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Case report

Anterior Pelvic Exenteration and Synchronous Bilateral Nephroureterectomy for BK Polyoma Virus Induced Urothelial Carcinoma of the Bladder: A Case Report

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Abstract

BK polyoma virus (BKV) is a known risk factor for the development of urothelial carcinoma. There is currently limited data on the management of BKV-induced urothelial carcinoma (BUC) of the bladder, with available data limited to case reports. It remains debatable whether radical cystectomy (RC) with removal of the native urinary tract or RC alone is the most optimal management for BUC of the bladder. BKV-induced urothelial carcinoma is rare, and its management is challenging in immunocompromised patients such as that of post-transplant patients. This case report provides additional insight into a rare disease, the management of which still lacks established guidelines and remains debatable.

We present a unique case of BKV-induced muscle-invasive urothelial carcinoma of the bladder in an immunosuppressed renal transplant patient who underwent open radical cystectomy, anterior pelvic exenteration, bilateral native nephroureterectomy and ileal conduit formation to transplant kidney. The patient remains recurrence-free with preserved graft function 2 years since surgery.

An aggressive management approach which involves anterior pelvic exenteration with removal of the native urinary tract may be favoured in young patients with BUC of the bladder with minimal comorbidities. However, treatment should be individualised for each individual patient.

Keywords

BK virus-induced urothelial carcinoma, radical cystectomy, renal transplant

INTRODUCTION

BKV is a non-enveloped double-stranded DNA virus which was first discovered by Gardner et al.[1] following culture of urine from a renal transplant patient in Vero cells. The genome of BKV consists of an early region which encodes for T antigens, a late region which encodes for capsid proteins VP1-3 and agnoprotein, and a non-coding control region.[1] Currently, there are six recognised BKV genotypes, with most polymorphisms occurring in VP1 and the large T-antigen gene.[1]

BKV has been strongly linked to oncogenesis in immu-

nosuppressed patients. However, the pathophysiology of UC development is unknown. The T antigen of BKV could promote oncogenesis by inhibiting tumour suppressor proteins from the p53 and pRB family as well as inducing chromosomal aberration.[2] BKV is known to be associated with various cancers, notably urothelial carcinoma of the bladder with numerous case reports reporting the association.[2-4] BKV-induced urothelial carcinoma (BUC) of the bladder is often diagnosed at an advanced stage and thus, prognosis is dismal. To date, the management of BUC of the bladder remains equivocal, with clinical management primarily based on case reports.

We present a unique case of BKV-induced muscle-invasive urothelial carcinoma of the bladder in an immunosuppressed renal transplant patient who underwent open radical cystectomy, anterior pelvic exenteration, bilateral native nephroureterectomy, and ileal conduit formation to transplant kidney.

CASE REPORT

A 47-year-old female presented to the emergency department with a 3-day history of fever, vomiting, dysuria, and reduced urine output. Her past medical history was significant for a live donor renal transplant 12 years prior (August 2009), for chronic kidney disease secondary to IgA nephropathy. Her initial immunosuppression regimen included tacrolimus 1 mg and prednisolone 5 mg daily. The patient was a non-smoker, with a past medical history of hypertension and post-transplant BK viraemia which was diagnosed in November 2011, with urine BKV load of >5×10^9 copies/ml and plasma BKV load of 9×10^4 copies/ml. Despite modification of her immunosuppression regimen, her BKV viral load persisted at a similar level since diagnosis, until June 2018 where there was significant improvement, with urine BKV load of 1×10^7 copies/ml and plasma BKV load of less than 5×10^2 copies/ml. Since then, the patient has been on diltiazem MR 360 mg, prednisolone 5 mg once daily, tacrolimus 0.5 mg twice daily, and everolimus 0.75 mg twice daily. The patient was on no other medications.

She was found to be hypotensive on arrival with a blood pressure of 90/60 mmHg, but the rest of her vital signs were unremarkable. She had a leucocytosis of 30×10^9/L and had developed an acute kidney injury with a creatinine of 160 µmol/L (baseline 80 µmol/L). Urine was sent off for cultures, which grew Enterococcus faecalis and Proteus mirabilis. An ultrasound of her renal tract showed a 21×24×24 mm vascular bladder mass. Additionally, a flexible cystoscopy was performed, which revealed a large, calcified mass consistent with likely urothelial carcinoma (UC). She was initially treated with intravenous meropenem and then deescalated into oral ciprofloxacin and planned for an elective transurethral resection of bladder tumour (TURBT). She recovered from the

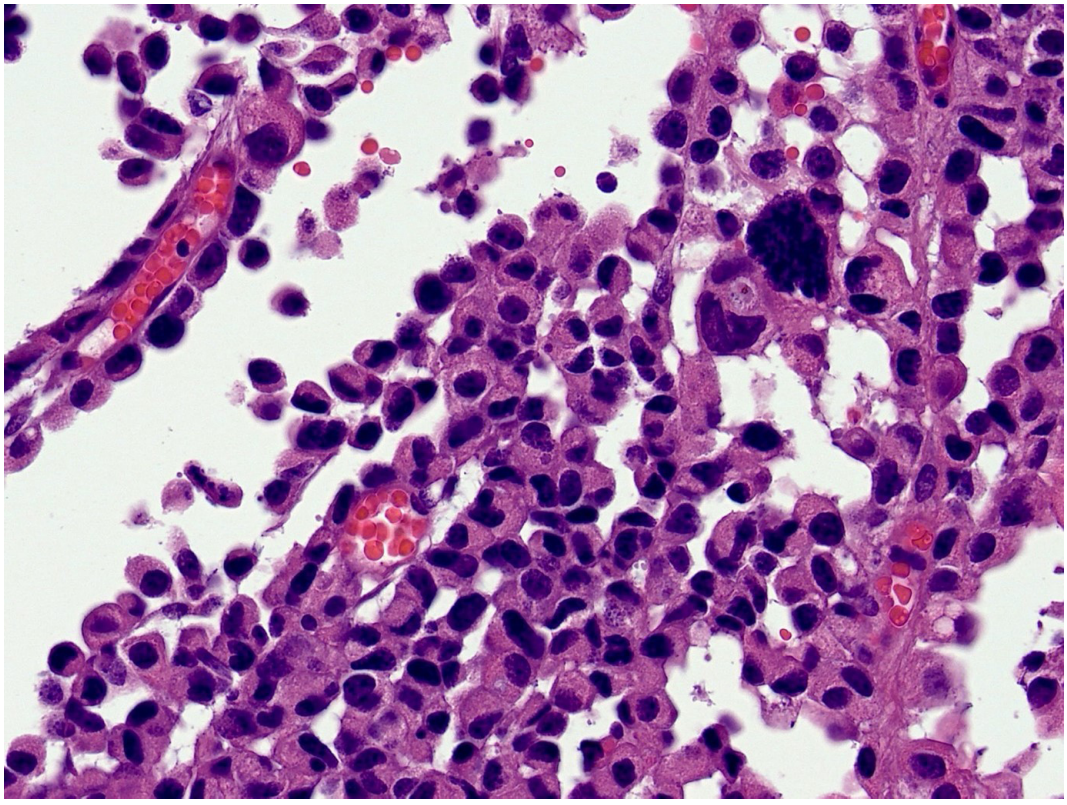

Figure 1. The urothelial carcinoma cells are characterised by markedly hyperchromatic, often eccentric nuclei with scant eosinophophilic cytoplasm (HE stain, ×40 magnification).

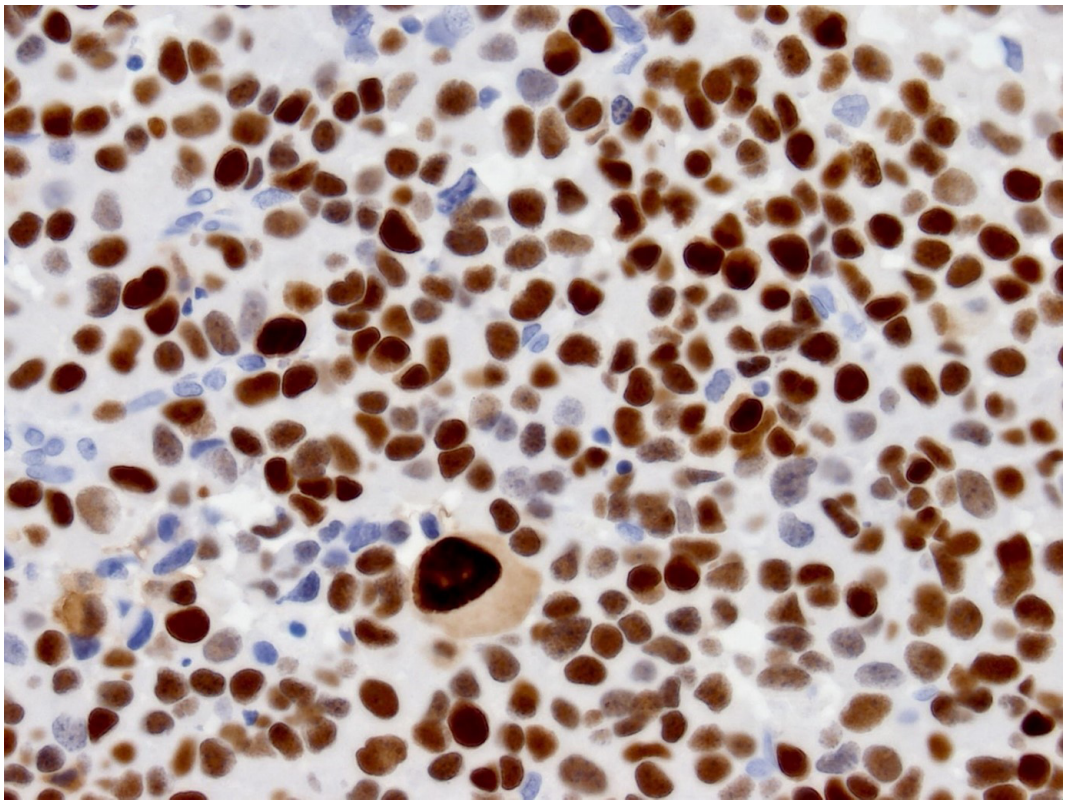

Figure 2. Immunoperoxidase staining for SV40 TAg shows strong positive nuclear staining, supporting infection with BK polyoma virus (SV40 TAg stain, ×40 magnification).

urosepsis and underwent an elective TURBT, with subsequent histopathological assessment and immunoperoxidase staining demonstrating BK polyomavirus (BKV)-induced muscle-invasive papillary UC of the bladder ***(Figs 1, 2)****. Her upper tracts were assessed with bilateral retrograde pyelogram, both of which were normal. She was diagnosed with BK-virus urothelial carcinoma 9 years after developing BK-viremia.*

This case was discussed at the tertiary hospital's Uro-Oncology multidisciplinary team meeting. Whole body fluorodeoxyglucose position emission tomography (FDG-PET) staging demonstrated no evidence of metastatic disease. Due to her immunosuppressed state, the patient was unsuitable for neoadjuvant chemotherapy and concerns were raised regarding the risk of UC development in her native upper urinary tract, in the setting of non-functioning native kidneys and a kidney transplant. Subsequent surgery following anterior pelvic exenteration would be more complex and associated with greater risk. Hence, the patient proceeded to radical cystectomy (RC) with left pelvic lymphadenectomy, hysterectomy with bilateral salpingo-oophorectomy, urethrectomy, bilateral nephroureterectomy plus ileal conduit formation with a transplant uretero-enteric anastomosis. Resection was completed en bloc, with the specimen sent for histopathology ***(Fig. 3)****. The transplant kidney was in the right pelvis, therefore only left lymphadenectomy was performed. The uretero-enteric anastomosis was at the left of the transplant renal pelvis.*

Post-operatively, the patient was transferred to the Intensive Care Unit for monitoring and transferred to the Urology ward one day post-surgery. Ongoing consultation and immunosuppression monitoring were performed by the Renal Transplant team. The patient was discharged 8 days post-surgery.

Histopathology of the en bloc specimen revealed no residual urothelial malignancy, with five benign lymph nodes (Stage pT0N0Mx). The gynecological organs showed no tumour infiltrations. The native kidneys demonstrated near total interstitial fibrosis and tubular atrophy, with no evidence of BKV nephropathy.

At 24-month follow-up, FDG-PET demonstrated no evidence of metastatic disease. The patient maintains a stable renal function and continues on her immunosuppressive regimen.

DISCUSSION

BKV infection is a relatively common disease in the general population with up to 50% of healthy adults being BKV-positive.[5,6] It typically infects individuals early in childhood through respiratory droplets from infected patients, manifesting as mild respiratory symptoms before disseminating via the blood to various organs including but not limited to liver, stomach, lungs, and most notably, kidneys.[7] In immunocompetent individuals, BKV remains clinically latent in these organs, with potential

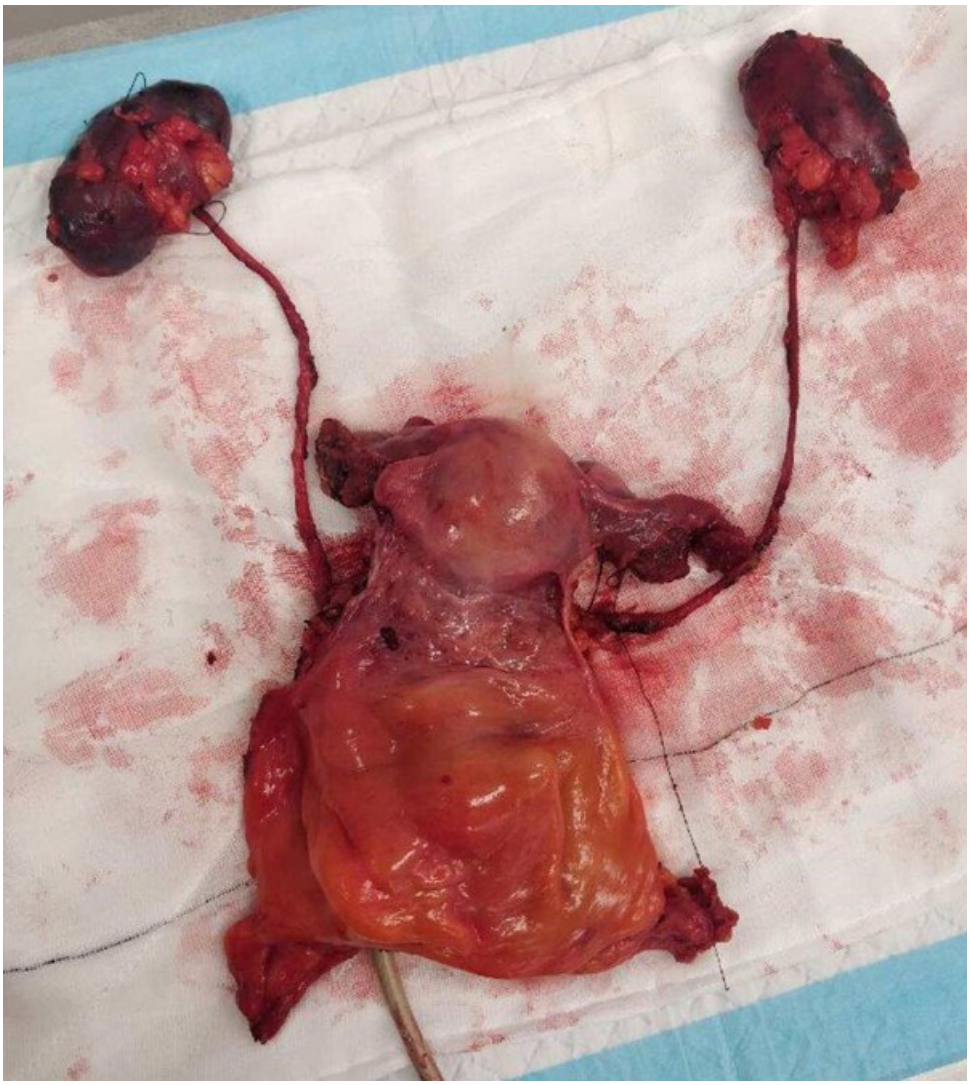

Figure 3. En bloc resection of the native urinary tract and anterior pelvic organs - radical cystectomy with bilateral nephroureterectomy and hysterectomy with bilateral salpingo-oophorectomy.

for reactivation in immunocompromised patients such as bone marrow and renal transplant patients.[5,8,9] Numerous case reports have described the association between BKV and bladder carcinoma, mostly in the setting of post-renal transplant.[2,4,10] However, it is understood that it can also occur in clinical situations of impaired immunocompetence such as post-hematopoietic stem cell transplant patients, AIDS, multiple sclerosis, administration of chemotherapy or biologic therapy.[5]

The management of BUC of the bladder remains controversial with no established guidelines and treatment is guided primarily by case reports.[2,4,10] In immunosuppressed patients with high-risk non-muscle invasive bladder cancer, intravesical BCG immunotherapy is controversial; however, intravesical chemotherapy (such as mitomycin, gemcitabine and epirubicin) can be considered. Upfront RC should also be offered and is likely associated with the highest chance of cure. Additionally, RC would be preferable if a patient has an absolute contraindication to chemotherapy such as significant immunosuppression in the setting of post-transplant patients. Radiotherapy as a single modality is inferior to surgery. It remains debatable whether RC with removal of the native urinary tract or RC alone, with transplant uretero-enteric anastomosis should be standard of care in BUC of the bladder. Given that BUC of the bladder is aggressive and renal transplant patients remain in a state of life-long immunosuppression, which is a significant risk factor for carcinogenesis, it is not unreasonable to offer synchronous bilateral nephroureterectomies together with RC, especially if the patients are young with minimal co-morbidities. Additionally, it may be worthwhile considering a transplant ureterectomy with ileal ureteric reconstruction as UC has also been previously shown to develop in the allograft ureter.[4] However, despite the aforementioned aggressive approach, UC may also develop in the transplanted kidney, eventually necessitating kidney re-transplantation or dialysis.[2] In patients with advanced age and multiple comorbidities, it would be more reasonable to consider a more conservative

approach such as RC alone without removal of the native urinary tract or radiotherapy at the expense of risk of recurrence of UC of the upper tract. Treatment for BUC of the bladder should be individualised for each patient.

CONCLUSIONS

In conclusion, BKV is not an uncommon risk factor for malignancy of solid organs such as UC, particularly in transplant patients. Routine screening for BKV in these patients is crucial to allow prompt management to be initiated if BKV infection exists. While there are no established guidelines on the management of BUC of the bladder in renal transplant patients, an aggressive approach involving a RC and removal of the native urinary tract with anastomosis of the transplanted kidney's ureter to an ileal conduit is currently thought to be the most favourable approach, especially in a young patient with minimal comorbidities.

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Competing Interests

The authors have declared that no competing interests exist.

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Передняя тазовая экзентерация и синхронная двусторонняя нефроуретерэктомия при уротелиальной карциноме мочевого пузыря, индуцированной вирусом полиомы BK: клинический случай

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Резюме

Вирус полиомы BK (BKV) является известным фактором риска развития уротелиальной карциномы. В настоящее время имеется ограниченное количество данных о лечении BKV-индуцированной уротелиальной карциномы (BUC) мочевого пузыря, при этом доступные данные ограничены сообщениями о случаях заболевания. Остаётся спорным вопрос о том, является ли радикальная цистэктомия (РЦ) с удалением нативных мочевыводящих путей или только РЦ наиболее оптимальным методом лечения BUC мочевого пузыря. BKV-индуцированная уротелиальная карцинома встречается редко, и её лечение у пациентов с ослабленным иммунитетом, таких как пациенты после трансплантации, является сложной задачей. Этот клинический случай даёт дополнительную информацию о редком заболевании, лечение которого до сих пор не имеет установленных рекомендаций и остаётся спорным.

Мы представляем уникальный случай BKV-индуцированной мышечно-инвазивной уротелиальной карциномы мочевого пузыря у пациента с иммуносупрессивным трансплантатом почки, который перенёс открытую радикальную цистэктомию, переднюю тазовую экзентерацию, двустороннюю нативную нефроуретерэктомию и формирование подвздошного канала для трансплантата почки. У пациента нет рецидивов с сохранённой функцией трансплантата через 2 года после операции.

Агрессивный подход к лечению, который включает переднюю экзентерацию малого таза с удалением нативных мочевыводящих путей, может быть предпочтительнее у молодых пациентов с BUC мочевого пузыря с минимальными сопутствующими заболеваниями. Однако лечение должно быть индивидуализировано для каждого отдельного пациента.

Ключевые слова

вирус-индуцированная уротелиальная карцинома, радикальная цистэктомия, трансплантация почки