CASE REPORT

Urothelial carcinoma of an allograft ureter 10 years after deceased donor kidney transplantation

Kevin P Gaughan, Usman Haroon, Niall F Davis, Ponnusamy Mohan

Department of Urology,
Beaumont Hospital, Dublin,
Ireland

Correspondence to
Dr Kevin P Gaughan,
kevingaughan@rcsi.ie

Accepted 27 April 2018

SUMMARY

The incidence of urothelial carcinoma (UC; formerly transitional cell carcinoma) is higher among renal transplant recipients compared with the general population. Upper urinary tract UC (UUT-UC) of allograft urothelium is a rare event with approximately 40 cases reported in the literature. Herein, we describe the clinical presentation and management of UUT-UC in a transplant ureter 10 years after deceased donor kidney transplantation.

BACKGROUND

Renal transplantation is the gold-standard treatment option for patients with end-stage renal disease (ESRD). Morbidities associated with the renal transplantation include predisposition to bacterial and viral infections and a threefold increased risk of malignancy due to the recipient's chronically immunosuppressed status.¹ The incidence of urothelial carcinoma (UC) ranges from 0.5% to 4.1% among renal transplant recipients (RTRs) (RR 1.9).^{2–4} A feature unique to RTRs is that upper urinary tract UC (UUT-UC) can affect either native urothelium or renal allograft urothelium. We describe the clinical presentation and management of a donor-derived UC in the transplanted ureter after deceased donor renal transplantation.

CASE PRESENTATION

A 68-year-old Caucasian male with ESRD secondary to hypertensive nephropathy underwent bilateral nephron-dosing cadaveric renal transplantation. He was an ex-smoker (quit 5 years; 30 pack-year history) and had previously worked as a farmer with no other occupational exposures. Prior to transplantation, he had been on peritoneal dialysis for 5 months. Perioperative and postoperative immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil and prednisolone. The donor was a 59-year-old male non-smoker with a history of ischaemic heart disease and no occupational hazard exposures who sustained a subarachnoid haemorrhage. Dual-kidney transplantation was performed, as it is associated with similar graft survival for older transplant recipients (>55 years old) when compared with single-kidney transplantation from ideal donors (those <60 years old with no cardiovascular disease).⁵ The patient's renal allograft function deteriorated 10 years postoperatively (creatinine levels increased from 100 $\mu\text{mol/L}$ to 210 $\mu\text{mol/L}$ and estimated glomerular filtration

rate (eGFR) decreased from 65 mL/min to 31 mL/min, respectively). The patient also presented with painless visible haematuria.

INVESTIGATIONS

Renal ultrasonography demonstrated severe hydronephrosis and hydroureter of the right transplanted kidney. Flexible cystoscopy demonstrated a solid mass protruding from the transplanted right ureteric orifice. An urgent transurethral resection of the mass was performed and histopathological findings confirmed a pT1 high-grade UC. Staging MRI of the bladder and pelvis revealed a smooth enhancing mass with the epicentre in the right distal transplanted ureter extending into the urinary bladder (figure 1). No lesions were identified elsewhere including the left allograft or the two native kidneys. No lymphadenopathy or metastatic disease was noted.

TREATMENT

Following discussion at a multidisciplinary team meeting, the patient underwent a right-sided transplant nephroureterectomy with partial cystectomy. The functioning left transplant kidney was left in situ so that the patient would not be dialysis dependent. Histopathology confirmed high-grade UC, stage pT3a, with the tumour arising at the ureteric orifice and extending through the bladder wall, microscopically into the perivesical fat (figure 2). All margins were negative. The distal margins showed normal bladder mucosa and proximally there was only inflammatory change secondary to ureteric obstruction.

OUTCOME AND FOLLOW-UP

The patient underwent an uncomplicated postoperative course and was discharged home. Since his operation, he has attended his nephrologist every 3 months where his creatinine level is monitored and urinalysis is performed. To date, his urine has remained clear and his kidney function has been reduced but remains stable (creatinine $\sim 200 \mu\text{mol/L}$ and eGFR 34 mL/min). He has not undergone any subsequent MRI or CT imaging as a decision was reached to only perform such investigations if he was to become symptomatic. He remains well 13 months after his surgery.

DISCUSSION

The incidence of UC in RTRs ranges from 0.5% to 4.1%^{2–4} and this varies with geographical location.

To cite: Gaughan KP, Haroon U, Davis NF, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223087

Figure 1 An MRI pelvis which on sagittal view (A) demonstrates an enhancing mass (arrow) in the right ureter at the vesicoureteric junction above the bladder (arrowheads). On an axial view (B–D), the same mass can be seen at the level of the right transplanted kidney extending into and compressing the bladder (arrowheads).

Tobacco exposure is a well-established risk factor worldwide for UC and was likely a contributory influence given our patients' history. McLaughlin *et al* demonstrated that smokers have an increased risk of UUT-UC (OR 3.1)⁶ and was augmented by degree of exposure (OR 4.8 when >40 cigarettes/day) and duration (OR 6.2 when >60 pack-years). Conversely, those who had quit for greater than 10 years have a 60%–70% reduction in their risk. The percentage of UUT-UC attributable to smoking was 70% and 37% for males and females, respectively. Both peritoneal dialysis and haemodialysis are associated with an increased risk of urinary tract cancer⁷ and this is compounded by duration (HR 2.57 for those on dialysis preoperatively >4.5 years).⁸ Other known risk factors pertinent to this case would include immunosuppression,⁹ deceased donor allograft² and increased age of the recipient.² Other published aetiologies for UC include analgesic overuse,²⁴ aristolochic acid (AA) consumption⁴ and Balkan endemic nephropathy.¹⁰ Viral infections such as BK virus¹¹ and human papilloma virus (HPV) (particularly HPV-16)¹² are also described as risk factors for UC in RTRs.

There are 41 cases of UC of graft urothelium described in the literature, and visible haematuria is the most common presenting symptom followed by asymptomatic hydronephrosis and abdominal pain.^{4 13–19} The mean duration from transplantation to diagnosis is approximately 12 years (range: 0.6–39 years) and the landing site is usually within the urothelium of the renal pelvis or calyces. Our recipient was diagnosed 10 years

post-transplantation with the epicentre of the urothelial mass arising in the lower transplant ureter.

Typically, allograft UUT-UC is associated with a higher grade and stage at presentation and these features adversely affect prognosis. The mean survival of RTRs with UC is significantly lower compared with RTRs without UC (34 months vs 222 months, respectively).² The 1, 5 and 10 year overall survival is 80%, 54%, 30%, respectively, and the 1, 5 and 10 year tumour-specific survival is 85%, 67% and 58%, respectively.³ The most frequent sites of UUT-UC metastasis are, in descending order of frequency, the lymph nodes, lung, liver, bone and peritoneum.²⁰ A significant morbidity is removal of the affected allograft that renders the patient anephric and dialysis dependent. In rare cases, the renal allograft may be spared by less invasive surgical approaches, for instance, endoscopic laser ablation, where there is favourable conditions such as low grade and smaller tumour size.

A routine screening process should be offered to all RTRs for early detection of UC. Tsaur *et al* has proposed a vigilant screening process involving annual cystoscopies in RTRs with at least one significant risk factor for UC.³ We would advocate that a screening protocol should at least consist of regular urinalysis and ultrasonography. Any RTR who presents with unexplained visible haematuria or lower urinary tract symptoms, particularly those who have risk factors for UC, should undergo urgent investigations including cystoscopy and upper tract imaging.

Figure 2 (A) Macroscopic image of specimen removed by radical nephroureterectomy including the fungating mass arising from the ureter (arrow) and the transplant kidney (arrowhead). (B) Cross-section of mass arising from the ureter (arrow). (C) Low power view (10× magnification) of tumour showing islands of high grade urothelial carcinoma (UC) (arrow) invading muscle. (D) High power image (20×) of UC showing nuclear pleomorphism, hyperchromasia and clumping of nuclear chromatin.

In summary, we describe the clinical presentation, risk factors and management of UUT-UC in a donor renal allograft. Urgent investigation of symptoms is of paramount importance for improving prognosis in transplant recipients with UC.

Learning points

- The incidence of urothelial carcinoma (UC) in renal transplant recipients (RTRs) ranges from 0.5% to 4.1%.
- RTRs with UC present with painless visible haematuria, hydronephrosis and abdominal pain.
- Risk factors for UC for RTRs include tobacco exposure, immunosuppression, dialysis, deceased donor allograft and recipient age.
- The authors would advocate annual screening urinalysis for RTRs and prompt urological workup if positive.
- UC of RTRs tends to be high grade and significantly impacts life expectancy and as such urgent investigation of symptoms is of paramount importance for improving prognosis in transplant recipients with upper urinary tract UC.

Acknowledgements The authors of this paper would like to acknowledge those who contributed to its production. This would include Dr Maeve Redmond (Consultant Pathologist, Beaumont Hospital) who analysed the histopathology specimens of this case and advised on the images used in this paper. Dr Martina Morrin (Consultant Radiologist, Beaumont Hospital) advised on the radiology images presented in this case.

Contributors KPG was the primary author of this paper. UH and ND revised and corrected the paper from its initial drafts. PM was the lead consultant and provided final revision and approval for this paper. All authors of this report were directly involved in the care and treatment of the patient described in this case.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Vajdic CM, McDonald SP, McCredie MR, *et al.* Cancer incidence before and after kidney transplantation. *JAMA* 2006;296:2823–31.
- 2 Ardelt PU, Rieken M, Ebbing J, *et al.* Urothelial cancer in renal transplant recipients: incidence, risk factors, and oncological outcome. *Urology* 2016;88:104–10.
- 3 Tsaor I, Karalis A, Blaheta R, *et al.* Transitional cell carcinoma of the native urinary tract after kidney transplantation: recommendations following a long-term retrospective analysis. *Am J Med Sci* 2011;341:478–83.
- 4 Wu MJ, Lian JD, Yang CR, *et al.* High cumulative incidence of urinary tract transitional cell carcinoma after kidney transplantation in Taiwan. *Am J Kidney Dis* 2004;43:1091–7.
- 5 D'Arcy FT, O'Connor KM, Shields W, *et al.* Dual kidney transplantation with organs from extended criteria cadaveric donors. *J Urol* 2009;182:1477–81.
- 6 McLaughlin JK, Silverman DT, Hsing AW, *et al.* Cigarette smoking and cancers of the renal pelvis and ureter. *Cancer Res* 1992;52:254–7.
- 7 Lee YC, Hung SY, Wang HK, *et al.* Is there different risk of cancer among end-stage renal disease patients undergoing hemodialysis and peritoneal dialysis? *Cancer Med* 2018;7:485–98.
- 8 Wong G, Turner RM, Chapman JR, *et al.* Time on dialysis and cancer risk after kidney transplantation. *Transplantation* 2013;95:114–21.
- 9 Tremblay F, Fernandes M, Habbab F, *et al.* Malignancy after renal transplantation: incidence and role of type of immunosuppression. *Ann Surg Oncol* 2002;9:785–8.
- 10 Basic-Jukic N, Hrsak-Puljic I, Kes P, *et al.* Renal transplantation in patients with Balkan endemic nephropathy. *Transplant Proc* 2007;39:1432–5.
- 11 Saquib R, Barri YM, Saad R, *et al.* Transitional cell carcinoma of renal allograft associated with BK virus infection. *Dial Transplant* 2009;38:518–9.
- 12 Li N, Yang L, Zhang Y, *et al.* Human papillomavirus infection and bladder cancer risk: a meta-analysis. *J Infect Dis* 2011;204:217–23.
- 13 Olisburgh J, Zakri RH, Horsfield C, *et al.* TCC in transplant ureter – when and when not to preserve the transplant kidney. *Am J Transplant* 2016;16:704–11.

- 14 Ferreira GF, de Oliveira RA, Jorge LB, *et al.* Urothelial carcinoma transmission via kidney transplantation. *Nephrol Dial Transplant* 2010;25:641–3.
- 15 Bakirtas H, Guvence N, Ozok HU, *et al.* Ureterovesical malignancy following renal transplantation: a case report. *Transplant Proc* 2007;39:3474–6.
- 16 Floyd MS, Khattak AQ. Total urinary tract exenteration including donor nephrectomy for transitional cell carcinoma 41 years following transplantation. *Int Urol Nephrol* 2015;47:107–8.
- 17 Zivčić-Cosić S, Grzetić M, Valencić M, *et al.* Urothelial cancer in patients with Endemic Balkan Nephropathy (EN) after renal transplantation. *Ren Fail* 2007;29:861–5.
- 18 Zhang A, Shang D, Zhang J, *et al.* A retrospective review of patients with urothelial cancer in 3,370 recipients after renal transplantation: a single-center experience. *World J Urol* 2015;33:713–7.
- 19 Kojima Y, Takahi Y, Ichimaru N, *et al.* Successful treatment of metastatic urothelial carcinoma arising in a transplanted renal allograft with paclitaxel, cisplatin, and gemcitabine combination therapy: a case report. *BMC Res Notes* 2015;8:25.
- 20 Shinagare AB, Fennessy FM, Ramaiya NH, *et al.* Urothelial cancers of the upper urinary tract: metastatic pattern and its correlation with tumor histopathology and location. *J Comput Assist Tomogr* 2011;35:217–22.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow