Clear cell papillary renal cell carcinoma in a transplant kidney

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Large renal cell carcinomas (RCC) arising in allograft kidney transplants are rarely encountered. The distinct RCC sub-type, clear cell papillary RCC (CP-RCC), has mostly been described in non-immunosuppressed patients. Here we report the presentation, management and pathologic diagnosis of a large (11.2 cm, pT2b), multifocal, CP-RCC in a poorly functioning renal allograft of a 63-year-old woman 19 years following kidney transplant. Preoperative angiographic kidney embolization was successfully performed prior to allograft nephrectomy, with an excellent surgical, oncologic and clinical outcome.

Key Words: clear cell papillary renal cell carcinoma, allograft nephrectomy, preoperative angiographic kidney embolization

Introduction

Recipients of kidney transplants have an increased risk of renal cell carcinoma (RCC) compared to the general population. Most of these post-transplant RCCs occur in the native kidney, with a minority developing in the renal allograft.[1] Multifocal and large renal masses in transplanted kidneys have rarely been reported, with the vast majority of renal allograft tumors solitary and ≤ 4cm (stage pT1a).[2,3] Subtyping of RCCs in transplanted kidneys reveal an increased incidence of papillary RCC (papRCC) and decreased incidence of conventional clear cell RCC (ccRCC) compared to the general population.[2,4] In 2016, the World Health Organization updated the classification of renal tumors to now include clear cell papillary RCC (CP-RCC), which is a distinct subtype of RCC characterized by indolent clinical behavior and unique pathologic features.[5] At least five cases of CP-RCC have been reported in renal allografts, all of which were pT1a tumors.[3,6]

Management of renal allograft RCC mimics management in the non-transplant population with a preference for nephron sparing strategies (NSS) whenever possible, especially for smaller lesions.[4] Large, solid renal masses in a poorly functioning transplant kidney are likely still optimally treated by radical transplant nephrectomy with return to dialysis, assuming adequate patient health. Allograft nephrectomy can be a technically demanding procedure secondary to obscured tissue planes, altered anatomy and the potential for significant morbidity and blood loss. Preoperative angiographic kidney embolization

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(PAKE) has been proposed as an intervention prior to planned allograft nephrectomy that may decrease blood loss and morbidity, with preliminary experiences in transplanted kidneys promising but limited.[7,8]

In this report, we discuss the presentation and management of a large (11.2 cm, pT2b), multifocal, CP-RCC in a poorly functioning renal allograft followed by a brief review of literature.

Case report

The patient is a 63-year-old white female, body mass index 21 kg/m^2, with end stage renal disease secondary to Fabry's Disease who received a deceased donor kidney transplant in February 1998 at another institution. She did well for the next 19 years (maintenance immunosuppression: cyclosporine, azathioprine and prednisone) and then was evaluated by her nephrologist in October 2017. On physical exam, firmness and swelling were noted over her transplanted kidney. These findings prompted renal transplant ultrasonography that identified two complex renal masses that were highly suspicious for RCC. A subsequent non-contrast magnetic resonance imaging (MRI) study was performed to better characterize the masses, Figure 1. The MRI study revealed a 7.7 cm x 8.2 cm upper pole mass and a 10.8 cm x 10.9 cm lower pole mass of mixed signal intensity. Interestingly, a previous abdominal computerized tomography scan in 2010 performed for unclear reasons was available for comparison and revealed a 5.4 cm x 5.7 cm upper pole lesion and a 4.1 cm x 4.8 cm lower pole lesion, which were both believed to represent hemorrhagic cysts at the time.

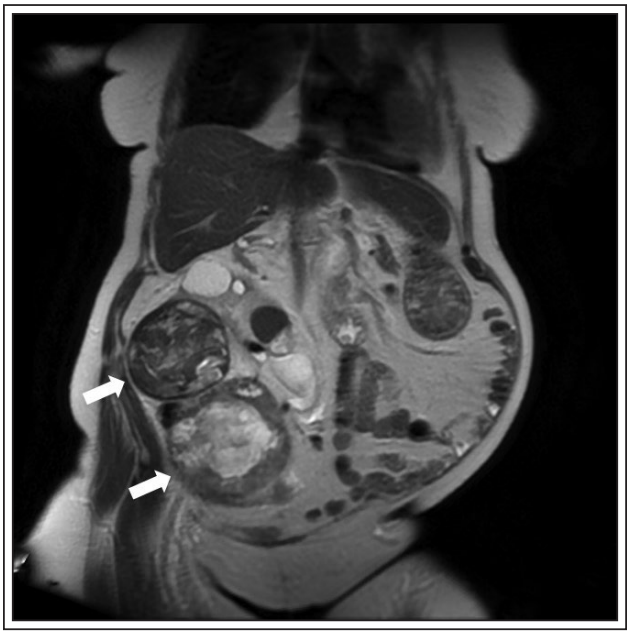

Figure 1. Coronal MRI demonstrating two large renal masses of mixed signal intensity in the right lower quadrant arising from the transplant kidney (upper mass 7.7 cm x 8.2 cm; lower mass 10.8 cm x 10.9 cm).

Given the worrisome appearance of the lesions and the interval growth over time, the patient was referred to our Transplant Clinic for immediate evaluation. At the time of presentation, she still made normal amounts of urine but had evidence for chronic rejection with a serum creatinine level ranging from 220 to 265 umol/L (2.5 to 3.0 mg/dL; eGRF 18). Aside from fatigue, poor appetite and abdominal bloating, the patient denied any other symptomatology. Further work up was unremarkable.

A decision was made to proceed with radical allograft nephrectomy. Approximately 24 hours prior to the procedure, she underwent right femoral artery cannulation and iliac arteriography. Angiography identified a single transplant renal artery with significant anatomic distortion of the renal arterial vasculature. The transplant renal artery was isolated and embolized with coils, Figures 2a and 2b. On the following day, she underwent radical transplant nephrectomy through a Gibson right lower quadrant incision with simultaneous placement of a peritoneal dialysis catheter. The renal masses were noted to be large and encapsulated, with the most lateral mass abutting the right anterior superior iliac spine. Fortunately, the kidney was fairly mobile without apparent growth into surrounding structures, allowing for wide dissection without violation of the tumor, renal parenchyma, or

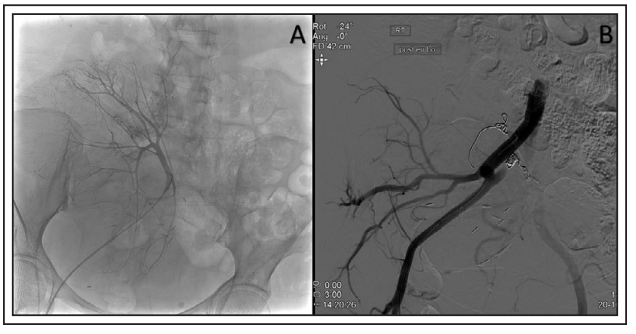

Figure 2. A) Pre-embolization arteriography demonstrates renal artery with significant anatomic distortion of renal vasculature related to the transplant kidney with hypervascular masses. **B)** Post-embolization arteriography demonstrates patent iliac arterial system with occlusion of the transplant renal artery.

vasculature. No complications were encountered with an estimated blood loss of 150 cc. Her postoperative course was unremarkable aside from a Permcath placed for temporary hemodialysis. Because of deconditioning, the patient did require physical therapy needs and was discharged to a rehabilitation facility 1 week following surgery at which time peritoneal dialysis was initiated and Permcath removed. Immunosuppression was stopped at the time of embolization except for low dose prednisone. The patient was discharged after 2 weeks in rehabilitation.

Gross pathologic evaluation of the surgical specimen revealed a weight of 1765 g and measurements of 20.0 cm x 15.0 cm x 9.5 cm in overall dimensions, Figure 3a. Two well-defined ovoid tumor masses were identified upon sectioning, with a lower pole mass measuring 11.2 cm x 10.0 cm x 10.0 cm and the upper pole mass measuring 6.0 cm x 5.0 cm x 4.0 cm. The cut surfaces of the tumors revealed brown tan tissue with extensive necrosis (~70%) and cystic changes. The tumors were confined to the kidney, with no invasion of the collecting system, renal sinus, perinephric fat or vasculature. Microscopic pathologic evaluation revealed small tubules and papillae composed of clear cells with uniform, low grade nuclei (Fuhrman 2) in a linear arrangement away from the basal membrane, Figures 3b and 3c. Immunohistochemistry stains revealed tumor cell positivity for CK7 (diffuse and strong), epithelial membrane antigen (EMA - diffuse and strong), vimentin, E-cadherin and PAX-8 (focal) while negative for CD10, AMACR and CD117. The morphology and immunoprofile of both tumors were felt to be most consistent with a diagnosis of clear cell papillary RCC (TNM stage: pT2b, N0, M0). Surgical resection margins were negative and a single lymph node evaluated was benign.

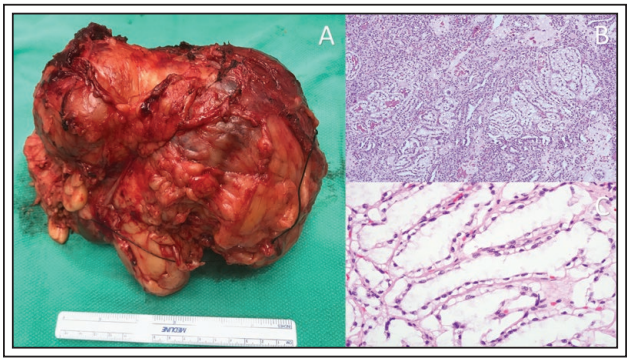

Figure 3. Clear cell papillary renal cell carcinoma. **A)** Gross specimen. **B)** Tubular and papillary architecture; papillae are covered by cuboidal cells with clear cytoplasm. H&E, 20x. **C)** Tumor clear cells with subnuclear vacuoles; nuclei oriented away from papillary core. H&E, 40x.

The patient is now 1 year following surgery. She is tolerating dialysis well. There is no evidence of tumor recurrence and she will be considered as a kidney re-transplant candidate following a 2 year disease-free interval.

Discussion

Solid renal masses in transplanted kidneys are rare, with an incidence estimated to be 0.18%-0.23% of all transplanted kidneys.[4,9] When encountered, allograft tumors are typically small (≤ 4 cm) and diagnosed at an earlier clinical stage compared to the general population.[2] A recent systematic analysis of 56 studies by Griffith et al identified 174 solid transplant renal masses with a mean tumor size of 2.75 cm (range 0.5 cm - 9.0 cm).[4] In this study, only 18% of presentations were symptomatic, with the remainder noted incidentally on routine screening ultrasonography or at the time of nephrectomy for other reasons. A recent European systematic analysis of 69 publications with 201 solid transplant renal masses by Tillou et al echoed these findings.[9] The vast majority of tumors were solitary, pT1a lesions (size range 0.7 mm - 100 mm) with asymptomatic presentation in 85.9% of patients. Our patient was essentially asymptomatic at presentation aside from vague complaints, with her large, multifocal allograft masses suspected only following physical examination and confirmed with imaging.

Large renal tumors, such as our case depicts (11.2 cm in greatest dimension), are infrequently encountered in transplanted kidneys, likely for a variety of reasons. Surveillance bias certainly plays a role as this patient population is closely monitored in the post-transplant setting with imaging studies often performed for unrelated reasons. It has also been shown that the spectrum of disease is different in kidney transplant patients. ccRCC in the transplant population ranges from 35%-46%, papRCC ranges from 42%-58%, while CP-RCC is thought to occur in 3%-6% of allograft kidney tumors.[2,4,6,9] In the general population, ccRCC, papRCC and CP-RCC are estimated to occur in 75%-80%, 10%-15% and 1%-4% of tumors, respectively.[6] Localized papRCC is thought to metastasize less frequently than ccRCC, which may help account for the high frequency of asymptomatic and lower stage presentations. Additionally, the true incidence of CP-RCC, which follows an indolent course and does not typically become large, is almost certainly underreported given the recent classification change.

Surgical management of renal allograft tumors has evolved over time. Our patient had a large multifocal tumor within an imminently failing renal

allograft. Radical transplant nephrectomy offered the opportunity for control of tumor and cessation of immunosuppression, with immediate return to dialysis. In well-functioning renal allografts, or even those with functional impairment, the presence of a solid renal mass does not mandate nephrectomy. Active surveillance of renal tumors is gaining favor in the non-transplant population, however, its role in allograft RCC is not well defined. Ultimately, when considering active surveillance, one must balance the benefit of preserving the graft (and avoiding dialysis) with the risk of morbidity and mortality associated with surveying solid renal masses in a patient on chronic immunosuppression. Our patient had a CP-RCC tumor that grew to considerable size, clearly remaining indolent even though on immunosuppression. If this is indeed the natural history of this lesion, perhaps this tumor type could be monitored without surgical intervention until renal function declines. Although not appropriate for the case presented, NSS, accomplished by either partial nephrectomy, radiofrequency ablation, or cryotherapy, may be considered in most cases of renal allograft tumors given the propensity for pT1a lesions and the desire to avoid metastatic disease while preserving allograft function.[2,4]

Allograft nephrectomy morbidity is a very real concern, with peri-operative transfusion rates up to 50%, surgical complication rates ranging from 17%-60%, and mortality ranging from 1.5%-14%.[7] Both intracapsular and extracapsular allograft nephrectomy techniques have been described, with the latter preferred for renal allograft malignancies. PAKE was initially developed for use with the intracapsular technique, however, it may also play a role in planned extracapsular procedures. Two small retrospective studies of PAKE prior to allograft nephrectomy have found similar results; less intra-operative blood loss, fewer blood transfusions, and reduced operating time.[7,8] In addition, Al-Geizawi et al reported a decreased length of hospital stay in the PAKE group, which resulted in similar costs to allograft nephrectomy without PAKE.[7] In our institution, subspecialty trained interventional radiologists perform PAKE the day prior to all planned allograft nephrectomies. In the case presented, PAKE allowed a relatively bloodless field to help facilitate safe, extra-capsular dissection of the kidney, renal hilum and masses. Estimated blood loss was low (150 cc), blood transfusion was avoided, negative surgical margins were achieved, and no significant intra-operative or postoperative morbidity occurred.

CP-RCC is a recently characterized renal neoplasm with indolent behavior and morphologic and molecular profiles distinct from those of ccRCC or papRCC.[5] There are no recorded cases of local recurrence, lymph node involvement, distant metastasis or cancer-related death associated with this particular RCC subtype in transplant patients or the general population.[3,6,10] Most typically, these tumors are singular, small (≤ 4 cm) and incidentally identified in asymptomatic patients. However, multifocality is possible, especially in those with end-stage renal disease. Histologically, clear epithelial cells with low Fuhrman nuclear grade arranged in tubules and papillae are present, with the nuclei polarized away from the basement membrane in linear fashion.[10] Signs of biologic aggressiveness, such as renal sinus or vascular invasion, tumor necrosis, and high nuclear grade are typically absent. In our patient, the tumors displayed up to 70% necrosis, related to the large size, lack of internal vascularity, and preoperative embolization. The immunohistochemical profile of CP-RCC overlaps with ccRCC (carbonic anhydrase IX and CD 10 positive) and papRCC (CK7 and AMACR positive), but with distinct differences.[10] CP-RCC displays positive carbonic anhydrase IX and negative CD10 staining, distinguishing it from ccRCC, while CK7 is diffusely positive with negative AMACR, distinguishing it from papRCC. Our patient was positive for CK7, while being negative for CD10 and AMACR. Carbonic anhydrase IX staining was not performed. Taken along with the tumor architecture, the diagnosis of CP-RCC in both dominant tumors was established.

This case highlights the lack of consensus recommendations for renal malignancy screening and follow up in transplant patients. Earlier imaging, 7 years before the final diagnosis, showed masses felt to represent hemorrhagic cysts, however, inadequate further follow up resulted in delayed diagnosis. An alternative pathologic diagnosis may have led to a very different outcome for this patient. Patients who have been on dialysis with acquired cystic disease of the native kidneys are at increased risk for malignancy compared to the general population even after transplantation. Even so, the majority of transplant guidelines recommend against renal cancer screening in the kidney transplant population given the relatively low prevalence of the disease, potential for false positives and over-diagnosis of slow-growing RCCs that may not need treatment.[11] A decision analysis study by Wong et al found that routine ultrasound screening for RCC in renal transplant recipients may not provide meaningful benefit to patients and may not be cost effective, however, this study did advocate an individualized screening program for each individual kidney transplant recipient based on risk factors for RCC.[12] Ultimately, we agree with targeted screening

in this population that takes into account RRC risk factors, personal and family medical history along with the patients anticipated life-expectancy. Given the abnormal, large hemorrhagic cysts seen 7 years earlier, our patient likely deserved additional screening examinations to confirm or refute the original diagnosis.

Conclusion

To the best of our knowledge, this is the first report of a pT2b allograft kidney RCC, one of the largest tumors in a transplant kidney (11.2 cm) and the first report of a multifocal CP-RCC in an allograft kidney. This case suggests that large, multifocal CP-RCC follows an indolent course despite immunosuppression. Preoperative angiographic kidney embolization may reduce the need for transfusion and may make the allograft nephrectomy procedure less difficult. □

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