Renal Cell Carcinoma from a Transplanted Allograft: Two Case Reports and a Review of the Literature

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Clinical Genitourinary Cancer,
Vol. 6, No. 1, 53-55, 2008

Key words: Cadaveric transplantation, Multifocal disease, Nephrectomy

Submitted: Oct 19, 2007; Revised: Feb 12, 2008; Accepted: Feb 18, 2008

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Abstract

We report 2 cases of renal cell carcinoma (RCC) in which the tumor arose from a transplanted allograft. The first case is a 52-year-old man with a failed cadaveric renal transplantation found to have metastatic RCC. The tumor was proven to be from the allograft, as fluorescence in situ hybridization analysis of biopsy material showed a female karyotype, consistent with his female donor. The second patient is a 45-year-old man who had undergone cadaveric renal transplantation in 1985 for chronic glomerulonephritis and, after 22 years, presented with renal failure. Biopsy and subsequent allograft nephrectomy revealed innumerable microscopic foci of RCC. There are only a few reported cases of RCC arising in kidney allografts and even fewer with reports of metastatic disease from the allograft. Treatments in patients with disease confined to the kidney have included partial nephrectomy and total nephrectomy. A literature search did not find any reports of treatment of metastatic RCC that arose from a renal allograft.

Introduction

There is a slightly higher proportion of cancer cases that are renal cell carcinoma (RCC) reported among patients who have undergone organ transplantation compared with the general population.[1] Most commonly, these tumors arise in the recipient's native kidneys. Penn et al reported that, of 239 RCCs arising in 7248 patients with renal transplantation, only 21 developed cancer in the allograft itself. In this study, 2 patients were mentioned to have died of metastatic disease, although the type of treatment that these patients received was not described.[2]

We report 2 patients with renal allografts who subsequently developed RCC, one localized and multifocal and the other metastatic. In the patient with the multifocal localized disease, the allograft was entirely removed. The patient with metastatic RCC from his allograft was treated with sunitinib.

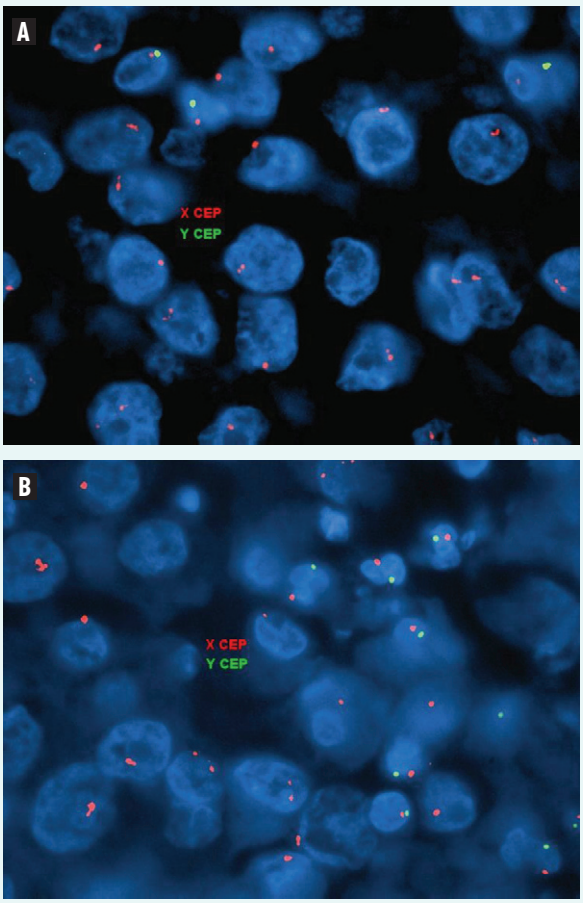
Case Reports

Case 1

A 52-year-old man developed end-stage renal disease (ESRD) of unknown etiology thought to be secondary to a long history of sarcoidosis. In 1996, he underwent cadaveric renal transplantation from a female donor. His immunosuppressive regimen included prednisone, tacrolimus, and mycophenolic acid. In 2002, the patient suffered graft failure and was started on hemodialysis. His immunosuppressive therapy was discontinued, but the graft was never removed.

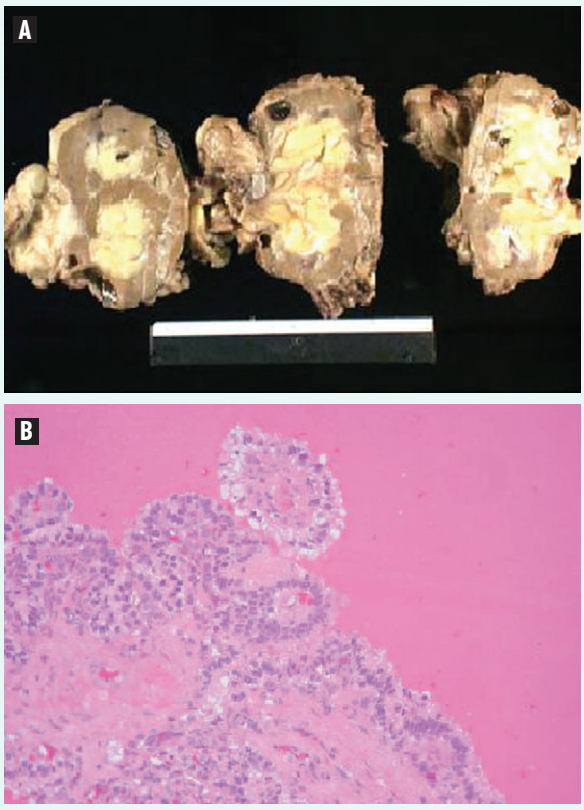
In 2006, he presented with a new left chest wall mass by physical examination. Biopsy of the left chest wall mass revealed poorly dif-

Figure 1 Fluorescence In Situ Hybridization Sex Chromosome Analysis in Case 1



Two FISH analyses of tumor tissue from case 1. Note tumor tissue with 2 X chromosomes (shown in red) consistent with donor origin versus the normal host lymphocytes with both X and Y (green) chromosomes.

Figure 2 Gross and Microscopic Analysis of Tumor Tissue from Case 2



(A) Photograph of the allograft nephrectomy specimen showing multiple subcortical cysts involving the upper and lower poles of the kidney. The cysts are unilocular and range from 0.5 cm to 3.5 cm in dimension. No solid mass lesions are identified upon gross examination. **(B)** A representative microscopic photograph showing the presence of multifocal RCC.

ferentiated carcinoma. He subsequently developed left leg pain and weakness. A computed tomography (CT) scan at that time showed abnormal adenopathy in the mediastinum, retroperitonium, and iliac regions. There was also a soft-tissue mass in the left hemipelvis extending to the sacrum with involvement of the left neural foramen. Multiple lytic bony lesions involved the pelvis, lumbar spine, and possibly the thoracic spine. A pattern of heterogeneous contrast enhancement within the nonfunctioning, calcified renal graft was suspicious for tumor involvement. Re-evaluation of the pathology specimen revealed the tumor to be consistent with poorly differentiated clear-cell carcinoma, probably of renal origin. Further testing by fluorescence in situ hybridization (FISH) analysis, using probes specific to the X and Y chromosome, revealed that tumor cells contained 2 X chromosomes consistent with the donor's sex (Figure 1). The patient was treated with sunitinib; despite dose reduction by 50% secondary to renal dysfunction, the patient experienced major gastrointestinal side effects, and the treatment was discontinued after 2 cycles because of disease progression.

Case 2

A 45-year-old man with ESRD from chronic glomerulonephritis had undergone a cadaveric renal transplantation placed in the right pelvis after a short period of hemodialysis in 1985. He did well for 23 years with no signs of rejection on prednisone, until a preoperative evaluation for knee surgery revealed decreased renal function with a serum creatinine level of 2 mg/dL. The patient underwent a right allograft biopsy in 2006, which showed RCC with papillary features. Mild chronic allograft nephropathy was also seen. He underwent further imaging with magnetic resonance imaging of the abdomen, which showed 3 cortically based nonenhancing lesions within the renal allograft. Differential diagnoses for the additional lesions were thought to be complex cysts versus papillary neoplasm.

The patient underwent allograft nephrectomy in December 2006. The kidney showed multiple areas of cystic change. The specimen revealed renal cell carcinoma with multiple foci of tumor confined within the walls of the cysts, the largest being 0.2 cm in a background of tubular intraepithelial neoplasia, Fuhrman nuclear grade 2. There were papillary and clear-cell features. There was no involvement of the renal capsule. The

margins were clear. The pdathologic stage was T1a (Figure 2). Molecular analysis revealed monosomy of chromosomes 7 and 17 in 60% of the cells examined by FISH.

The patient had a good postoperative recovery and has returned to hemodialysis. He continues to show no evidence of recurrent disease.

Discussion

Renal cell carcinoma is the fifth most common posttransplantation malignancy.[3] Development of RCC from the allograft is uncommon, however, and in this report we have presented 2 cases with distinct clinical presentations.

Cases of allograft RCC have been reported sporadically in the medical literature. The mean duration between transplantation and development of RCC was reported to be about 3.5 years in one case series,[4] much shorter than observed in the present 2 cases. However, in some cases, transplantation of an allograft with preexisting RCC occurs with a quoted rate of about 0.3%,[5] but the latency in the present cases suggest that this was not the case. Risk factors for RCC such as analgesic abuse, obesity, tobacco use, and repeated pyleonephritis appear to also be risk factors for the development of RCC in an allograft.[6] It is also felt that posttransplantation immunosuppression likely facilitates development of recipient and allograft-derived RCC. Most cases have been localized RCCs confined to the kidney and have been treated with partial nephrectomy or total nephrectomy with good long-term outcomes.[1,7] Radiofrequency ablation has been used in a patient with poor performance status.[7] There were 2 cases with metastatic RCC mentioned in 1 case series, but it is unclear how the metastases in these patients were deemed to be from the allograft or how they were treated.[2]

Each of our 2 cases has a unique aspect compared with cases previously reported in the literature. In case 1, the metastatic deposit was evaluated by FISH, confirming that the sex chromosomes were consistent with the donor and not the recipient. To our knowledge, this is the first cited case using this technique to determine the origin of the tumor. Case 2 is notable in that the RCC was found to be multifocal, with innumerable sites within the kidney allograft. Six other cases of multifocal disease are reported in the literature with one showing 29 lesions within the kidney at the time of resection.[3]

It is also interesting to note that monosomy 7 and 17 was found by FISH in a significant proportion of tumor cells derived from case 2, from the biopsy and later surgical specimens. The most common cytogenetic abnormalities in papillary renal cell cancers are trisomy 7 and 17.[8] The *MET* proto-oncogene is located on chromosome 7q. Duplication and activating mutation of *MET* has been observed in familial and sporadic cases of papillary RCC.[9] It is unclear what role, if any, the loss of chromosomes 7 and 17 played in malignant transformation in case 2. Apparent monosomy by FISH could be explained by trisomy with internal deletion of sequences hybridizing to the FISH probe in the duplicated chromosome.

Long-term follow-up is not yet available for each of our cases. In case 2, we do anticipate that the patient should have good long-term outcome without recurrence based on similar reports in the literature.[10]

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