Partial nephrectomy for renal cell carcinoma in long-term renal allografts: operative and post-operative considerations

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The majority of immunosuppressive agents used to prevent rejection in transplant patients have also been shown to increase malignancy risk. Renal transplant patients are dependent upon their solitary allograft kidneys in order to remain dialysis free, and the discovery of a primary malignancy within the allograft poses a therapeutic dilemma. We describe two cases of primary renal allograft malignancies and discuss nephron-preserving surgical treatment. Furthermore, we discuss the potential anti-tumor role of the immunosuppressive agent sirolimus in the treatment of these complex patients.

Key Words: renal transplant, renal cell carcinoma, partial nephrectomy

Introduction

It has been known for some time that malignancy rates are increased in transplant recipients compared with the general population.[1] Multiple factors may contribute to augmented mutagenesis including the effects of long term immunosuppression, chronic antigenic stimulation from the in-situ allograft, chronic renal insufficiency and the presence of viral oncogenes. Genitourinary malignancies account for 15% of tumors found in renal transplant patients with renal cell carcinoma (RCC) the most prevalent followed by bladder, prostate and testis.[2] Native renal tumors have a 1.6% greater incidence over the general population in renal transplant patients. However, the incidence of renal cortical tumors of the allograft is more rare. A recent review of the Cincinnati Transplant Tumor Registry demonstrated that only 24 of 256 RCC in renal transplant recipients were found originating from the allograft.[3] Treatment options present a dilemma as often patients depend solely on the allograft kidney for renal function. With this caveat in mind, several authors have proposed nephron

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sparing approaches as alternatives to allograft nephrectomy in these situations, but the long-term effects of nephron-sparing surgery in patients under immunosuppressive therapy is unknown.[4] However, sirolimus, a newer immunosuppressive agent has demonstrated anti-tumor activity in vitro and its analogue, CCI-779, is currently being investigated as anti-tumor agent in clinical trials.[5,6]

We report two cases of incidentally detected RCC in renal allografts surviving greater than 10 years post transplant successfully treated with nephron sparing surgery. We describe a surgical technique using the harmonic scalpel to achieve hemostasis without employing arterial clamping or induction of hypothermia. Additionally, the potential role of sirolimus in tumor mass reduction was explored in one case.

Case report

Case1

A 49 year old man with end stage renal disease secondary to type I diabetic nephropathy underwent cadaveric renal transplantation in March of 2000. Fifteen years later, he was found to have incidentally discovered microscopic hematuria. Upon investigation, ultrasound revealed a heterogeneous, hyperechoic mass in the posterior cortex of the mid-upper aspect of the transplanted kidney, Figure 1. Computerized tomography (CT) scan of the abdomen and pelvis revealed a 2.8 cm x 3.0 cm intraparenchymal mass of the renal allograft, Figure 2. Ultrasound guided biopsy and fine needle aspiration concluded the presence of a Furhman grade I/IV renal cell carcinoma. The options were discussed with the patient and an explorative laparotomy with partial nephrectomy was performed in an attempt to allow this brittle diabetic patient to remain dialysis independent. It was felt that a nephron sparing approach would be well tolerated by the allograft as it was functioning well with a baseline creatinine of 140 μmol/l.

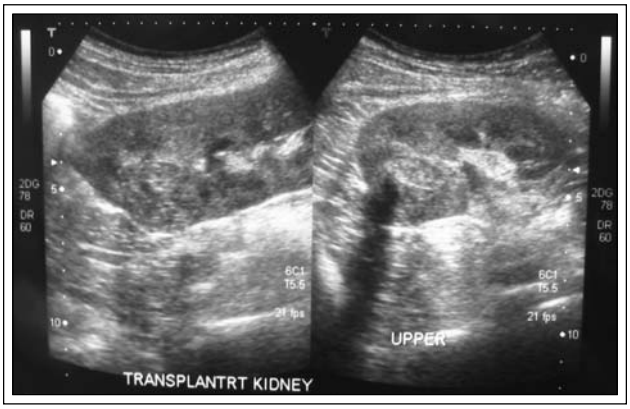

Figure 1. Transabdominal ultrasound of renal allograft in Case 1 demonstrating presence of posteriorly based renal cortical tumor.

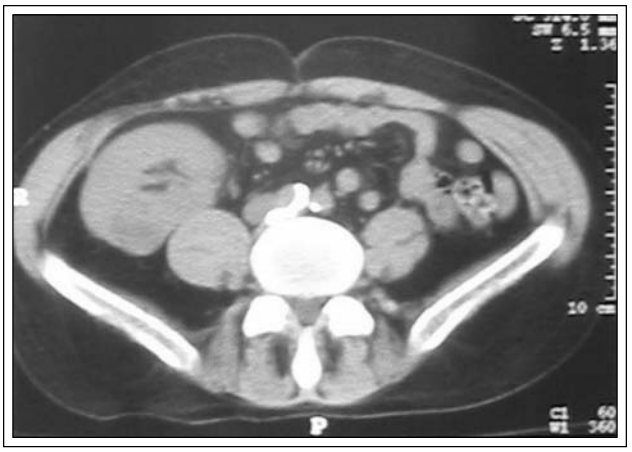

Figure 2. Noncontrast computed tomography of the pelvis confirming renal allograft tumor in posteromedial aspect.

In an effort to exploit its anti-tumor effects, the patient's immunosuppressive regime was altered from cyclosporine- to sirolimus- based therapy 12 weeks prior to surgery. Unfortunately, the patient suffered Candidal pyelonephritis requiring initial hospitalization followed by a prolonged course of outpatient antifungal therapy. When clinically resolved, the patient was reassessed for surgery and subsequently taken to the operating room.

Case 2

In 1986, a 29 year old man underwent cadaveric renal transplant for renal failure secondary to glomerulonephritis and hypertension. Sixteen years later, routine abdominopelvic ultrasonography discovered an incidental 2.1 cm x 2.2 cm homogenous, hypoechoic lesion suspicious for hemorrhagic cyst as well as three other large cortical cysts in the allograft. Magnetic resonance scan revealed a cortical neoplasm consistent with renal cell carcinoma. Metastatic workup was otherwise negative and the patient refused an ultrasound guided biopsy. As this patient was otherwise healthy with a baseline creatinine of 142 μmol/l, a partial nephrectomy of the allograft was planned to preserve as much renal function as possible. Preoperatively, the patient's immunosuppressive regime, consisted of cyclosporine, azathioprine and prednisone.

Operative technique

In both cases, the same operative technique was performed. Preoperative antibiotic prophylaxis was administered and the patient prepared supine.

Through the previous Gibson incision, intraperitoneal access to the allograft was established. Dissection of the cephalad portion of the allograft was undertaken with the posterior limits of dissection limited by the psoas fascia. Additionally, the peritoneum was mobilized medially away from the allograft and packed off. In this way, the possibility of inadvertent hilar trauma and subsequent hemorrhage could be controlled through vascular clamping of the renal pedicle along this previously dissected plane.

Full inspection of the renal mass was performed and intraoperative ultrasonography used to visually confirm the location, depth and margins of the lesion. Under ultrasound guidance, long 22 gauge spinal needles were placed in a 1 cm expanded circumference around the tumor mass, along the plane of lateral dissection to the depths required for complete tumor excision. These needles were left in place while excision of the mass with the harmonic scalpel is performed. Frozen section biopsies from the bed of the resection site were sent off and returned negative for malignancy. Hemostasis was achieved by manual compression of the allograft and collecting system entries and vascular defects are closed with figure-of-eight 4-0 PDS suture. The argon beam coagulator was used to achieve further hemostasis of the resection site, taking care to avoid the previously placed sutures. A Surgicel mesh sheet was placed over the resection bed followed by Surgicel bolsters, and the two edges of the resection site were reapproximated using interrupted 2-0 PDS. Tisseal (Baxter) coagulum was then sprayed over the closure as a final measure. Compression of the allograft was released which demonstrated hemostatic resection in both cases. A closed suction Blake drain was placed in the retroperitoneum, the operative site retroperitonealized and the wound closed in standard fashion.

Results

Case 1

Prior to the undertaking of partial nephrectomy, the patient was reevaluated with repeat pelvic ultrasound to examine sirolimus effects on tumor size. No significant change in the size of the mass was noted over 8 weeks compared with initial imaging. The operation was then carried out as described above and tolerated well. Estimated blood loss was 200 cc and urine output was maintained throughout the procedure. Pathology reported a well circumscribed nodule of 3 cm x 3 cm x 4 cm with no lymphatic or vascular invasion. Margins were negative for malignancy, and a diagnosis of conventional RCC was confirmed on final pathology. The patient continues to be dialysis independent with a good functioning graft and a serum creatinine of 170 μmol/L, 6 months postoperatively.

Case 2

As in Case 1, the procedure was performed as described above and well tolerated. There was minimal blood loss. The initial pathology report of the specimen was inconclusive; further consultation concluded the tumor to be a low grade tubulopapillary RCC. At last follow up 3 years following his extirpative procedure, his serum creatinine remained only slightly above preoperative baseline at 172 μmol/L.

Discussion

The identification of renal masses in the allograft of renal transplant recipients requires careful management strategies. By definition, these patients rely on their in-situ allograft to remain dialysis independent and a balance between cancer control and renal preservation is complicated once again by the requirement of ongoing immunosuppressive therapy.

A variety of minimally invasive techniques have been attempted in an attempt to address this difficult problem including cryotherapy,[7] and partial allograft nephrectomy.[8-13] There has been limited experience to date with regards to the aforementioned procedures, although the surgical approach appears to be favored in the literature. As with open partial nephrectomy of native kidneys, there is ongoing discussion as to best technical approaches to various components of the procedure including hilar clamping, manual compression, resection technique/energy modality, and effective hemostasis. Certain considerations regarding partial nephrectomy in the renal allograft must be highlighted: 1) desmoplastic reaction of the peri-nephric space precludes easy identification of the renal hilum and immediate vascular control, 2) complete excision of the tumor is required as patients will remain immunocompromised post-operatively, and 3) the long-standing renal allograft has been affected by chronic allograft nephropathy and will not tolerate

significant ischemia without significantly impacting on its long-term function. In this report, we document the use of intraoperative ultrasound in establishing accurate dimensioning of the allograft tumor and the adjunctive use of spinal needle margin-scoring to assist in the dissection. Additionally, we report the use of the harmonic scalpel as an efficacious and hemostatic energy modality in the resection of these masses obviating the need for absolute vascular pedicle clamping and hypothermia.

The issue of immunosuppression conversion to sirolimus-based therapy remains a question yet to be answered. Sirolimus is one of the most recently introduced immunosuppressive agents indicated for renal transplantation. This agent binds to FK-binding protein in the cell cytoplasm and this interaction in turn inhibits the mammalian target-of-rapamycin (mTOR) kinase which is involved in cellular proliferation, and the final result is cell cycle arrest in G_1. Promising work in vitro has led to the development of CCI-779 (Temsirolimus (Wyeth)), a rapamycin ester, currently being evaluated in a number of large clinical trials as an anti-cancer chemotherapeutic.[5] A recent randomized phase II trial using CCI-779 in patients with refractory metastatic RCC demonstrated an overall response rate of 7% (CR=1, PR=7, n=111) and the authors proposed significant median survival benefits following risk stratification.[6] Additionally, the recent finding of complete regression of cutaneous Kaposi's sarcoma lesions following conversion of immunosuppressive regimens from cyclosporine to sirolimus-based in 15/15 renal transplant patients is further evidence for an clinically significant anti-neoplastic effect of this agent requiring more research.

Conclusion

Nephron sparing partial nephrectomy of the renal allograft is a safe and effective procedure in the long term renal transplant patient. Use of intraoperative ultrasound and the harmonic scalpel facilitate this procedure. □

References

1. Doak PB, Montgomerie JZ, North JDK, Smith F. Reticulum cell sarcoma after renal homotransplantations with azathioprine and prednisone therapy. *Br Med J* 1968;4:745-746.
2. Penn I. Posttransplant Malignancies. *Transplant Proceedings* 1999;31:1260-1262.
3. Penn I. Primary kidney tumors before and after renal transplantation. *Transplant* 1995;59:480-485.
4. Feldman JD, Jacobs SC. Late development of renal carcinoma in allograft kidney. *J Urol* 1992;148:395-397.
5. Temsirolimus : CCI 779, CCI-779, cell cycle inhibitor-779. *Drugs R D* 2004;5:363-367.
6. Atkins MB, Hidalgo M, Stadler W, Logan T, Dutcher J, Hudes G, Park Y, Liou S, Marshall B, Boni J, Dukart G, Sherman M. Randomized phase II Study of Multiple Dose Levels of CCI-779, a Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients with Advanced Refractory Renal Cell Carcinoma. *J Clin Onc* 2004;22:909-918.
7. Shingeton W. Sewell P. Percutaneous cryoablation of renal cell carcinoma in a transplanted kidney. *BJU Int* 2002;90:137-138.
8. Krishnamurthi V, Novick, A. Nephron-sparing surgery in a renal allograft. *Urology* 1997;50:132-134.
9. Lamb, GW, Baxter GM, Rodger RS, Aitchison M. Partial nephrectomy used to treat renal cell carcinoma arising in a live donor transplant kidney. *Urol Res* 2004;32:89-92.
10. Siebels M, Theodorakis J, Liedl B, Schneede P, Hofstetter A. Large de novo renal cell carcinoma in a 10-year-old transplanted kidney; successful organ-preserving therapy. *Transplantation* 2000;69:677-679.
11. Park KI, Inoue H, Kim CJ, Tomoyoshi T. Nephron-sparing surgery for de novo renal cell carcinoma in an allograft kidney: a case report. *Int J Urol* 1997;4:611-614.
12. DeSimone P, Antonacci V, Rosa F, Verzaro R. Nephron sparing surgery for de novo renal cell carcinoma in a 19 year old transplanted kidney. 2004;77:478-481.
13. Hoppner W, Grosse K, Dreikorn K. Renal cell carcinoma in a transplanted kidney: successful organ preserving procedure. *Urol Int* 1996;56:110-111.