Case Report

High-grade urothelial carcinoma in a kidney transplant recipient with BK virus infection

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Abstract
Bladder malignancy in the kidney transplant recipient is rare and compared with the general population tends to be of high grade and have an aggressive clinical course. In this report, we describe a case of urothelial carcinoma developing in a kidney transplant recipient 6 years after the diagnosis of polyomavirus nephropathy (PVN). BK virus (BKV) DNA was identified in urine and serum by PCR. The diffuse strong staining of SV40 T-antigen and p53 within both the in situ and invasive carcinoma suggest that BKV may play a role in the oncogenic pathway in this clinical setting.

Keywords: BK virus; kidney transplant; PVN; urothelial carcinoma

Introduction
Cancer is second to cardiovascular disease as one of the major causes of morbidity and mortality in kidney transplant recipients [1–3]. An Australian and New Zealand (ANZ) study showed a 3- to 5-fold increase in overall cancer incidence (excluding non-melanoma skin cancer). The risk of developing a neoplasm, skin neoplasms excluded, is ~15–20% at 10 years, but the rate may rise to 40% at 20 years [2]. Viral-related neoplasia appears to incur the greatest risk when compared with the general population; malignancies include those related to human papillomavirus (HPV) (tongue, mouth, vulva, vagina, penis), Epstein Barr virus (lymphoma), hepatitis B and C (hepatocellular carcinoma) and human herpesvirus 8 (Kaposi’s sarcoma). In the ANZ study, there was no excess post-transplantation risk for the two most common cancers in the Australian population, breast and prostate cancer [3]. Bladder malignancy in the kidney transplant recipient is rare with only a limited number of reported cases [2,4–7]. Although the incidence of bladder cancer in organ recipients appears to parallel the general population, the tumours are more likely to be high grade with an aggressive clinical course and poor response to chemotherapy.

Case report
A 46-year-old Asian man with chronic kidney failure due to tuberculosis received a deceased donor kidney transplant in February 2000. He received triple immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil (MMF) and prednisolone. His subsequent course was uneventful until 2 years post-transplantation (February 2002) when a rise in serum creatinine to 2.1 mg/dL (190 umol/L) prompted a kidney biopsy. The biopsy showed severe polyomavirus nephropathy (PVN) stage B [8], and BK virus (BKV) DNA was identified in urine and serum by PCR. Cyclosporin A and azathioprine were substituted for tacrolimus and MMF. Over the following 6 years, creatinine was stable at 2.1–2.3 mg/dL (190–200 umol/L); BKV DNA remained detectable in the serum at fluctuating low levels of 422–570 copies/mL (2.63–2.76 log10 copies/mL) on the seven occasions when it was measured over these 6 years. Regular urine cytology was performed in the first 2 years following the diagnosis of PVN with no malignant cells seen. In May 2007, urine examination showed a small number of red cells (20 × 10⁶ RBC/L) and in December 2007 urine examination showed 600 × 10⁶ RBC/L. Subsequent urine cytology revealed malignant cells; no definite ‘decoy cells’ were seen. The patient was referred to a urologist, and during cystoscopy urinary bladder biopsies were performed. These showed a high-grade urothelial carcinoma with invasion of the muscularis propria and a focal invasive micropapillary pattern. On immunohistochemistry, the tumour showed diffuse strong nuclear staining for Simian virus 40 T-antigen (T-Ag) and P53 in >90% of cells (Figure 1). No normal mucosa was present.

The patient underwent cystectomy with ileal conduit formation and removal of the left native kidney. Within the cystectomy specimen, residual high-grade urothelial carcinoma with invasion into perivesical fat and prominent lymphovascular space invasion was seen (Figure 2). The tumour...
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Fig. 1. Transurethral biopsy of bladder tumour. Immunohistochemistry shows diffuse strong positive nuclear staining of the invasive high-grade urothelial carcinoma for SV40 T-antigen (A) and p53 (B) (original magnification ×100).

showed a predominant invasive micropapillary pattern. Elsewhere, the urothelium showed focal evidence of in situ carcinoma (Figure 3). No polyomavirus nuclear changes were evident in the non-malignant urothelium, and there was no convincing cystitis. Diffuse strong expression of SV40 T-Ag was seen in both the invasive and in situ carcinoma (Figure 3), whereas the non-malignant urothelium and atrophic native kidney were negative. P53 also showed diffuse strong nuclear staining in the malignant epithelium in both the in situ and invasive tumour, exactly mirroring the SV40 T-Ag staining (Figure 3).

Discussion

Urothelial carcinoma in the general population is more common in men, with male-to-female ratio of 4:1, and has its highest incidence in the sixth and seventh decades. The majority of bladder tumours (~75%) are low-grade non-invasive urothelial carcinomas that are usually controlled by local resection; however, multiple recurrences are common [5]. In contrast, high-grade urothelial carcinomas are more likely to be invasive and require radical surgery such as complete cystectomy and ileal conduit. Following cystectomy, 5-year survival for tumours invading the muscularis is 40% and for tumours invading perivesical fat, 20% [5]. Arynlanes, analgesics, schistosomiasis infection, smoking and cyclophosphamide are known risk factors for bladder cancer by causing prolonged local irritation of the mucosa [5]. In the current case, there was no history of cyclophosphamide therapy.

Compared with the general population, the age of onset of bladder cancers in the transplant recipient is younger (average 44 years) with no male predominance [4–7]. The
duration of immunosuppression to development of the urothelial malignancy varies from 2 years to >10 years. The majority of the earlier reported cases had received cyclosporine and azathioprine [4,5], but more recent cases have occurred in patients with immunosuppressive regimens including cyclosporine or tacrolimus and MMF [6,7]. The majority of cases are invasive high-grade urothelial carcinoma or squamous carcinoma. This could relate to ongoing immunosuppression and susceptibility to oncogenic viruses.

Studies have investigated possible roles for virus in the aetiology of urothelial carcinoma. Some studies have demonstrated a positive association between HPV and urothelial cancer in humans [9,10]; however, others have failed to confirm this [11]. The potential role of polyomaviruses in bladder cancer has also been investigated in both humans and animal models [6,11,12]. Polyomaviruses code for a non-structural protein, the large T-Ag, which can bind to and inactivate tumour suppressor proteins p53 and pRB, resulting in aberrant cell cycle regulation [12]. Expression of T-Ag induces high-grade bladder tumours in transgenic mice [12]. One study demonstrated a statistically significant association between polyomavirus infection and bladder cancer in a large series of patients [13]. In addition, in an Italian series BKV sequences were reported in 55% of 32 bladder tumours using PCR techniques [11]. However, other studies using identification of polyomavirus DNA have failed to confirm an association of BKV with urothelial malignancy varies from 2 years to >10 years.

In conclusion, we report a case of bladder cancer developing in a kidney transplant recipient with a history of PVN [6]. This earlier report showed positive staining of the invasive urothelial carcinoma for SV40 T-Ag and p53, whereas surrounding non-neoplastic urothelium and stromal cells were negative. We have also demonstrated strong expression of SV40 and P53 not only in the invasive tumour but also within in situ urothelial carcinoma in the cystectomy specimen in our patient. This supports the proposal that in situ carcinoma may represent an early stage in the progression to invasive urothelial carcinoma and also suggests that BKV may play a role in the oncogenic pathway in this clinical setting. However, consideration should also be given to the possibility that the virus is demonstrable in the tumour simply because replicating cells provide a better milieu for BKV replication than non-neoplastic cells (BKV depends exclusively on host replication machinery to complete its own life cycle) [19].

Conflict of interest statement. None declared.

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