Donor-Derived Neuroendocrine Carcinoma Transmission to Two Kidney Transplant Recipients Demonstrated by Short Tandem Repeat Analysis: A Case Report

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ABSTRACT

Cancer transmission from a donor organ to a transplant recipient is a rare but not infrequently fatal event. We report a case of lung cancer transmission from a deceased donor to 2 kidney recipients. Approximately 1 year after uneventful kidney transplantation, both recipients developed acute kidney failure. Computed tomography imaging of abdomen and pelvis for both recipients showed masses in the transplanted kidneys along with innumerable masses in the livers. Pathologic examinations for both cases demonstrated high-grade neuroendocrine carcinoma with "mirror image" histologic findings in the transplant kidneys with liver metastases. Short tandem repeat (STR) analyses were performed to determine the origin of the tumors. STRs of both tumors were nearly identical to that of the donor, proving that both tumors were from the same donor. Immunohistochemical analyses showed that both tumors were positive for thyroid transcription factor 1, supporting a lung primary. One recipient died as a direct sequela to metastatic tumor, and the other required transplant nephrectomy and chemotherapy. Awareness of this largely nonpreventable complication and prompt molecular testing if cancer transmission is suspected are important.

KIDNEY transplantation has improved the quality of life in patients with end-stage renal disease (ESRD). However, transplantation is associated with a number of complications, including an increased risk for malignancy, partially because of the need for chronic immunosuppression [1-4]. Posttransplant malignancy includes not only recipient-derived cancers but also transmission of donor-derived cancers. At the time of donation, organ donors are screened for possible malignancy by medical history review, x-ray imaging, and blood testing; therefore, the risk for cancer transmission is considered to be very low [5]. However, occasionally cancers in a potential donor are undetected and organs are transplanted. Organ recipients receive chronic immunosuppression, and thus the transmitted cancer can escape host immune surveillance, grow rapidly, and metastasize, potentially causing the death of the recipients.

We have experienced a case of donor-derived cancer transmission. Donor-derived neuroendocrine carcinoma was transmitted to 2 recipients through kidney transplantation, and extensive liver metastases were found approximately 1 year after transplantation in both recipients. One of the recipients died as a result of cancer transmission.

CASE PRESENTATION

Organ Donor

The donor was a 62-year-old man with a history of heavy smoking. The donor was reported to have no medical history of malignancy and had no signs of malignancy at the time of death according to complete physical examination, laboratory testing, and imaging, including abdominal ultrasound and chest x-ray. The kidneys were allocated to 2 male recipients from our transplant center.

Kotaro Takeda and Rhonda Mittenzwei contributed equally to this work.

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Recipient 1

The right kidney was transplanted to a 75-year-old man with ESRD secondary to systemic lupus erythematosus. The transplant surgery was uneventful, and the renal function improved (pretransplant creatinine 13.0 mg/dL; day 10 posttransplant creatinine 2.3 mg/dL). After 14 months, he developed fatigue, shortness of breath, diarrhea, and acute renal failure (creatinine 4.9 mg/dL, potassium 6.1 mEq/L). He was emergently admitted for evaluation and hemodialysis. Computed tomography (CT) imaging of abdomen and pelvis showed moderate hepatomegaly with innumerable hypoattenuated masses throughout the liver (Fig 1A) and a 5.5 × 4.6 cm mass involving the inferior pole of the transplanted kidney Fig 1B).

Needle core biopsy of hepatic masses was performed. Microscopically, the tumor cells had round to oval nuclei with coarse chromatin, inconspicuous nucleoli, and scant amounts of eosinophilic cytoplasm. The tumor cells formed cribriform or solid nests that infiltrated through the hepatic parenchyma (Fig 2A and B). The tumor cells were positive for synaptophysin and thyroid transcription factor-1 (TTF-1) by immunohistochemical studies (Fig 2C and D). The Ki-67 proliferation index was >20% (Fig 2E). The pathologic diagnosis was metastatic high-grade neuroendocrine carcinoma in the liver. He was weak and failed to thrive; thus, palliative care was chosen and after several days he died.

Recipient 2

The left kidney was transplanted to a 63-year-old man with ESRD secondary to focal segmental glomerulosclerosis and diabetes mellitus. The transplant surgery was uneventful; however, a postoperative complication included hyperglycemia requiring insulin administration. Posttransplant renal function was improved (pretransplant creatinine 7.2 mg/dL; day 10 posttransplant creatinine 2.0 mg/dL). After 13 months, he presented to the emergency department with fever and was found to have acute kidney failure (creatinine 9.1 mg/dL, potassium 5.4 mEq/L). He was admitted for evaluation and hemodialysis. CT of the abdomen and pelvis showed multiple hypoattenuated masses throughout the liver (Fig 1C) and a 3.3 × 2.8 cm mass at the inferior pole of the transplanted kidney (Fig 1D).

The transplanted kidney was resected. The kidney contained a collection of multiple tan-white masses ranging from 0.7 to 2.8 cm in diameter infiltrating into the renal parenchyma and calyces. Microscopically, the tumor cells had hyperchromatic round to oval nuclei and scant cytoplasm and infiltrated as cribriform and solid nests (Fig 2F and G). The morphology fully resembled that in the hepatic tumor in recipient 1. The tumor cells were positive for synaptophysin and TTF-1 (Fig 2H and I). The Ki-67 proliferation index was >20% (Fig 2J). The pathologic diagnosis was high-grade neuroendocrine carcinoma in the transplanted kidney. Immunosuppression was discontinued and chemotherapy (cisplatin/irinotecan) was initiated. He is alive with significant shrinkage of the hepatic masses 3 years later.

Short Tandem Repeat Analysis

STRs are repeated deoxyribonucleic acid (DNA) sequences within the human genome, composed of 1 to 6 base pairs adjacent to one another. As a result of slippage during DNA replication and repair, these STRs become highly variable, which

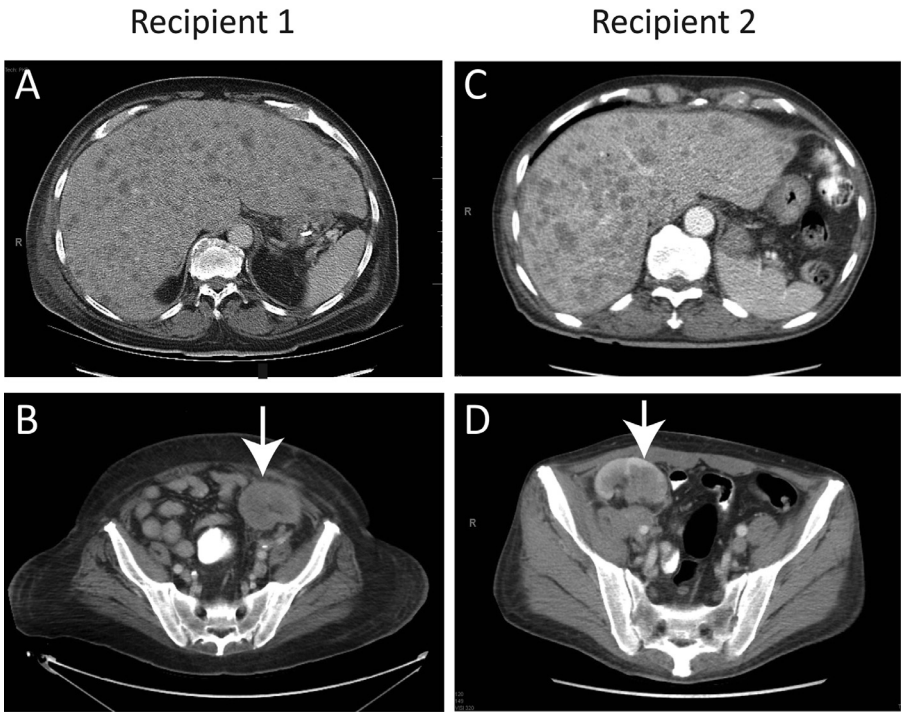

Fig 1. Computed tomography images of abdomen and pelvis (axial view) of recipients 1 and 2. **(A)** Recipient 1 had innumerable hypoattenuating masses throughout the liver. **(B)** A 5.5 × 4.6 cm mass at the inferior pole of the transplanted kidney (white arrow) in recipient 1. **(C)** Recipient 2 also had multiple hypoattenuating masses throughout the liver. **(D)** A 3.3 × 2.8cm mass at the inferior pole of the transplanted kidney (white arrow) in recipient 2.

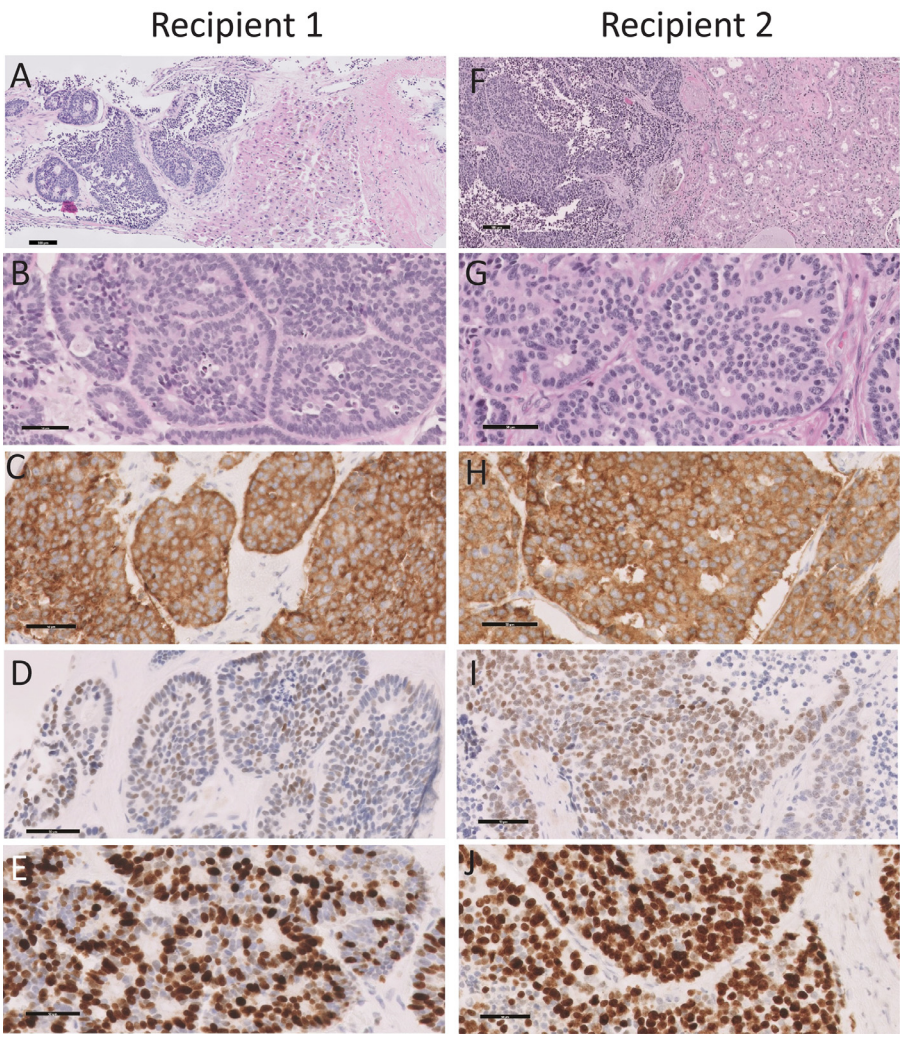

Fig 2. Photomicrographs and immunohistochemical studies in tumors in recipients 1 and 2. (**A** and **B**) The liver mass biopsy of recipient 1 showed infiltrative growth of neuroendocrine carcinoma into the liver parenchyma (**A**: low magnification, **B**: high magnification). **(C-E)** The tumor cells were positive for **(C)** synaptophysin and **(D)** TTF-1 and **(E)** the Ki-67 proliferation index was over 20%**.** (**F** and **G**) The explanted kidney of recipient 2 showed infiltrative growth of neuroendocrine carcinoma into the renal parenchyma (**F**: low magnification, **G**: high magnification). The morphologic findings were similar to those in the liver biopsy sample in recipient 1 (compare B and G). **(H-J)** The tumor cells were positive for **(H)** synaptophysin and **(I)** TTF-1 and **(J)** the Ki-67 proliferation index was over 20%. (Scale bar, **A** and **F:** 100 μm, **B-E** and **G-J:** 50 μm).

results in a different number of repeat units in different alleles [6]. The STR analysis was performed to evaluate whether the tumors in recipients 1 and 2 were donor- derived. Reference DNA samples from the donor and each recipient were used to compare to DNA within each recipient's tumor. Fifteen loci (plus sex chromosomes) were used to analyze genetic derivation of the tumor. As an example, the STR locus D5S818 is shown in Fig 3. The donor alleles exhibited tandem repeats of 11 and 13 (Fig 3A), whereas both alleles in recipient 1 exhibited 12 repeats (Fig 3B), and recipient 2 alleles showed tandem repeats of 11 and 12 (Fig 3C). Both tumors in recipient 1 and 2 similarly exhibited tandem repeats of 11 and 13, the pattern of which was identical to the donor's pattern; the allele containing 13 repeats can be only donor-derived (Fig 3D and E). These data demonstrated that both tumors exhibited the same donor-derived genetic signature. Similar findings were present in 11 other loci. The tumors exhibited identical genetic signatures in both recipients at all 15 loci. These findings are compatible with a donor-derived tumor in both donated kidneys, with similar genetic signatures identified by STR analysis.

DISCUSSION

Cancer transmission from a deceased organ donor is a rare event. A study of over 30,000 organ transplant recipients from nearly 15,000 organ donors in the United Kingdom between the years of 2001 and 2010 demonstrated that the risk for donor-derived cancer transmission was 0.05% [5]. In this study, cancer diagnoses were not known at the time of donation. Donor-transmitted cancers were subdivided into early-detected and late-detected cancers. The early-detected cancers were found within 6 weeks of transplantation incidentally on routine screening, had no evidence of cancer spread outside the transplanted organs, and underwent explant surgery, allowing for the survival of all recipients. In contrast, the late-detected cancers were found after a median duration of 318 days. Of the late-detected cancers, metastases outside the graft were present at the time of diagnosis in 75% of the cases. Of recipients with donor-transmitted cancers, 20% died as a direct result of their tumor, and all of these patients had late-detected cancers. In our cases, the transmitted cancers were detected at 14 months and 13 months

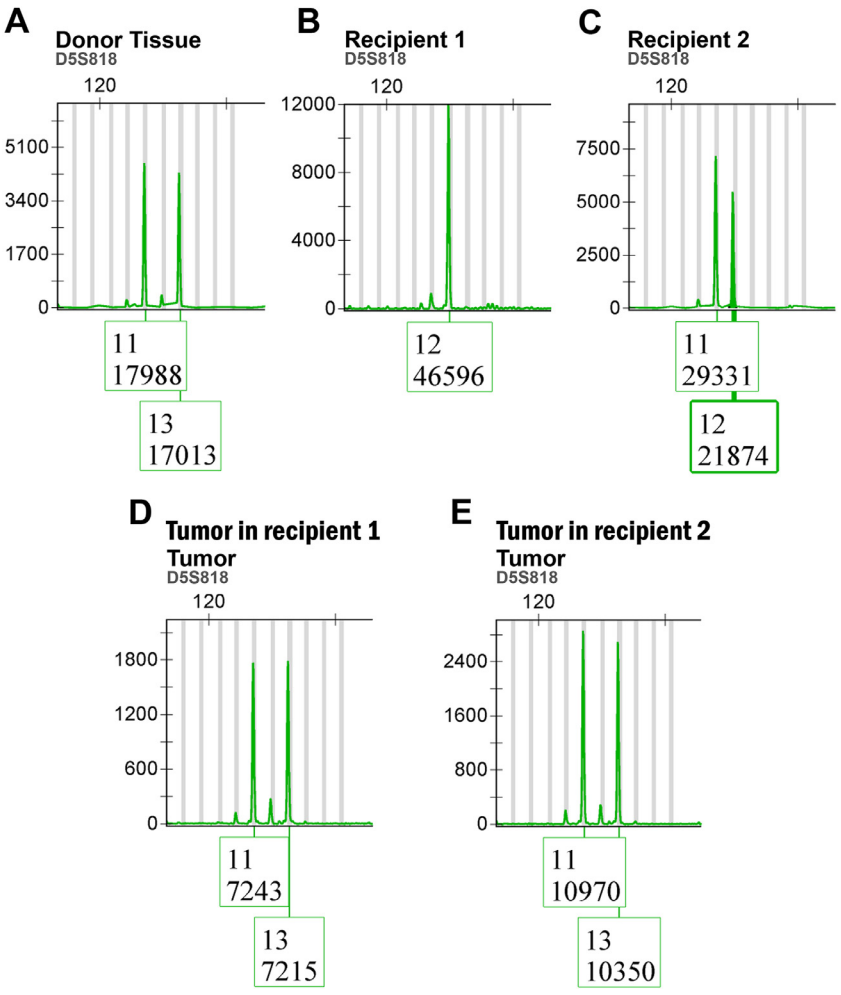

Fig 3. Exemplar short tandem repeat (STR) analysis. The STR locus D5S818 was analyzed along with 14 other STR loci to evaluate the relationship between donor tissue reference DNA, recipient reference tissues, and tumor tissues. In these figures, the X-axis refers to number of repeated units and the Y-axis indicates fluorescence. The values represented in the boxes below each graph are the number of STR units and the area under the curve. **(A)** The donor alleles exhibited tandem repeats of 11 and 13; 13 is unique to the donor. **(B)** Recipient 1 donor tissue exhibited a peak at 12, representing both of that patient's alleles. **(C)** Recipient 2 exhibited peaks at 11 and 12. (**D** and **E**) Both tumors exhibited peaks at 13, indicative of a donor-derived tumor in both recipients. It is likely, in this case, that the peak at 11 is also donor-derived because this repeat pattern is present in the reference donor tissue.

posttransplant in recipients 1 and 2, respectively, which can both be categorized as late-detected cancer.

It has been reported that a variety of donor cancers could be transmitted to recipients, such as malignant melanoma [7], malignant lymphoma [8], renal cell carcinoma [9], glioblastoma multiforme [10], pineoblastoma [11], non-small cell lung carcinoma [12], breast carcinoma [13], urothelial carcinoma [14], intestinal carcinoma [15], and Kaposi sarcoma [16]. One systematic review for cancer transmission showed renal cell carcinoma (20.19%) was the most common transmitted cancer, followed by malignant melanoma (18.17%), malignant lymphoma (15.14%), and lung cancer (9.9%) [9]. A recent study of donor-transmitted cancer in kidney recipients demonstrated that the most frequently transmitted cancer types were malignant lymphoma (20.5%), followed by renal cell carcinoma (17.9%), malignant melanoma (17.1%), non−small cell lung cancer (5.6%), and neuroendocrine carcinoma (4.7%) [17]. Based on these studies, transmission of neuroendocrine carcinoma is relatively rare; however, it is frequently metastatic at the time of diagnosis, and 73% of neuroendocrine carcinoma transmission cases exhibited distant metastases [17]. Consistent with this, both of our recipients exhibited extensive liver metastases at the time of diagnosis. Neuroendocrine carcinoma can occur anywhere in the body, with lung being the most common site. In our cases, TTF-1 positivity with a history of heavy smoking in the donor strongly supports a lung primary. Primary lung neuroendocrine carcinoma is usually found in the central portion of the lung, occasionally precluding early detection by chest x-ray. Primary neuroendocrine carcinoma of the kidney is exceedingly uncommon.

STR analysis currently has a multitude of applications, including forensic DNA investigations in the context of identity testing and chimerism analysis in hematopoietic stem cell transplantation [6]. STR analysis is also performed to ascertain the origin of tumors in posttransplant malignancies [12,18], as we have demonstrated. The STR analysis in both of our recipient tumors unequivocally demonstrated that both tumors were genetically similar and donor- derived.

Cancer transmission is a rare but frequently fatal event; it is important to consider its possibility when posttransplant malignancy has occurred. In our case, renal transplantation was performed for both recipients in our transplantation center, and both posttransplant cancers were detected within a similar time range. In this setting, clinical suspicion of cancer transmission

in the transplanted organ should be high. STR analysis plays a crucial role for rapid and unequivocal determination of donor tumor transmission and may significantly alter patient management, including reduction of immunosuppression and/or organ explant. Furthermore, it may spur investigation among other recipients of organs from the same donor. Awareness of this largely nonpreventable complication and prompt implementation of molecular testing if cancer transmission is suspected are vital to the proper management of these patients.

DATA AVAILABILITY

Data will be made available on request.

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