

Case Reports

Concurrent Urothelial Carcinoma in the Renal Pelvis of an Allograft Kidney and Native Recipient Bladder: Evidence of Donor Origin

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A 44-year-old woman was admitted to the hospital for asymptomatic gross hematuria. At the age of 28, she underwent transplantation of a kidney from her father for end-stage renal disease secondary to rapidly progressive glomerulonephritis. She resumed peritoneal dialysis when the allograft kidney stopped functioning at the age of 42. Dialysis was continued for the next 2 years, when the hematuria occurred and she was readmitted. Radiologic evaluation and transurethral resection of the bladder tumor revealed a tumor of the renal pelvis of the allograft kidney (cT3N0M0) and multiple bladder tumors (cT1N0M0). Total cystectomy and allograft nephroureterectomy were performed. Histopathological examinations revealed high grade urothelial carcinoma in the renal pelvis of the allograft kidney (pT3) and native bladder (pT1). Fluorescence *in situ* hybridization of both specimens demonstrated that the renal pelvic tumors and bladder cancer possessed XY karyotypes. These results indicated that the urothelial carcinoma developed *de novo* in the renal pelvis of the allograft kidney and was implanted into the recipient's native bladder.

Key words: allograft kidney – urothelial carcinoma – implantation – fluorescence in situ hybridization

INTRODUCTION

Renal transplantation offers improved survival rates and quality of life compared with other treatments for end-stage renal disease (1). According to the United Network for Organ Sharing (UNOS) database, >15 000 people received renal transplants in the USA in 2011 (2). One important issue after renal transplantation is the development of malignancy, which might be related to immunosuppressive therapy. The most common genitourinary malignancy after renal transplantation is renal cell carcinoma of the native kidney (3), although in rare cases *de novo* carcinoma develops in the allograft kidney. Only 11 cases of urothelial carcinoma in the pelvis or ureter of an allograft kidney have been reported (4–9). Here, we report

a case of concurrent development of urothelial carcinoma of the renal pelvis of an allograft kidney and recipient bladder. Genetic analysis indicated that the renal pelvic carcinoma originated from the donor and was implanted into the recipient bladder.

CASE REPORT

A 44-year-old woman was admitted to the hospital because of asymptomatic gross hematuria. At the age of 28, she had undergone transplantation of a kidney from her father for end-stage renal disease secondary to rapidly progressive glomerulonephritis. Her father had no significant history of

medical illness. He was an office worker and former smoker. At the age of 42, 15 years after renal transplantation, she had resumed peritoneal dialysis due to chronic rejection. Immunosuppressive therapy was maintained during dialysis, and continued until age 44, when she was readmitted for hematuria. Cystoscopy to determine the cause of the hematuria showed multiple papillary tumors on the posterior wall of the native bladder. Contrast-enhanced computed tomography revealed a thick wall at the pelvi-ureteric junction of the allograft kidney (Fig. 1), which was infiltrated with adjacent fat tissue (cT3). There were no abnormal findings in native kidney and no distant metastases. Transurethral resection of the bladder tumors (TURBT) demonstrated high-grade invasive urothelial carcinoma with squamous differentiation. The pathological stage was pT1. Based on the clinical diagnosis of renal pelvic carcinoma (cT3N0M0) of the allograft kidney and high-grade T1 bladder carcinoma, total cystectomy and allograft nephroureterectomy were performed in December 2011. A flat ulcerated tumor 35 × 20 mm in size was observed in the renal pelvis of the allograft kidney. Hematoxylin and eosin-stained sections demonstrated invasive urothelial carcinoma beyond the muscle layer (pT3) with squamous differentiation in the renal pelvis of the allograft kidney (Fig. 2A) but no residual carcinoma in the bladder. The surgical margin was negative. Severe glomerulosclerosis was observed in the renal parenchyma around the tumor. There was no lymph node metastasis. To clarify whether the carcinoma cells originated from the donor or the recipient, we performed dual-color fluorescent *in situ* hybridization (FISH) using a CEP X and CEP Y probe cocktail (Vysis, Abbott Molecular, IL, USA) (8, 9). Single separate orange (chromosome X) and green (chromosome Y) signals were identified in the nuclei of carcinoma cells from the renal pelvis tumors of the allograft kidney and bladder tumors of the native bladder. These results indicated that the renal pelvic and bladder carcinoma represented an XY phenotype (Fig. 2B–G).

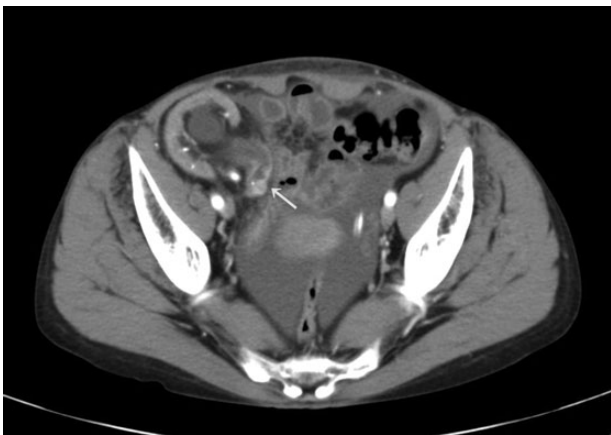


Figure 1. Computed tomography showed a thick wall at the pelvi-ureteral junction of the allograft kidney that had infiltrated adjacent fat tissue (arrow).

After surgery, systemic adjuvant chemotherapy was not performed. Cyclosporine was discontinued, and no recurrence has been observed in the 12 months since the operation.

DISCUSSION

Generally, the induction of immunosuppression after renal transplantation may lead to the development of malignancies (10). Such malignancies have been observed in the native kidney, upper urinary tract and bladder after renal transplantation. The Cincinnati Transplant Tumor Registry (CTTR) database reported 236 cases (~2%) of bladder cancer among 9688 *de novo* cancers in renal allograft recipients (3). Thus, development of malignancies in an allograft kidney or the upper urinary tract is very rare. In the present case, urothelial carcinomas were concurrently identified in the renal pelvis of the allograft kidney and also in the native bladder 16 years after renal transplantation. Interestingly, FISH analysis clearly demonstrated that both cancers possessed XY karyotypes, indicating that these carcinoma cells came from her father. To our knowledge, only 11 cases of *de novo* urothelial carcinoma developing in the renal pelvis of an allograft kidney or ureter have been reported (4–9). In addition, there has been no case of synchronous urothelial carcinoma of the native bladder and allograft kidney, so the present concurrent case is the first case report in the literature.

Generally, urothelial carcinomas develop synchronously or metachronously in multiple sites of the upper urinary tract and bladder. Traditionally, the multifocal nature of urothelial carcinoma has been explained by the ‘field cancerization theory,’ according to which the entire uroepithelium is exposed to a common carcinogenic insult and multifocal urothelial carcinomas arise from independent clones of transformed urothelial cells (11). However, detailed clinical observations and molecular genetic studies suggest that such multifocal tumors can develop by seeding (implantation) of viable intraluminal cancer cells or by intraepithelial spread. For example, in clinical observations, patients with tumors of the renal pelvis and ureter have ~30–40% risk of developing bladder carcinoma after nephroureterectomy (12, 13), while such patients have only a 2–6% chance of developing tumors in the contralateral upper urinary tract (13, 14). Patients with primary bladder carcinomas also have only a 0.5–2% risk of subsequent upper urinary tract tumors. However, the risk of subsequent upper urinary tract tumor is reported to rise to ~6–20% if the patient has vesicoureteral reflex (15, 16). These observations suggest the importance of urinary flow in heterotopic recurrence, thus underscoring the role of implantation or seeding of a transformed cell in the process of multifocality. In addition, the results of recent molecular genetic studies, which have included analyses of X-chromosome inactivation (17), p53 mutations (18) and loss of the heterozygosity pattern (19) of heterotopic synchronous or recurrent urothelial carcinomas, have provided evidence for a common clonal origin in most multifocal urothelial cancers. In the present case, FISH

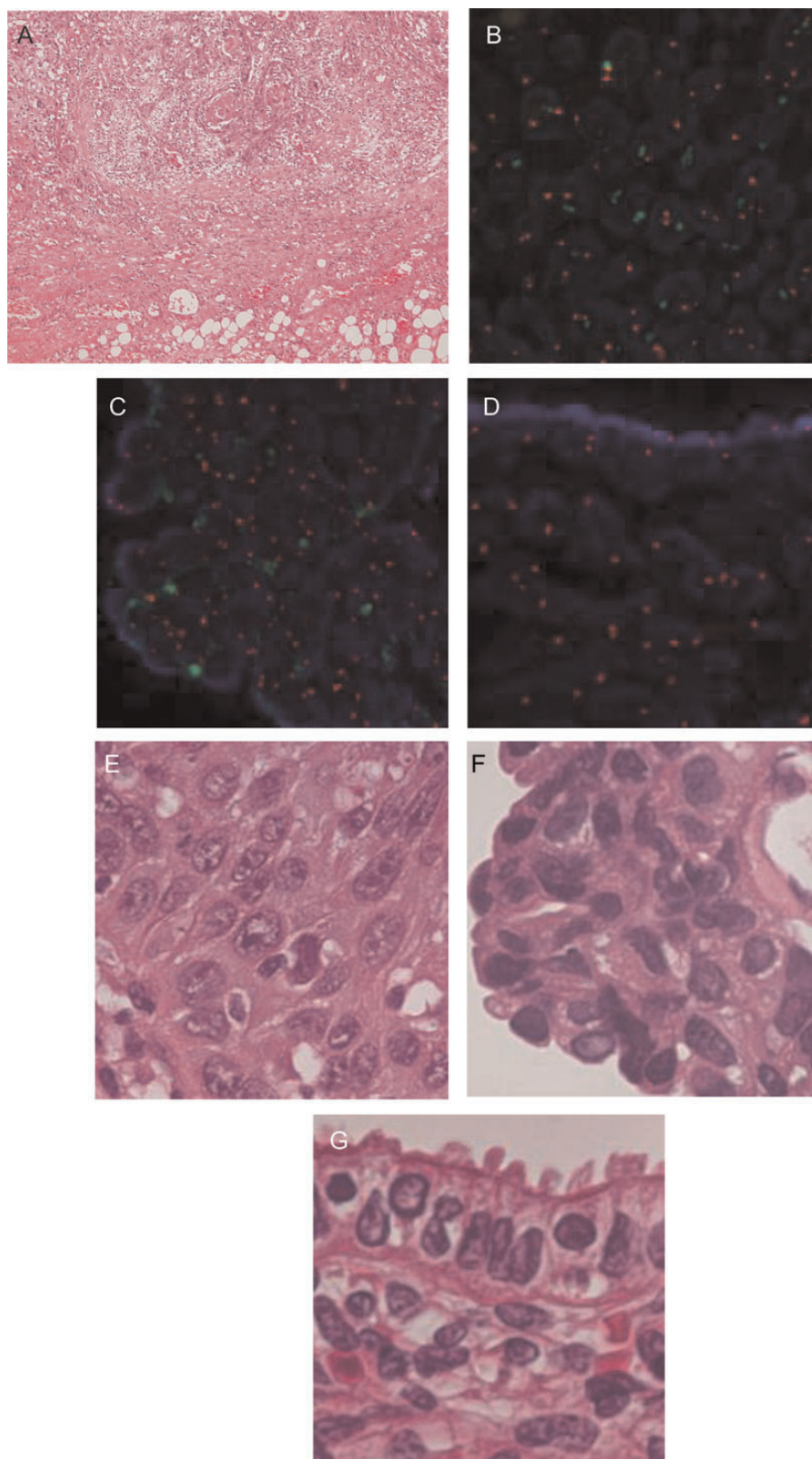


Figure 2. Hematoxylin and eosin-stained tissue sections demonstrated invasive urothelial carcinoma beyond the muscle layer (pT3) with squamous differentiation in the renal pelvis of the allograft kidney (A). Separate orange (chromosome X) and green (chromosome Y) signals were seen in the nuclei of carcinoma cells in the renal pelvis of the allograft kidney (B) and native bladder (C). Hematoxylin and eosin-stained tissue sections of the same tissue are also shown (carcinoma cells in allograft kidney (E); native bladder (F)). This result demonstrated that the renal pelvic carcinoma and bladder carcinoma presented an XY phenotype, which meant that these carcinoma cells were from the donor, her father. The native uterus examined as a control showed only orange signals (D); hematoxylin and eosin-stained sections of the same tissue (G).

analysis of the renal pelvic carcinoma and bladder carcinoma tissues demonstrated that both carcinomas possessed XY karyotypes, indicating that these carcinoma cells came from her father and demonstrating the common clonal origin of the renal pelvic carcinoma and bladder carcinoma. Taking into account the previous clinical observations, we conclude that cancer cells in the renal pelvis were present in the urinary flow and implanted in the native bladder.

It is of clinical importance to determine whether a tumor originates from the donor or the recipient in order to determine the type of additional therapy and follow-up. In this case, we discontinued immunosuppressive therapy after resection of the allograft kidney, which might have led to restoration of the immunity to carcinoma cells derived from the allograft. Vervloessem et al. also supported this view in their case report of a 55-year-old man with transitional cell carcinoma in a renal allograft. They removed the renal allograft and discontinued immunosuppressive therapy. They considered that this allowed the immune system to recover and eventually to reject residual tumor cells (4). In other cases, Penn described 10 patients with donor-associated renal cell carcinoma with distant metastases, in whom removal of the renal allograft and cessation of immunosuppressive therapy brought about complete remissions of the metastases. They considered that removal of the allograft kidney reduced the tumor burden, and the discontinuation of immunosuppressive agents allowed the immune system to recover and to reject the cancer cells (20). In consideration of these findings, we did not perform adjuvant chemotherapy, because we considered the risk of recurrence or metastasis in this recipient relatively low, although we will closely monitor this patient for recurrence.

In conclusion, we have presented a rare case of *de novo* urothelial carcinoma in the renal pelvis of an allograft kidney and native bladder. Genetic analysis demonstrated that both cancers originated from the donor.

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Conflict of interest statement

None declared.

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