Urol Res (2004) 32: 89–92
DOI 10.1007/s00240-003-0380-8

ORIGINAL PAPER

G. W. A. Lamb · G. M. Baxter · R. S. C. Rodger
M. Aitchison

Partial nephrectomy used to treat renal cell carcinoma arising in a live donor transplant kidney

Received: 7 August 2003 / Accepted: 24 September 2003 / Published online: 3 October 2003

Abstract There are few reported cases of renal cell carcinoma (RCC) arising in kidney allografts. Whether these tumours occur due to post-transplant malignant transformation or are present at the time of transplantation is unclear. The influence of immunosuppression must be considered in their development, progression and treatment. We report a case of a RCC presenting asymptomatically in a functioning live donor renal allograft 173 months after transplantation. In an attempt to avoid return to dialysis treatment, a partial nephrectomy was carried out. To optimise the procedure, and to assure cancer clearance, combined intraoperative ultrasound and frozen section analysis were used. Our patient remains disease free and dialysis independent at 22 months follow up. To our knowledge, this patient represents the only live donor organ transplant tumour reported to be treated using nephron-sparing surgery and remain dialysis independent. Partial nephrectomy should be considered as a treatment option in such cases.

Keywords Renal cell carcinoma · Live donor · Transplanted kidney · Partial nephrectomy · Intra-operative ultrasound

G. W. A. Lamb (✉) · M. Aitchison
Department Of Urology,
Gartnavel General Hospital,
1053 Great Western Rd, Glasgow, G12 0YN, UK
E-mail: glam@doctors.org.uk

G. M. Baxter
Department of Radiology,
Western Infirmary, Glasgow, G11 6NT, UK

R. S. C. Rodger
Renal Unit, Western Infirmary,
Glasgow, G11 6NT, UK

Introduction

Renal cell carcinoma accounts for 4.6% of cancers in transplant recipients, compared with 3% of tumours in the general population [1]. These tumours are reported to behave more aggressively in transplant compared to long-term dialysis patients, due to the influence of immunosuppression [2].

Tumours most commonly arise in the native kidneys of transplant recipients. The first case of de novo tumour arising in a transplanted kidney was described in 1988 by Scott et al. [3]. In reviewing the Cincinnati Transplant Tumour Registry, Penn et al. identified 239 renal tumours out of 7,248 tumours arising in allograft recipients [4]. Of these lesions, 208 developed in the native kidneys of the patient, ten were of unknown origin and 21 developed in the allograft itself.

Tumours arising in allograft kidneys have been treated in several ways. Reported cases include those of incidental histology following removal of transplant kidney that has failed to function [3, 7]. Others report the use of radical or partial nephrectomy for incidental or symptomatically detected lesions [8, 9, 10].

We report a patient who developed RCC in a live donor allograft, which was successfully treated combining nephron sparing surgery, intraoperative ultrasound and frozen section analysis. Using these techniques the patient is alive, continues on immunosuppression and is disease free with no haemodialysis requirement 22 months following surgery. To our knowledge, this patient represents the only reported live donor transplanted kidney patient treated in this way who remains dialysis independent.

Materials and methods

Case report

We report a 47-year-old male who developed renal failure following Henoch-Schonlein Nephritis: he became dialysis dependent first in 1977 and received a cadaveric transplant in 1980. This failed after 4 days due to acute rejection and was removed. The patient

returned to dialysis before a further cadaveric transplant was performed in 1982; the graft rejected after 9 months. After a further period on dialysis, a third transplant was carried out in 1986. This was a live donor transplant from the patient's brother that was placed intra-peritoneally due to the previous transplant surgery. An upper pole artery from the main renal artery had to be sacrificed due to its proximity to the aorta, resulting in a small area of infarction of the upper pole of the donor kidney.

Following surgery, the maintenance immunosuppressive agents were Prednisolone and Ciclosporin, and he did not receive induction antibody therapy.

At 173 months after transplantation the serum creatinine (Cr) was elevated at 222 μmol/L (2.51 mg/dL) and urinalysis was dipstix positive for blood, but he was otherwise asymptomatic. An ultrasound scan (USS) identified a 2-cm lesion in the upper pole of the transplant kidney and USS guided biopsy confirmed this lesion to be a renal cell carcinoma. A routine USS carried out 1 year previously was reported to be normal and urinalysis at this time demonstrated no haematuria.

Computed tomography (CT) scan was performed, which confirmed a 2-cm mass confined to the upper pole of the transplant kidney with no evidence of metastases. The native kidneys were noted to be shrunken, consistent with end-stage renal disease.

The patient underwent a partial transplant nephrectomy that was performed through a right paramedian incision, with a wedge excision under intra-operative USS guidance. Macroscopically, approximately 30% of the kidney was excised and frozen section margins examined intraoperatively were clear. Formal histology confirmed a T1 N0 M0 clear cell carcinoma Fuhrman Grade 3.

Postoperative recovery was complicated by a persistent urinary leak that settled following percutaneous nephrostomy and antegrade stent insertion. Following partial nephrectomy, the Cr remained stable at 225 μmol/L (2.54 mg/dL), which was equivalent to pre-operative values.

At 22 months the patient remains asymptomatic and disease free on follow-up CT scanning. He remains dialysis independent (Cr 180 μmol/L (2.03 mg/dL). Since diagnosis, the patient's immunosuppressive therapy has been reduced to prednisolone only. The patient's brother is followed up with regular surveillance USS of his remaining kidney, and has also no evidence of disease to date.

Discussion

Partial nephrectomy is becoming more widely accepted as a treatment alternative in the management of patients with RCC for whom preservation of renal function is a relevant clinical consideration. Data is accumulating to suggest that preservation of renal function can be achieved by this technique without sacrificing cancer control [5]. Thus, patients developing renal cell carcinoma (RCC) in allograft kidneys should be considered for partial nephrectomy on this basis.

Concerns exist about the continuing use of immunosuppressive agents in these patients following removal of the tumour in case residual micro-metastases may have more potential to grow due to reduced immunosurveillance. Reducing immunosuppression in renal transplant recipients who develop malignancy does not appear to be associated with a high risk of developing acute rejection (AE Alfonso et al., unpublished data). For these reasons, ciclosporin was discontinued. The long-term improvement in renal function which has occurred may be due to reversal of ciclosporin nephrotoxicity.

Based on the reported literature, the time involved in the development of RCC in transplanted kidneys is extremely variable, ranging from 9–258 months (Table 1). Whether the tumours observed in allograft kidneys represent de novo transformation or transplanted disease is unknown. Evidence exists to support the aetiology in both cases and, as not mutually exclusive, both may occur in clinical practice. In our patient it seems most likely that the malignancy developed after transplantation, taking into account the transplant interval along with negative ultrasound and urinalysis a year before presentation.

Wunderlich et al. [11] in their study of 10,997 donor kidneys identified 30 kidneys 0.273% (0.546% of renal donors) with RCC at the time of preparation before transplantation. Of these tumours, 67% were smaller than 20 mm. Sixteen patients developed RCC between 3 and 12 years after transplantation, with the conclusion that a significant number of these were present as an intraparenchymal lesion at the time of grafting. Wunderlich concludes that because of the significant incidence (total 0.836%) of asymptomatic lesions in renal donors, pre-operative ultrasound of donor kidneys is advised [11].

Park et al. [9] consider the tumour they report to represent de novo transformation, due to the significant interval from transplantation to presentation: 258 months. They further supported this argument by performing DNA banding that confirmed the tumour had arisen from the donor. This is not conclusive, as the natural history of RCC is variable, and both de novo and in situ tumours would be expected to demonstrate donor banding. Gunji suggests that de novo RCC may develop rapidly after transplantation, as the time to recognise tumour was only 9 months in their case report [10] (Table 1).

Although no controlled trials have been performed, transplantation probably benefits life expectancy and usually improves quality of life when compared to haemodialysis in end-stage renal failure. With this in mind, it would seem appropriate, where possible, to preserve the transplanted kidney in the treatment of allograft RCC.

Current evidence suggests that adequate surgical clearance of RCC can be achieved in the non-immunosuppressed patient with a minimal margin of 5 mm, as opposed to the previous recommended margins of 10–20 mm [12]. Having confirmed intraoperative clear margins, local recurrence is unlikely, which essentially assures local cancer control. Sutherland et al. describes no cases of local recurrence with negative margins [12].

To assist in gaining satisfactory clearance and preserve optimal renal function, the use of intraoperative ultrasound (USS) is advised. This allows precise determination of the extent of renal lesions and polycentricity [13, 14]. It is also reported to assist in accurate assessment of the feasibility of partial nephrectomy intraoperatively. USS provides a guide to more accurate nephrotomy, facilitating the attainment

Table 1 Reported cases of RCC arising in allograft kidneys

Author	Patient Age	Sex	Transplant/ Presentation Interval (months)	Allograft Type	Presentation	TNM Stage (6)	Treatment	Follow Up (months)	Dialysis	Disease Status
Scott et al. [3]	46	M	85	Cadaveric	Incidental Histology	T1N0M0	Nephrectomy	9	Yes	Alive Disease Free
Williams et al (7)	54	M	228	Cadaveric	Incidental Histology	T1N0M0	Nephrectomy	-	Yes	Alive Disease Free
Feldman et al. [8]	37	M	157	Cadaveric	Abdominal pain. USS	T1N0M0 X2	Partial Nephrectomy	13	No	Alive Disease Free
Park et al [9]	45	F	258	Live Donor	Incidental USS	T1N0M0	Partial Nephrectomy	11	Yes	Alive Disease Free
Gunji et al. [10]	37	M	9	Cadaveric	Abdominal pain. USS	T2N0M0	Nephrectomy	36	Yes	Alive Disease Free
Current Case	47	M	173	Live Donor	Incidental USS	T1N0M0	Partial Nephrectomy	22	No	Alive Disease Free

of negative resection margins during partial nephrectomy [14].

All the previously reported cases of RCC in allograft kidneys arose in patients receiving azathioprine and prednisolone as immunosuppression [3, 7, 8, 9, 10]. One patient was also taking ciclosporin. It is not known whether the incidence will be higher in patients receiving newer agents such as tacrolimus and mycophenolate, but sirolimus has been reported to have anti-tumour effects in laboratory studies [16].

Our patient received a live donor transplant from his brother. In view of the frequency of bilateral renal adenocarcinoma 0.5–1.5% [15], we have commenced a routine surveillance ultrasound programme of the brother's remaining kidney. Due to the uncertainty about the aetiology of RCC in the transplanted kidney, surveillance of the paired transplanted organ from a cadaveric donor is also advisable.

Interestingly, in our case it was noted intraoperatively, during original live donor transplantation, that it was necessary to sacrifice an upper pole artery due to its proximity to the aorta. This resulted in a degree of continued upper pole ischaemia. The tumour resected arose from the upper pole of the kidney and raises the question as to whether ischaemia and associated hypoxia to this pole contributed to de novo transformation.

Conclusions

As the natural history of independent tumours is difficult to define, particularly in an immune-compromised individual, it is impossible to categorically state whether a tumour arising from an allograft kidney represents de novo transformation or transplanted tumour. This uncertainty makes it important to consider surveillance of the partner kidney, either in the live donor or paired cadaveric transplant. In treating these tumours, a partial nephrectomy should be considered because of the reduced quality of life which a transplant nephrectomy will cause. For this to be performed optimally, clear frozen section margins should be confirmed intraoperatively. To assist in obtaining satisfactory clearance, intraoperative ultrasound is advisable. Using these guidelines, it is possible for a patient to remain dialysis independent and disease free at 22 months post procedure. The role of ischaemia is unclear in the development of RCC; however, cold and warm ischaemic time may have relevance in this select group of patients.

Summary of recommendations: treatment of donor kidney RCC

- Where possible, consider partial nephrectomy.
- Combine intraoperative ultrasound with frozen section to assure clear margins.

– In live donor cases, follow up of the organ donor is advised by annual surveillance ultrasound.
– In recipients of cadaveric allografts, the recipient of the paired organ should be traced and annual surveillance ultrasound performed.

Acknowledgements The authors gratefully acknowledge the funding provided by the ''Fischer Foundation'', a charitable organisation dedicated to research in renal cancer.

References

1. Penn I, et al (1995) Primary kidney tumours before and after renal transplantation. Transplantation 59:480–485
2. Pope JC, Koch MO, Bluth RF, et al (1994) Renal cell carcinoma in patients with end stage renal disease: a comparison of clinical significance in patients receiving haemodialysis and those with renal transplants. Urology 44:497–501
3. Scott MH, Sells RA, et al (1988) Primary adenocarcinoma in a transplanted cadaveric kidney. Transplantation 46:157–158
4. Penn I et al. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant 1993 12:328–336
5. Uzzo RG, Novick AC, et al (2001) Nephron sparing surgery for renal tumours: Indications, techniques and outcomes. J Urol 166 (1):6–18
6. Sobin LH, Wittekind C (1997) TNM classification of malignant tumours, 5th edn. pp 180–182
7. Williams JC, Merguerian PA, Schned AR, Morrison PM, et al (1995) Acquired renal cystic disease and renal cell carcinoma in an allograft kidney. J Urol 153:395–396
8. Feldman JD, Jacobs SC, et al (1992) Late development of renal carcinoma in allograft kidney. J Urol 148:395–397
9. Park KII, Inoue H, Kim CJ, Tomoyoshi T, et al (1997) Nephron sparing surgery for de novo renal cell carcinoma in an allograft kidney: a case report. Int J Urol 4:611–614
10. Gunji Y, Sakamoto K, Yamada K, Hamaguchi K, Kashiwaraba H, Hori S, Shimada H, Suzuki T, Ochiai T, et al (2001) Successful surgical treatment of renal cell carcinoma in a transplanted kidney from a cadaveric donor: report of a case. Surg Today 31:374–377
11. Wunderlich H, Wilhelm S, Reichelt O, Zermann DH, Borner R, et al (2001) Renal cell carcinoma in renal graft recipients and donors: incidence and consequence. Urol Int 67:24–27
12. Sutherland SE, Resnick MI, Maclennan GT, Goldman HB, et al (2002) Does the size of the surgical margin in partial nephrectomy for renal cell cancer really matter? J Urol 167:61–64
13. Marshall FF, Holdford SS, Hamper UM, et al (1992) Intraoperative sonography of renal tumours. J Urol 148:1393–1396
14. Assimos DG, Boyce WH, Woodruff RD, Harrison LH, McCullough DL, Kroovand RL, et al (1991) Intraoperative renal ultrasonography: a useful adjunct to partial nephrectomy. J Urol 146:1218–1220
15. Bennington JL, Beckwith JB, et al (1975) Tumours of the kidney, renal pelvis and ureter. Atlas of tumor pathology 2nd series, Fasc 12. Armed forces institute of pathology
16. Huang S, Houghton PJ, et al (2002) Inhibitors of mammalian target of rapamycin as novel antitumour agents: from bench to clinic. Curr Opinion in Invest Drugs 3(2):295–304