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Letter to the Editor

De novo papillary renal cell carcinoma in an allograft kidney: Evidence of donor origin

To the Editor:

An increased incidence of primary malignancies has been recognized in transplant recipients. Renal cell carcinomas (RCC) represent 4.6% of all malignancies in renal transplant recipients, whereas RCC constitutes 2% of all cancers in the general population.[1] According to the Cincinnati Transplant Tumor Registry, there are fewer instances of RCC that develop in the allograft kidneys (up to 10%), while nearly 90% of RCC in renal transplant recipients have been found in native kidneys.[1] *De novo* RCC has been described as the opposite of pre-existing tumors before transplantation.[1–3] Pathological characteristics of *de novo* RCC occurring in the allograft kidney have not been well described. Furthermore, genetic studies to determine the tumor origin, whether from the donor or the recipient, have been performed in only a few reported RCC cases, although it is clinically important considering the association of tumor transmission. We report a case of *de novo* papillary RCC developing in an allograft kidney diagnosed 13 years after renal transplantation, and which was genetically confirmed to be of donor origin.

A 49-year-old Japanese male presented with end-stage renal disease secondary to chronic glomerulonephritis of unknown etiology when he was at the age of 25. The patient had no family history of renal disease. After 5 years of hemodialysis, he underwent renal transplantation at the age of 29 from a deceased donor. The donor was a 37-year-old Japanese male who died of cerebral hemorrhage. The donor had no significant medical illness in his family history or past history according to medical records. Immunosuppressive therapy was maintained with methylprednisolone, cyclosporine and mizoribine. The patient presented with an episode of chronic rejection that successfully treated by steroids 7 years after transplantation. At that point, ultrasonography showed no evidence of a solid or cystic lesion in the allograft kidney. Graft function had been stable with serum creatine level of 1.1 to 1.3 mg/dL, although the patient exhibited 30 mg/dL of proteinuria on rare occasions. However, 13 years after transplantation, ultrasonography revealed a 2.3 cm solitary cystic lesion in the lower pole of the allograft kidney. During the following 7 years, the cyst had increased in size to 4.0 cm with slight blood flow inside, which led to suspicion of malignancy. There was no other cystic lesion in the allograft kidney or native kidneys. An extensive workup ruled out any primary or metastatic lesion. The patient underwent a partial nephrectomy of the allograft kidney in 2010, 20 years after transplantation. No recurrence has been found on most recent evaluation. Graft function has resumed and the patient has maintained dialysis-free status. The contralateral kidney of this particular donor, which had been transplanted to a Japanese female and resected 12 years after transplantation due to chronic rejection, presented no solid or cystic lesion.

In the resected specimen, a well-circumscribed tumor was located in the renal cortex. The tumor measured 4.0 × 3.5 × 3.5 cm in size. The cut surface was solid and yellowish-white with tiny hemorrhages. No necrosis was noted. Histologically, a unilocular cyst was densely filled with small cuboidal cells with scanty basophilic cytoplasm. The cuboidal cells also lined the cyst wall (Fig. 1a). The tumor cells formed papillae and tubules, arranged in a single layer on the basement membrane. The nuclei were small, uniform and had hyperchromatic chromatin with a finely granular pattern. The papillary cores frequently contained aggregates of foamy macrophages and hemosiderin laden macrophages. Kidney parenchyma around the tumor showed mild interstitial fibrosis and slight tubular atrophy. Formalin-fixed paraffin-embedded tissue sections were immunohistochemically stained. The antibodies used were vimentin (DAKO, Glostrup, Denmark, monoclonal, clone V9, dilution 1:100), high molecular weight cytokeratin (DAKO, monoclonal, clone 34βE12, dilution 1:100), cytokeratin 7 (DAKO, monoclonal, clone OV-TL12/30, dilution 1:100), CD10 (DAKO, monoclonal, clone SS2/36, dilution 1:100), and alpha-methylacyl-coenzyme A racemase (AMACR) (DAKO, monoclonal, clone 13H4, dilution 1:100). Prostate tissue and the allograft kidney parenchyma around the tumor were used as positive control. The tumor cells were positive for vimentin, cytokeratin 7 (Fig. 1b), CD10 and AMACR, but negative for high molecular weight cytokeratin (Fig. 1c). Pathological diagnosis was papillary RCC type 1, Fuhrman's nuclear grade 2, and stage pT1aN0M0. Comparative microsatellite analysis was performed to detect tumor origin according to a previously described method.[4] Recipient peripheral blood and paraffin-embedded tissue from the tumor and the allograft kidney parenchyma (donor tissue) were used. In total, 15 short tandem repeat (STR) markers were compared for microsatellite analysis. All of the analyzed STR markers were detected and the predominant DNA patterns of the tumor matched those of the donor, confirming that the tumor was of donor origin (Fig. 1d).

The present case provides some insights into the nature of *de novo* RCC developing in an allograft kidney. First, the present case of RCC was confirmed to be of donor origin by microsatellite analysis on genomic DNA. It is of clinical

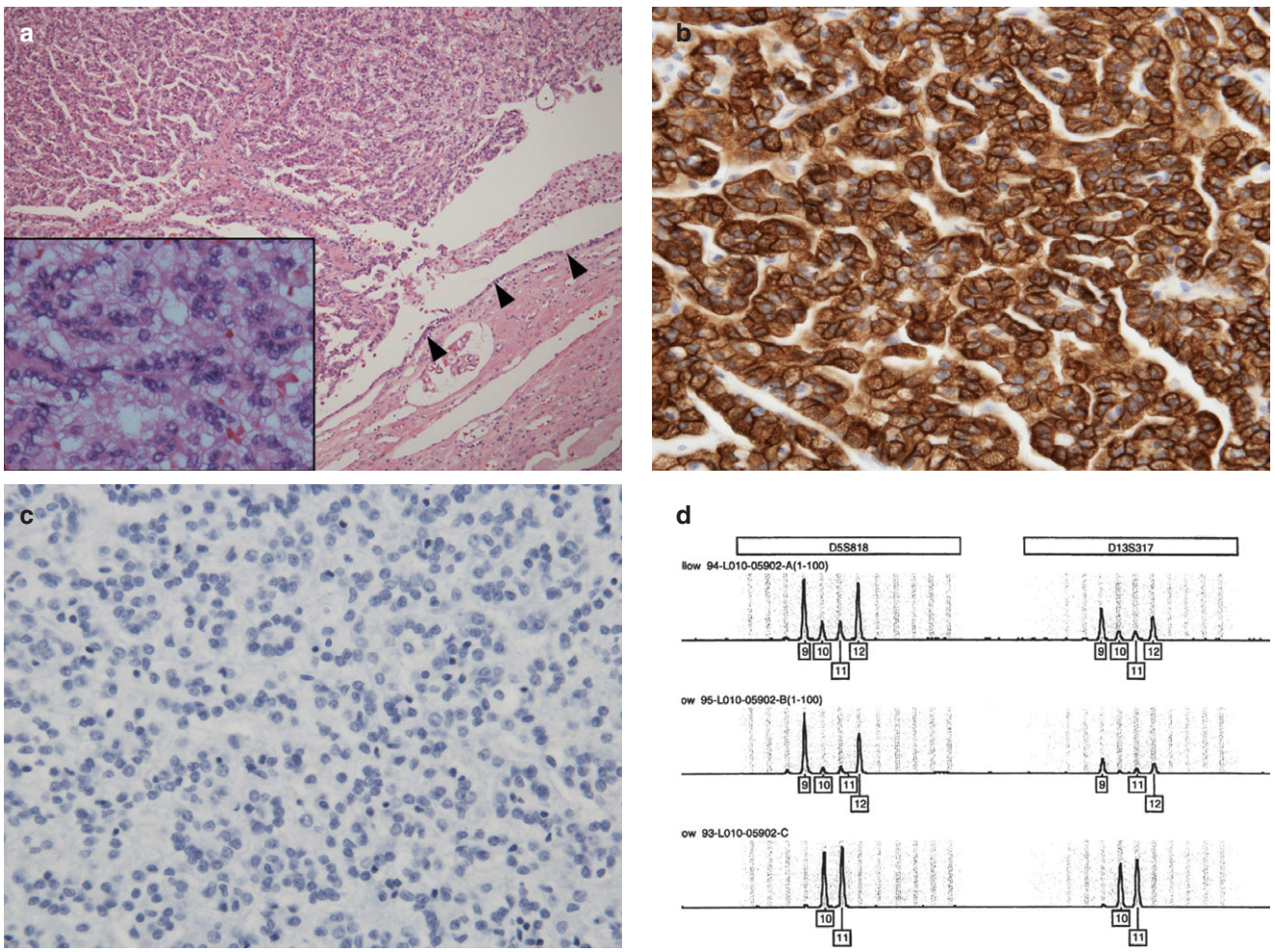

Figure 1 (**a**) Histological findings of the tumor (HE). Small cuboidal cells form papillae and tubules, which also line the cyst wall (arrow heads). The nuclei are small, uniform and have hyperchromatic chromatin with a finely granular pattern (inset). Immunohistochemically, the tumor cells are positive for cytokeratin 7 (**b**), but negative for high molecular weight cytokeratin (**c**), which supports the diagnosis of papillary renal cell carcinoma. (**d**) Comparative microsatellite analysis on genomic DNA. Allotype of tumor cells (upper), parenchyma donor cells (middle), and recipient blood cells (bottom). The predominant DNA patterns of the tumor match those of donor, confirming the tumor is of donor origin.

importance to determine the tumor origin, whether from the donor or the recipient. In case of sex-mismatched transplantation, a fluorescent *in situ* hybridization of sexual chromosomes is available to confirm tumor origin. In this case, however, both donor and recipient were males. Therefore, microsatellite analysis was adopted because it reflects individual differentiation that is not sex-linked. Most of the previous reports on *de novo* RCC developing in the allograft kidney have been confirmed to be of donor origin,[2–7] yet only a limited number of reported cases were genetically analyzed (Table 1). In cases of RCC of donor origin, tumor transmission from the donor should be considered. In the present case, however, the possibility of tumor transmission could be eliminated from consideration because no cystic or solid lesion in the allograft kidney had been detected 7 years after transplantation. So far, only one case of RCC in the allograft kidney has been established by microsatellite analysis to be of recipient origin.[4] In the case of RCC of recipient origin, metastasis from the native kidney should be considered. In addition, recent studies have demonstrated epithelial microchimerism in transplanted organs, which indicate that recipient-derived circulating pluripotent stem cells could originate tumors in the graft.[8] Second, in the present case, a solitary cortical cyst was first demonstrated with ultrasonography, and then it seemed to transform into malignancy. The growth pattern was consistent with previous reports, which have observed the process of RCC developing from cystic lesions by sequential radiological studies.[9] The association between a renal cyst and RCC has not been well documented, although several congenital and acquired cystic kidney diseases have been postulated to increase the risk of developing RCC.[10] In this case, the recipient had no family history of renal disease, including polycystic kidney disease. The patient was not a case of acquired cystic kidney disease

Table 1 List of reported *de novo* RCC in kidney allografts

Recipient		Donor				Tumor			
Age† (y)	Sex	Age (y)	Sex	Transplant	Duration (y)	Size‡ (cm)	Histology	Origin	Reference
45	F	ND	ND	LRD	21	3.4	CCRCC	Donor	Park *et al*.[2]
43	F	ND	M	CAD	13	2.5	PRCC	Donor	Rotman *et al*.[3]
58	M	ND	ND	CAD	14	5	CCRCC	Recipient	Boix *et al*.[4]
30	F	ND	ND	ND	16	1.5	PRCC	Donor	Roy *et al*.[5]
24	M	27	M	CAD	13	2.5	CCRCC	Donor	Feldman and Jacobs[6]
29	F	63	M	ND	5	4	RCC	Donor	Schostak *et al*.[7]
29	M	38	M	CAD	13	4.0	PRCC	Donor	Present Case

†Age at transplantation.

‡Maximum diameter.

CAD, cadaveric donor; CCRCC, clear cell renal cell carcinoma; F, female; LRD, living related donor; M, male; ND, no data; PRCC, papillary renal cell carcinoma.

either, as there was no other cystic lesion in the allograft kidney or native kidneys. Furthermore, the possibility that the donor had congenital or acquired cystic kidney disease was unlikely because the contralateral kidney of the particular donor had no cystic lesion when it was resected 12 years after transplantation.

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