Allograft Nephrectomy for Malignancy: Report of Seven Cases and Review of the Literature

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Abstract

Purpose: Present and discuss seven cases of allograft nephrectomies performed at our institution for malignancy as the primary indication.

Methods: We reviewed retrospectively all patients undergoing allograft nephrectomy at our institution from January 2002 to May 2015.

Results: Over a 13 year period, we performed 74 allograft nephrectomies, of which 7 (9.5%) were indicated for malignancy. All 7 cases underwent angiographic embolization of the allograft prior to removal; 3 cases involved renal cell carcinoma (RCC), including 2 in previously failed allografts. Both of these patients are currently disease-free and receiving chronic immunosuppression for functioning kidney retransplants. The third case involved metastatic (and probably recurrent) RCC in a failing allograft in a patient who previously underwent radical native nephrectomy for RCC. Two cases involved transitional cell carcinomas (TCC); both were discovered during evaluation of acute kidney injury. Both are currently disease-free following allograft nephrectomy and cessation of immunosuppression. The last 2 cases were donor derived malignancies (myeloid sarcoma) in two separate recipients who received kidneys from the same donor. Both patients survived for at least one year following nephrectomy.

Conclusions: The above cases are representative of the spectrum of malignant disorders (de novo, recurrent, or donor-derived) that may affect either the functioning or failed renal allograft and result in nephrectomy. Although most recent literature has emphasized the role of nephron-sparing procedures, allograft nephrectomy remains the treatment of choice in selected cases.

Keywords: Allograft nephrectomy; De novo malignancy; Donor-derived malignancy; Renal cell carcinoma; Transitional cell carcinoma; Renal transplant

Introduction

Previous studies have reported that 25% to 40% of surviving patients with kidney graft failure eventually undergo allograft nephrectomy [1-6]. Indications for allograft nephrectomy include symptoms attributable to the failed allograft (including pain, swelling or localized tenderness, fever, hematuria or bleeding), thrombosis, infection, anemia with erythropoietin resistance, failure to thrive and graft intolerance syndrome, which occurs secondary to rejection and/or allograft ischemia. In other instances, allograft nephrectomy may be performed for malignancy, as treatment for diseases such as polyomavirus nephropathy or post-transplant lymphoproliferative disease, or for space considerations in planning of a subsequent kidney transplant. The rate of allograft nephrectomy in patients with graft failure varies widely from 0.5-43% according to individual center policies [3-9]. Although the role of allograft nephrectomy in the management of kidney transplant recipients with graft failure remains controversial, most clinicians agree that the presence of malignancy in the allograft is usually a robust indication for nephrectomy coincident with a requisite withdrawal of immunosuppression.

The aging donor and recipient populations have led to new challenges in kidney transplantation. Current data demonstrate an increasing proportion of elderly patients in an already rising end stage renal disease (ESRD) population [10-13]. Both aging and chronic immunosuppression are associated with an increased risk of malignancy [10-13]. Renal cell carcinoma (RCC) carries a higher prevalence in older individuals, in patients receiving dialysis and in those with a kidney transplant compared to the general population [10-12,14,15]. In addition, the overall risk of malignancy in kidney transplant recipients ranges from 4 to 30-fold higher depending on the type of malignancy analyzed [10-12,14,15]. Surprisingly, there are few reports of allograft nephrectomy for malignancy in the literature other than isolated case studies. The purpose of this study was to review our overall experience with allograft nephrectomy for malignancy at a single center including the use of pre-operative angiographic embolization of the allograft as a bridge to planned nephrectomy to reduce blood loss and prevent tumor dissemination.

Methods and Results

Over a 13 year period from 2002 to 2015, we retrospectively reviewed indications for allograft nephrectomy in 74 consecutive cases. A total of 7 patients (9.5%) underwent nephrectomy for allograft malignancy. A summary of case studies follows.

Case 1

A 39 year old Caucasian male with ESRD secondary to focal segmental glomerulosclerosis-collapsing variant and diffuse nodular diabetic glomerulosclerosis underwent living related donor kidney transplant from his 44 year old human leukocyte antigen (HLA)-identical sister in 1998. In 2010, this transplant failed secondary to chronic allograft nephropathy and the patient started dialysis. As part of a retransplant screening evaluation, the patient underwent a renal ultrasonography,
which demonstrated a 1.5 by 1.3 cm solid tumor in the allograft. Subsequent ultrasound guided fine-needle aspiration biopsy and cytology demonstrated a papillary type 1 RCC, Fuhrman nuclear grade 3. A 1.3 x 1.1 x 1.0 cm tumor, which was well-circumscribed and confined to the kidney (Figure 1A). Following angiographic embolization of the allograft, the patient underwent an uncomplicated radical transplant nephrectomy. Following a period of recovery and in the presence of a negative work- up for residual or metastatic disease, the patient underwent successful living unrelated donor kidney retransplantation from a 25 year old donor in August 2010 without being subjected to a mandatory waiting period or disease-free interval because of the favorable histopathology and size of the tumor. The second donor was a zero HLA-match and the patient received alemtuzumab induction therapy. At nearly 5 years follow-up, the patient continues to exhibit normal renal function (serum creatinine level 1.2 mg/dl and estimated glomerular filtration rate [GFR] >60 ml/min) without any evidence of disease on an immunosuppressive maintenance regimen of tacrolimus, mycophenolate and prednisone.

Case 2

A 31 year old Caucasian male with ESRD secondary to type 1 diabetes mellitus underwent living related donor kidney transplant from his sister in 1991; this kidney functioned for 11 years before failing secondary to diabetic nephropathy. He was on dialysis for 3 months before undergoing simultaneous kidney-pancreas transplantation from a 19 year old male deceased donor in May, 2002. The second donor was a zero HLA-match; hence, the patient received rabbit anti-thymocyte globulin (rATG) induction in combination with tacrolimus and mycophenolate. During an evaluation for a ventral incisional hernia in 2011, a computerized tomographic (CT) scan revealed an incidental 2.3 cm solid mass in the failed left lower quadrant living donor kidney transplant, consistent with the diagnosis of RCC (Figure 1B). Following angiographic embolization of the failed allograft, the patient underwent uncomplicated radical transplant nephrectomy in June 2011. Final pathology demonstrated type 1 papillary RCC, Fuhrman grade 2, with clear margins. Moreover, an additional mass was identified on this allograft nephrectomy specimen—a well circumscribed tumor with tubule-acinar architecture, most consistent with acquired cystic disease-associated RCC. Thirteen years following his second transplant and nearly four years following nephrectomy, the patient continues to do well with a serum creatinine level of 0.9 mg/dl and an estimated GFR of >60 ml/min. He also remains insulin-free and disease-free. His current surveillance regimen consists of yearly CT imaging.

Case 3

A 63 year old Caucasian male with ESRD secondary to lupus nephritis was on peritoneal dialysis for nine months before receiving an ipsilateral dual kidney transplant from a standard criteria donation after cardiac death (DCD) donor in August 2011. The donor was a 49 year old white male with a history of smoking, hypertension, weakness and unexplained weight loss. The kidneys were considered for dual transplantation because of the requisite warm ischemia associated with the DCD process in concert with the kidney biopsy, which demonstrated 18% glomerulosclerosis with mild vascular changes. Both kidneys appeared anatomically normal except for atherosclerosis extending into the renal arteries. In May of 2012 (nine months from the index transplant), the patient developed right lower quadrant fullness and pain in the setting of an elevated serum creatinine level. A non-contrast abdominal and pelvic CT scan revealed enlarged and edematous allograft kidneys with standing in adjacent soft tissues and a small amount of ill-defined perinephric fluid. A renal transplant biopsy discovered a high-grade invasive urothelial carcinoma with extensive squamous differentiation. Subsequent contrast-enhanced CT scan showed extensive pelvic and retroperitoneal lymphadenopathy with possible spread to the mediastinum, consistent with metastatic urothelial carcinoma (Figure 2A). Cystoscopy of the bladder and the native ureters showed no evidence of urothelial carcinoma. Positron emission tomographic (PET) scan demonstrated local and metastatic disease (Figure 3A). Following angiographic embolization of both kidneys, the patient underwent attempted radical dual allograft nephro- ureterectomy, which was complicated by thick scar tissue and an extensive burden of extra-renal tumor that was not completely excised because it was encasing the iliac vessels and extremely adherent to surrounding vital structures. Final pathology revealed high-grade urothelial carcinoma with sarcomatoid features and lymphovascular invasion with tumor at the margins of resection and satellite lesions in the renal parenchyma.
Figure 2: Transitional Cell Carcinoma (TCC) in Kidney Allografts

Figure 2A: (Case 3): 63 year old male with ipsilateral dual kidney transplant underwent a renal transplant biopsy 9 months post-transplant for possible rejection and high grade TCC was discovered. A subsequent contrast enhanced CT demonstrated metastatic urethelial carcinoma (arrow). Antegrade nephrography demonstrated concern for TCC (insert).

Figure 2B: (Case 7): 67 year old female who developed elevated creatinine following transplant. Non-contrast CT scan demonstrated ureteropelvic junction obstruction and high density material within renal pelvis (arrow). Antegrade nephrography demonstrated concern for TCC (insert).

Cases 4 and 5

The next two cases involve donor-derived malignancies (myeloid sarcoma or acute myeloid leukemia) in kidney recipients from the same donor. The donor was a 38 year old female nursing home resident whose history was negative for any cancer or unintended weight loss. Furthermore, her complete blood count revealed no blasts on peripheral smear. Additionally, imaging with PET scan did not reveal any uptake of fluorodeoxyglucose (FDG) in locations other than bone.

Recipient 1: A 77 year old Caucasian female with a history of ESRD secondary to interstitial nephritis was on hemodialysis for 2 years and had a history of a prior failed renal transplant (at a different institution) secondary to renal artery thrombosis resulting in immediate allograft nephrectomy. She underwent uncomplicated kidney retransplantation and received alemtuzumab induction in combination with tacrolimus and mycophenolate. The recipient and donor were a three-HLA mismatch. She experienced immediate graft function and serum creatinine levels stabilized in the 1.4-1.7 mg/dl range. A three week allograft surveillance biopsy demonstrated recovered acute tubular injury and donor transmitted myeloid sarcoma. A subsequent bone marrow biopsy was negative for recurrent disease. He resumed hemodialysis and remained in remission until his death secondary to a cardiovascular event 13 months following nephrectomy.

Recipient 2: A 72 year old Caucasian male with a history of ESRD secondary to untreated diabetes mellitus. He experienced slow graft function with a serum creatinine level nadir of 2.4 mg/dl. The patient’s serum creatinine level rose to 4.5 mg/dl 4 months after transplant and renal ultrasonography and CT scan (Figure 4B) showed a significant increase in the volume of the transplanted kidney and elevated resistive indices. A subsequent renal allograft biopsy showed diffuse parenchymal infiltration with immature mononuclear cells positive on immunohistochemistry for CD34, CD117 and myeloperoxidase positive blasts consistent with a diagnosis of myeloid sarcoma. Furthermore, fluorescence in situ hybridization studies showed normal chromosomes and confirmed 93% of the cells in the biopsy to be of donor origin (female, XX) suggesting a donor-derived myeloid sarcoma transmitted with the transplanted kidney. The recipient’s bone marrow biopsy was negative for leukemic involvement and a metaphase cytogenetic analysis revealed a normal male karyotype with no apparent leukemic involvement. PET scan did not show any foci of involvement beyond the renal allograft. Following angiographic embolization of the allograft, the patient underwent an uneventful nephrectomy and completed chemotherapy with cytarabine and daunorubicin in accordance with the Hematology-Oncology recommendations. A bone marrow biopsy and repeat PET scan formed five months following the initial diagnosis did not show any evidence of disease. He resumed hemodialysis and remained in remission for 7 years following nephrectomy.
the renal allograft. Following angiographic embolization of the allograft, the patient underwent nephrectomy and subsequent pathologic analysis of the specimen showed a monotonous population of myeloid blasts that were morphologically identical to the pathology noted in the first transplant recipient. Further molecular genotyping analysis performed on the renal allograft established myeloid sarcoma of donor origin and identical haplotypes. The patient did not opt for systemic chemotherapy, but remained in remission and on hemodialysis until her death secondary to a cardiovascular event 18 months following nephrectomy.

Case 6

A 74 year old African American female with a history of end-stage renal disease secondary to glomerulonephritis underwent a5-HLA mismatch kidney transplant from a 50 year old male DCD donor in July 2011. She had a history of a prior right laparoscopic nephrectomy for RCC in her native kidney in 2010. She received alemtuzumab induction in combination with tacrolimus and mycophenolate and initially experienced delayed graft function. She subsequently did well with a serum creatinine level nadir of 2.1 mg/dl. Fourteen months following transplantation, she presented to the Emergency Department in September 2012 with nausea and vomiting and had a CT scan of the abdomen and pelvis, which showed lymphadenopathy and a 7 x 4 cm lobular soft tissue mass along the right pelvic side wall in close proximity to an enlarged, indistinct kidney transplant (Figure 4A). A CT scan of the chest showed multiple pulmonary nodules bilaterally and an enlarged left lower clavicular lymph node measuring 1.1 x 1.6 cm in size.

A biopsy of the mass was performed, which showed high grade RCC. Following angiographic embolization of the allograft, she underwent uncomplicated transplant nephrectomy for metastatic RCC with immediate cessation of immunosuppression. At this point, it was unclear whether the RCC was residual from her native kidney or if the cancer was donor-transmitted or de novo in the allograft. Follow-up pathology of the allograft revealed Fuhrman Grade 4 RCC with tubule-cystic features and focal clear cell change consistent with a primary renal cancer given the patient's history of RCC in the native right kidney in 2010. The pathology report concluded that the tumor was unifocal in nature with a size of 5.0 cm in the largest dimension and extension into perinephric tissue and renal pelvic fat most likely representing a metastasis from the primary RCC. Additionally, the margins were positive with intraluminal and soft tissue deposits identified at the vascular margins. Following nephrectomy, the patient resumed hemodialysis and underwent treatment with temsirolimus. She initially did well but was never disease-free and eventually died in hospice care 22 months later in July, 2014 secondary to metastatic RCC.

Case 7

A 67 year old Caucasian female was on hemodialysis following bilateral native nephrectomies in 2004 for malignancy (right kidney oncocytoma and left kidney RCC). She underwent one HLA-match expanded criteria (61 year old male donor) kidney transplantation in April 2005, and experienced immediate graft function with a serum creatinine level stabilizing in the 2.3-2.6 mg/dl range. She received rATG induction in combination with tacrolimus, mycophenolate, and prednisone. She did well for approximately 8.5 years until September 2013, when she presented with deteriorating renal function with a serum creatinine level of 3.9 mg/dl noted on routine follow-up. Renal ultrasonography revealed moderate transplant hydropnephrosis and an abdominal and pelvic CT scan confirmed transplant hydropnephrosis with high density material in the dependent renal collecting system and proximal ureter (Figure 2B). She subsequently underwent nephrostomy tube placement for a ureteropelvic junction (UPI) obstruction and further imaging with a fluoroscopic nephrostogram revealed a large, irregularly contoured filling defect in the renal pelvis with extension into multiple infundibula and the proximal ureter, suggesting a high likelihood of a neoplasm of urothelial origin. Subsequently, a biopsy of the mass noted in the renal pelvis collecting system revealed invasive urothelial malignancy consistent with transitional cell carcinoma (TCC). The patient underwent a metastatic work-up and cystoscopy; which did not show any evidence of disease in the bladder or her native ureteral remnants. Subsequently, the patient underwent angiographic embolization of the allograft followed by successful radical allograft nephro-ureterectomy in October 2013. Pathology of the removed
specimen revealed invasive papillary urothelial high grade carcinoma, 3.0 cm in size in the largest dimension. The neoplasm involved the inferior calyx and renal pelvis with focal extension into the proximal ureter, and the margins were free of neoplasia and no lymphovascular invasion was identified. Immunosuppression was discontinued immediately except for prednisone. She resumed hemodialysis through her previous fistula. A routine surveillance CT scan performed in January, 2014, did not reveal any evidence of residual disease or recurrent tumor in the resection bed. Her most recent imaging study in March 2015 (17 months following nephrectomy) showed no evidence of metastatic disease. Currently, she is alive and doing well on hemodialysis.

Discussion

Patients on renal replacement therapy have a higher risk of malignancy compared to age- and gender-matched control patients in the general population. The magnitude of the increased risk varies with the modality of renal replacement therapy and the type of malignancy, with kidney transplantation conferring a much greater risk of cancer compared to patients on dialysis [8,10-13,16-18]. Overall risk of malignancy may be as high as 15-20% at 10 years following kidney transplantation. Certain cancers that develop in patients on dialysis or following kidney transplantation share similar risk factors to patients in the general population [10-12,14,15]. Alternatively, however, different rates and patterns of site-specific cancers are observed in patients on renal replacement therapies that are related in part to the severity and duration of renal failure as well as the burden of immunosuppression and type of organ transplant.

It is well established that the requisite post-transplant immunosuppression in kidney transplant recipients contributes to their heightened cancer risk. In particular, the suppression of CD4+ and CD8+ T-cells, responsible for detecting and killing tumor cells and the susceptibility to tumorigenic viral infections are hypothesized as the main mechanisms driving malignancy following renal transplant. Kidney transplant recipients are at risk for 3 types of malignancies; pre-existing or recurrent tumors, de novo tumors occurring following transplantation, and donor-derived or transmitted tumors. In one study, the average time to cancer development following transplantation was 9.4 years, and all-cancer rates continued to rise with increasing time following transplantation. Conversely, in the case of occult or known donor-derived malignancy, average time to cancer discovery was 2 months (range 2 days to 38 months post-transplant) [12,13].

The above seven case studies are representative of the spectrum of malignant disorders affecting the renal allograft that may result in nephrectomy. For example, the first two case studies involve patients that developed incidental de novo RCCs in failed living donor renal allografts that functioned for greater than 10 years. In case 1, the localized RCC was detected during retransplant evaluation, was managed by nephrectomy alone, and did not preclude successful living donor kidney retransplantation performed 2 months later. In case 2, a localized RCC was detected 20 years following primary kidney transplant and 9 years following simultaneous kidney-pancreas transplant during work-up of a ventral incisional hernia. Once again, the lesion was treated by nephrectomy alone although a second localized malignancy was identified on the explant specimen. In both of these cases, because the lesions were localized and thought to be de novo in origin, no changes were made in immunosuppression and both patients continue to do well with excellent allograft (retransplant) function and exhibit no evidence of disease on surveillance imaging 4-5 years following nephrectomy of the primary transplant.

In comparison, cases 3-5 involve examples of donor-derived malignancies. Case 3 chronicles an unusual case of high grade urothelial neoplasia in a dual kidney transplant recipient diagnosed 9 months following the index transplant. This patient presented with localized signs and symptoms and was subsequently found to have a large burden of locally invasive and metastatic disease, which was not completely resectable. The timing of diagnosis, the absence of disease in the native urethelium and the history of unexplained weight loss in the donor all suggest a donor neoplasia.

etiology. Although histocompatibility typing of the tumor demonstrated donor and recipient elements, the tumor responded more like a donor-derived malignancy as the patient is completely free of disease and is doing well on dialysis at 3 years follow-up following dual nephrectomy, cessation of immunosuppression, and 6 months of pacitaxel.

In the unfortunate pair of elderly mate kidney recipients reported in cases 4 and 5; however, both patients developed biopsy-proven myeloid sarcoma of the allograft within a few months of transplant, which is more characteristic of donor-transmitted disease. Both patients presented with acute kidney injury and the diagnosis of malignancy in the allograft was serendipitous. Whereas one patient underwent bone marrow biopsy and received subsequent chemotherapy, the other refused both a bone marrow biopsy and post-nephrectomy chemotherapy. Molecular genotypic testing in both cases confirmed acute myeloid leukemia of donor origin with identical haplotypes. Both patients died more than one year following allograft nephrectomy for a malignancy-related indication. Due to the idiosyncratic nature of malignancies (of genitourinary malignancies such as RCC and TCC to blood/malignancy as the patient is completely free of disease and is doing well on dialysis at 3 years follow-up following dual nephrectomy, cessation of immunosuppression, and 6 months of pacitaxel.

Case 6 represents an example of recurrent RCC affecting the renal allograft in a patient who had previously undergone laparoscopic right native radical nephrectomy for a localized 1.4 cm, Fuhrman nuclear grade 3, acquired cystic disease-associated RCC 8 months prior to transplant. A mandatory waiting period or disease-free interval was not deemed necessary because of the favorable histopathology and localized nature of this tumor. Unfortunately, the patient presented 9 months following transplant with localized and metastatic RCC involving the renal allograft that had been performed ipsilateral to her previous native nephrectomy. Imaging did not show any evidence for suspicious lesions in her remaining atrophic left native kidney. Although the patient survived 22 months following allograft nephrectomy, she was never disease-free and died in hospice care.

The final case is an example of probable de novo high grade urothelial carcinoma presenting 8.5 years following transplantation. Similar to case 3, this patient presented with local signs and symptoms in conjunction with acute kidney injury. Although initial imaging studies suggested distant disease, the margins of resection were free of disease, lymph nodes were negative, and the patient is currently doing well at 17 months following nephrectomy.

Conclusion

Our case reports demonstrate the myriad and incidental presentations of malignancy in functioning and failed renal allografts (including localized and metastatic disease) and the unpredictable timeframe of their presentation ranging from months to years following the renal transplant. Furthermore, these cases illustrate the range of varied pathology ranging from genitourinary malignancies such as RCC and TCC to blood/malignancy as the patient is completely free of disease and is doing well on dialysis at 3 years follow-up following dual nephrectomy, cessation of immunosuppression, and 6 months of pacitaxel.

Conflict of Interest:

All authors declare that they have no conflict of interest.

(In case animals were involved) Ethical approval: This article does not contain any studies with animals performed by any of the authors.

(And/or in case humans were involved) Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

This article does not contain any studies with human participants or animals performed by any of the authors.

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Author Contributions

S H: Drafting article, data collection, data analysis/interpretation, concept/design
K W: Data analysis/interpretation, drafting article, imaging
A C F: Approval, Data collection
J R: Approval, Data collection
G O: Approval, Data Collection, Concept/Design
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