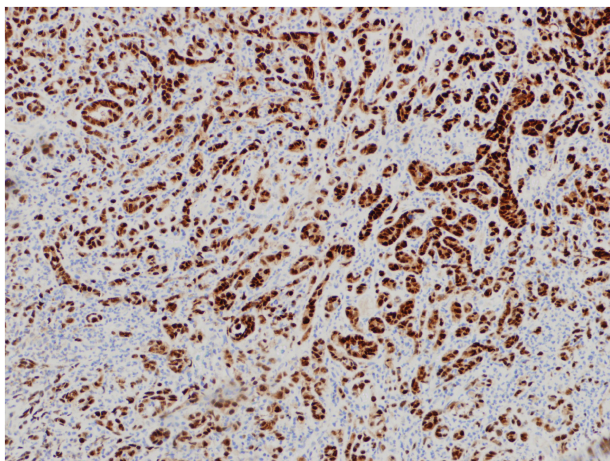


Fig. 1. SV-40 immunohistochemical positivity in the bladder tumour biopsy, with intense staining of neoplastic cells, and negative SV-40 staining in non-neoplastic cells.

substituted with sirolimus. Blood glucose levels were normal. Five months after transplantation, she had an episode of obstructive uropathy secondary to distal ureteral stenosis, which resolved with balloon dilatation followed by placement of a Double-J catheter. Four years after transplantation, the patient was admitted to the hospital because of renal function deterioration. Renal echography was normal, and plasma levels of sirolimus were within the therapeutic range. Renal biopsy revealed a tubulointerstitial lymphocytic inflammatory infiltrate in 25% of the sample, with more than four lymphocytes per section and cytomegalia. BKV DNA (170 000 copies/mL) was detected by real-time PCR, and immunohistochemical staining for SV-40 was positive. Mycophenolate mofetil was discontinued, and treatment with four doses of cidofovir was instituted. BK viraemia persisted, and 4 months later, haemodialysis was required due to the decline in renal function. In the presence of intermittent BK viraemia and with the purpose of performing a second kidney transplant, the renal graft was removed in May 2008. The surgical specimen showed the lymphocytic inflammatory infiltrate with SV-40 immunohistochemical positivity. An abdominal computer tomography (CT) scan disclosed bladder wall thickening. Cystoscopy demonstrated a large mass; the biopsy of which revealed adenocarcinoma. Immunohistochemical staining for SV-40 was intensely positive in neoplastic cells but negative in non-neoplastic cells (Figure 1). Radical cystectomy with hysterectomy and bilateral salpingo-oophorectomy was performed (Figure 2). Immunohistochemical staining of the surgical specimen showed positivity for PI3KC, phospho-AKT, p mTOR, p70S6K, pp70S6K, TGF β , VEGF and p53, and was negative for PTNE expression. Post-operatively, PCR BKV DNA assays were repeatedly negative. At follow-up, 1 year after cystectomy, the patient remained on dialysis, with normal pancreatic function, with negative BK viraemias and with no evidence of metastasis. At 18 months after cystectomy, the patient was admitted because of a pelvic mass in the renal post-transplantation territory, which was successfully removed. Histopathological examination revealed a tumour recurrence with positive immunohistochemical staining for SV-40.

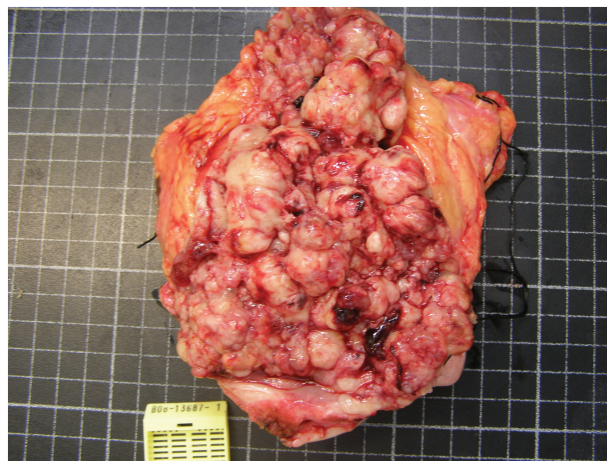


Fig. 2. Radical cystectomy. Large infiltrating adenocarcinoma involving almost the whole of the bladder except for the trigone.

Discussion

The increase in survival of renal and pancreatic transplant recipients experienced in the last decades has been associated with an increase in co-morbidities, including infection, cardiovascular disease and malignancy. Different factors are involved in the development of malignant tumours in these patients, and certain viral infections predispose transplant recipients to different types of malignancies [9]. Polyomavirus has recently attracted considerable clinical attention in renal and pancreato-renal transplant recipients as a risk factor for graft loss. The possible causative role of BKV Tag to inactivate the functions of tumour suppressor proteins p53 and pRB family as well as on its ability to induce chromosomal aberrations [7]. On the other hand, tumour suppressor gene hypermethylation due to activation of the DNA methyltransferase 1 gene is another mechanism involved in polyomavirus tumourigenesis [7,8].

In 2002, Geetha *et al.* [10] reported a case of urothelial carcinoma arising in a pancreato-renal transplant recipient with a severe BKV infection of the kidney, in which immunohistochemical staining for the large SV-40 T showed a strong nuclear positivity for both the primary tumours and the metastasis, although data on BK viraemia or BK viuria were not shown. The case here reported is similar to that described by Geetha *et al.*; although histopathological diagnosis was bladder adenocarcinoma, BKV infection was consistently demonstrated by detection of PCR BKV DNA in blood samples and renal tissue, and SV-40 immunohistochemical positivity in neoplastic cells. Hill *et al.* [11] described a case of urothelial carcinoma developing in a kidney transplant recipient 6 years after the diagnosis of polyomavirus nephropathy. BKV DNA was identified in urine and serum by PCR, and diffuse strong staining of SV-40 Tag in neoplastic cells. Different clinical series in paediatric and non-paediatric populations have shown an association between BKV infection renal tumours with SV-40 Tag positivity in tumour cells [10]. However, detection of BKV DNA in BKV-associated tumours by PCR or ultrastructural examination of tumour cells is infrequently reported. Other authors report that

the low copy number of viral genomes in human tumours suggests that polyomaviruses may transform human cells by a 'hit-and-run' mechanism [12].

In the patient here reported, results of immunohistochemical studies with positivity for PI3KC, phospho-AKT, p mTOR, p70S6K, pp70S6K, TGF β , VEGF and p53, and negative for PTNE expression suggest an activation of the PI3/Akt pathway as a mechanism of oncogenesis. In fact, the administration of sirolimus in our patient was unsuccessful, so that inhibition of mTOR may be insufficient for reverting the process or that other molecular pathways may be involved in tumour oncogenesis.

In summary, the present case adds evidence of the relevance of BKV infection as an etiologic agent in the development of bladder malignancy in solid organ transplant recipients who are immunosuppressed.

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Conflict of interest statement. None declared.

References

1. Bonvoisin C, Weekers L, Xhignesse P, Grosch S, Milicevic M, Krzesinski JM. Polyomavirus in renal transplantation: a hot problem. *Transplantation* 2008; 85: S42–S48
2. Ramos E, Drachenberg CB, Wali R, Hirsch HH. The decade of polyomavirus BK-associated nephropathy: state of affairs. *Transplantation* 2009; 87: 621–630
3. Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. A longitudinal molecular surveillance study of human polyomavirus viremia in heart, kidney, liver, and pancreas transplant patients. *J Infect Dis* 2005; 192: 1349–1354
4. Hirsch HH, Brennan DC, Drachenberg CB *et al.* Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; 79: 1277–1286
5. Saad ER, Bresnahan BA, Cohen EP *et al.* Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. *Transplantation* 2008; 85: 850–854
6. Geetha D, Tong BC, Racusen L, Markowitz JS, Westra WH. Bladder carcinoma in a transplant recipient: evidence to implicate the BK human polyomavirus as a causal transforming agent. *Transplantation* 2002; 73: 1933–1936
7. Tognon M, Corallini A, Martini F, Negrini M, Barbanti-Brodano G. Oncogenic transformation by BK virus and association with human tumors. *Oncogene* 2003; 22: 5192–5200
8. McCabe MT, Low JA, Imperiale MJ, Day ML. Human polyomavirus BKV transcriptionally activates DNA methyltransferase 1 through the pRb/E2F pathway. *Oncogene* 2006; 25: 2727–2735
9. Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. *J Am Soc Nephrol* 2004; 15: 1582–1588
10. Emerson LL, Carney HM, Layfield LJ, Sherbotie JR. Collecting duct carcinoma arising in association with BK nephropathy post-transplantation in a pediatric patient. A case report with immunohistochemical and in situ hybridization study. *Pediatr Transplant* 2008; 12: 600–605
11. Hill P, Slavin J, Goodman D. High-grade urothelial carcinoma in a kidney transplant recipient with BK virus infection. *NDT Plus* 2009; 2: 246–249
12. Brunner M, di Mayorca G, Goldman E. Absence of BK virus sequences in transformed hamster cells transfected by human tumor DNA. *Vir Res* 1989; 12: 315–330

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