De novo concurrent papillary renal cell carcinoma and angiomyolipoma in a kidney allograft: evidence of donor origin

Samuel Rotmana,*, Cédric Déruazb, Jean-Pierre Venetzb, Pascal Chauberta, Jean Benhattara, Jean-Yves Meuwlyc, Patrice Jichlinski, Louis Guilloua, Solange Moll, Manuel Pascual, Robert Lemoine

a Institute of Pathology, University Hospital, CH-1011 Lausanne, Switzerland
b Department of Nephrology, University Hospital, CH-1011 Lausanne, Switzerland
c Department of Radiology, University Hospital, CH-1011 Lausanne, Switzerland
d Department of Urology, University Hospital, CH-1011 Lausanne, Switzerland
e Institute of Pathology, University Hospital, CH-1211 Geneva, Switzerland
f Institute of Pathology, CH-2007 Neuchâtel, Switzerland

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Summary In the general population, renal cell carcinoma (RCC) is a relatively common neoplasm; however, the papillary RCC subtype is infrequent and represents only 10 to 15% of all RCC. Angiomyolipoma is a well-known common benign tumor. The occurrence of RCC in association with angiomyolipoma is a rare event, with only approximately 50 cases reported in the nontransplantation setting. In transplant recipients, RCC can develop in native kidneys, but its occurrence de novo in the renal allograft is very rare with an estimated incidence of less than 0.5%. We report here the case of a 39-year-old woman who underwent cadaveric renal transplantation in 1990. No lesion was observed in the allograft during the pre- and perioperative period or on early postoperative ultrasounds. No graft rejection occurred under a standard triple immunosuppressive therapy. Thirteen years later, during a routine ultrasonography, 2 solid masses were discovered in the allograft, both of them richly vascularized. She underwent allograft nephrectomy and the histologic findings revealed that one of the tumors was a chromophilic (type 1) papillary RCC (2.5 cm in diameter) and the other, an angiomyolipoma (1.5 cm). Microsatellite analysis of the allograft, as compared with the recipient peripheral blood leukocytes, demonstrated that the 2 tumors (1 malignant and 1 benign) were of donor origin. To our knowledge, this is the first report of de novo concurrent papillary RCC and angiomyolipoma in a renal allograft.

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1. Introduction

Cancer of the kidney represents 2% of the total human cancer burden, and papillary renal cell carcinoma (PRCC),
approximately 10% of renal cell carcinomas (RCCs) [1,2]. Two histomorphological types of PRCC, type 1 and type 2, have been described [3,4]. Type 1 PRCC is associated with a longer survival than type 2 PRCC, and a better prognosis than “classic” clear cell renal carcinoma [2]. Angiomyolipoma (AML) is a benign tumor frequently found in the kidney [5,6], the radiological detection of which poses the differential diagnosis of a malignant tumor [7]. The occurrence of RCC in association with AML in the native kidney is a very rare event, with only approximately 50 cases reported [8-12]. Most carcinomas were of the clear cell type [11,13].

Studies have reported an increase in the prevalence of RCC in native kidneys of renal transplant recipients compared with the general population [14-17]. However, “de novo” RCC in a renal allograft is a rare event with an estimated incidence of less than 0.5% [18].

We present the first case, to our knowledge, of concurrent de novo PRCC and AML developing in a renal allograft, with radiological, histological, and molecular (genetic) data.

1.1. Case report

A 39-year-old woman presented with advanced renal insufficiency of unknown etiology since 1986. She was treated by hemodialysis for 1 year and in 1987 underwent her first cadaveric renal transplantation. Three weeks later, severe vascular rejection required an aggressive immunosuppressive therapy with corticosteroids, antithymocyte globulin, and OKT3 without any amelioration of the renal function. Hemodialysis had to be restarted, and in 1988, the patient underwent her first allograft nephrectomy.

In May 1990, she received second renal allograft from a male cadaveric donor. No lesion was identified in the allograft during surgery, and in the 7 years after the transplantation, 3 renal ultrasounds confirmed the absence of lesions in the allograft. No graft rejection occurred under a standard immunosuppressive therapy with cyclosporine, prednisone, and azathioprine. In April 2003, during a routine ultrasonography, 1 large cortical cyst and 2 solid masses were discovered in the allograft. Both solid masses

Fig. 1  A, Longitudinal sonographic view of the transplanted kidney (B mode). A rounded hypoechoic mass (arrow) is visible at the lower pole. A hypoechoic badly delineated zone is visible on the convexity (arrowheads). B, Color Doppler ultrasound of the upper lesion demonstrates high-flow signal within and around the mass. C, Coronal T2 MRI shows a bright cyst and 2 solid masses. D, Nephrectomy specimen. a, papillary RCC (2.5 cm). b, simple cyst. c, angiomyolipoma (1.5 cm). Abbreviations: C, cyst; M1 and M2, masses.
appeared heterogeneous on B mode and richly vascularized on color Doppler ultrasound. A magnetic resonance imaging confirmed the presence of 1 cortical cyst and 2 solid masses. In June 2003, the patient underwent her second allograft nephrectomy, and she returned to hemodialysis.

2. Materials and methods

2.1. Radiology

Sonography was performed with a HDI 5000 instrument (Philips Ultrasound, Bothell, Wash) equipped with 5- to 12-MHz linear transducer. Gray scale (Fig. 1A) with panoramic reconstruction and color Doppler (Fig. 1B) explorations were obtained. The lower abdomen was imaged by using a phased-array torso coil with a 1.5-T unit (Magnetom Symphony; Siemens Medical System, Erlangen, Germany). Magnetic resonance imaging sequences included T1- and T2-weighted sequences (Fig. 1C) without fat saturation in transverse and coronal planes and T1-weighted sequences with fat saturation in transverse plane after intravenous injection of gadolinium.

2.2. Histology

For light microscopy examination, the tissue was fixed in 4.5% phosphate-buffered formalin, routinely processed, and embedded in paraffin wax using standard methods. Sections measuring 4 μm were stained with hematoxylin and eosin and examined by 2 independent pathologists (S.R. and L.G.). The morphological criteria described in the last World Health Organization classification of tumors [19] were used to establish the diagnosis of the renal tumors. Histologic grade was established using the Fuhrman grading system [20], and staging of RCC was performed according to the 2002 TNM classification [21].

Fig. 2  A and B, Papillary renal carcinoma, type 1, nuclear grade 1. The tumor consists of a papillary growth of small cells containing oval small nuclei with inconspicuous nucleoli. The fibrovascular cores often contain foamy macrophages (hematoxylin and eosin, original magnification ×100 and ×200). C and D, Angiomyolipoma: benign tumor composed of a mixture of fat, blood vessels, and smooth muscle. The vascular component shows tortuous and thick-walled blood vessels. The adipose tissue is of a mature type, and the smooth muscle demonstrates hypercellularity. A lymphocytic infiltrate (recipient cells) is admixed with the tumor (hematoxylin and eosin, original magnification ×40 and ×20).
2.3. Fluorescent in situ hybridization analysis

Briefly, for fluorescent in situ hybridization (FISH), 4-μm frozen sections were treated with a protein-digesting enzyme at 37°C for 40 minutes. Preparations were denatured in 70% formamide/2× standard saline citrate (SSC), pH 7, at 75°C, for 2 minutes. Then, a solution containing a specific probe for the centromere of chromosomes X, Y, 7, and 17, coupled with SpectrumGreen (Vysis, Downers Grove, Ill) was applied to the tissue sections at 37°C for 15 hours. After hybridization, the unannealed probe was washed in 0.4× SSC/NP40 0.3% at 73°C for 3 minutes then in 2× SSC/NP40 0.1% at 37°C for 2 minutes. Nuclei were counterstained using a 4,6-diamidine, 2-phenyllindol/antifade solution. A Zeiss Axioplan 2 imaging microscope (Zeiss, Feldbach, Switzerland) equipped with appropriate filters for 4,6-diamidine, 2-phenyllindol and SpectrumGreen was used to score the number of centromeres of each chromosome in tumoral tissue and nontumoral tissue.

2.4. Microsatellite analysis

Frozen tissue samples from tumoral and nontumoral renal allografts were used for microsatellite analysis. A blood leukocyte sample was obtained from the patient. DNA was extracted from blood and tissues using the DNeasy Tissue Kit (Qiagen, Hilden, Germany). Two highly polymorphic markers (D8S255 and D9S156) were used to determine the origin of the tumoral tissues. Primers were obtained from the Genome Data Base (http://gdbwww.gdb.org). Polymerase chain reaction cycling conditions were 35 cycles at 94°C for 30 seconds, 56°C for 45 seconds, and 72°C for 45 seconds, followed by 10 minutes at 72°C. Products were separated by electrophoresis in denaturing 6% polyacrylamide gels. Microsatellite analysis of the allograft and the 2 tumors were compared with that of leukocytes from the patient.

3. Results

3.1. Macroscopic findings

The nephrectomy specimen measured 12 × 6.5 × 4 cm with a weight of 237 g. A solid, yellowish, and well-demarcated mass, measuring 2.5 cm, was located in the lower cortical pole (Fig. 1D and A). A second mass (Fig. 1D and C), which measured 1.5 cm, was located between the hilar region and the medulla of the kidney. This mass was less well-demarcated than the first one and showed a gray-white and striped appearance. These 2 tumors were completely separate from each other. A cortical cyst (Fig. 1D and B) measuring 3.5 cm was located in the vicinity of the smaller mass but clearly separated from it. Except for these 3 lesions, the renal parenchyma was unremarkable.

Fig. 3  Fluorescent in situ hybridization on papillary RCC: the papillary RCC presents a triploidy and/or a polyploidy of chromosome 7, chromosome 17. The loss of chromosome Y is typically observed in this type of RCC but does not allow us to determine the origin of this tumor (male donor versus female recipient).
3.2. Histology

The 2.5-cm cortical mass (Fig. 1D and A) showed a papillary growth pattern. The central cores of the papillae were frequently filled with foamy macrophages. Papillae were covered by a single layer of small cells (Fig. 2A and B) with scant cytoplasm. This tumor corresponded to a PRCC type 1 according to the 2004 classification of renal tumors [19] and was of grade 1 according to the Fuhrman grading system [20].

The 1.5-cm medial mass (Fig. 2C and D) was composed of a mixture of adipose tissue, smooth muscle cells, and numerous thick walled vessels of varying size. The adipose tissue was composed of mature adipocytes. The smooth muscle component was composed of intersecting fascicles of smooth muscle cells without any visible mitotic activity or necrosis. A relatively abundant lymphocytic infiltrate accompanied all different tumoral components. This neoplasm corresponded to an angiomyolipoma according to the 2004 classification of renal tumors [19].

The cystic structure (Fig. 1D) corresponded to a simple cyst with no evidence of malignancy.

3.3. Fluorescent in situ hybridization analysis

Fluorescent in situ hybridization using chromosome 7 and 17 probes showed trisomy 7 and 17 in many PRCC cells (Fig. 3). In addition, a loss of chromosome Y and a conservation of chromosome X was observed in this tumor (Fig. 3) using chromosomes X and Y probes, confirming the diagnosis of PRCC.

Fluorescent in situ hybridization using chromosome X and chromosome Y probes on the AML showed the presence of these 2 chromosomes in endothelial and smooth muscle cells (Fig. 4). Two signals were observed in the lymphocytic nuclei originating from the recipient, whereas...
no signals were observed with chromosome Y probe (Fig. 4). This indicated that the AML tumor was of donor origin but that lymphocytes within it were of recipient origin.

3.4. Microsatellite analysis

Polymerase chain reaction amplification products obtained from the PRCC presented the same band profile as that of allograft DNA (non PRCC tissue) but was different from that of recipient peripheral blood leukocytes (Fig. 5), indicating the donor origin of the PRCC tumor.

For the AML, DNA amplification products showed a band profile corresponding to a mixture of that of donor allograft and recipient leukocyte profiles (Fig. 5).

4. Discussion

Papillary renal cell carcinoma comprises approximately 10% of RCC in the general population. Two morphological types of PRCC have been described. Type 1 PRCC is usually of lower stage and grade than type 2 neoplasm [3] and shows a better prognosis [2]. Papillary renal cell carcinoma is associated with karyotypic changes with trisomy or tetrasomy 7, trisomy 17, and a loss of chromosome Y [22].

Nephrectomy is a common treatment of malignant tumors, although partial nephrectomy is sometimes preferred to spare some renal tissue and preserve the renal function depending on tumor size and stage [23].

Angiomyolipoma is a relatively uncommon benign tumor of the kidney (1% of renal tumors), with a 4:1 female-to-male ratio [19]. It may arise either in the cortex or medulla of the kidney. It may occur sporadically or in patients with tuberous sclerosis (TS), an inherited autosomal dominant syndrome. The genes TSC1, located on chromosome 9p34 [24], and TSC2, located on chromosome 16p13 [25], play a pathogenic role in TS. AML frequently show a loss of heterozygosity of TSC2 gene locus in both sporadic and TS-associated neoplasms [25]. Loss of heterozygosity of the TSC1 gene in AML is also occasionally observed [26].

Because AML contains a significant vascular component, radiological imaging can be misleading, mimicking a malignant process. Because needle biopsy is generally contraindicated in this kind of highly vascularized tumor, definitive diagnosis relies upon pathological examination of excision specimens. The development of concurrent renal cell carcinoma and AML in a native kidney is a very rare event, with about only 50 cases described in the literature [8,10,13]. Sporadic cases of PRCC and AML developing together in the same native kidney have been reported, but to our knowledge, none of these concurrent tumors were described in a renal allograft.

In transplantation, the prevalence of tumors has been linked to the immunosuppression status [14,16]. The prevalence of renal malignant tumors in renal transplant recipients is 7.8% [27], compared with 4% to 5% in the general population [19]. The great majority of renal cell carcinomas are found in the native kidneys of renal transplant recipients [9,17]. The occurrence of de novo tumors in the renal allograft is very rare and represents less than 10% of RCC developing in renal transplant recipients [28]. Most cases of RCC are of clear cell type, but sporadic PRCC have also been reported. The type of renal cell carcinoma is of prognostic importance because clear-cell neoplasms show a more aggressive behavior than PRCC [1].

In this report, we present the first case, to our knowledge, of concurrent PRCC and AML in a renal allograft, developing several years after transplantation.

No lesions were identified in the allograft at the time of the operation, and routine postoperative radiological investigations of the allograft were normal. However, during a routine ambulatory ultrasound, the presence of these 2 renal tumors was discovered. Radiological imaging revealed 2 distinct richly vascularized tumoral lesions.

For technical reasons a nephrectomy of the allograft was performed after discussion with the urological team.

Microscopic examination revealed the presence of 2 distinct tumors, 1 type 1 PRCC, and 1 AML. In absence of any radiological lesions during the years after the renal allograft, these tumors were considered as de novo tumors. Differential diagnosis included a metastasis from a PRCC located in the native kidney of the recipient and an AML, which could have developed from the periallograft mesenchymal tissue of the recipient. Yet, knowing that the recipient was a woman and that the kidney allograft came from a male donor, the FISH analysis using chromosome X and chromosome Y probes clearly demonstrated that the AML came from the male donor. The lymphocytic infiltrate of the recipient within the AML provided a good “internal control” of the FISH technique. The presence of a large band obtained by microsatellite analysis of AML cells was explained by a mixture of this lymphocytic infiltrate (recipient cells) with tumoral cells (donor origin) in the amplification (polymerase chain reaction) product.

The loss of chromosome Y, which is classically observed in PRCC [22], cannot be used as a proof for the origin of the tumoral cells by FISH technology. However, this technique, which is able to detect the polyploidy 7 and 17 of the PRCC, allowed us to confirm the histologic diagnosis of PRCC [22]. A microsatellite analysis was subsequently performed to circumvent the problem of loss of chromosome Y in PRCC. This technique showed the same band profile for the PRCC cells and the normal (nontumoral) renal cells of the allograft and, thus, demonstrated the donor origin of the PRCC. As previously mentioned, the absence of a prior radiological lesion was consistent with a de novo PRCC developing in the allograft.

To conclude, we report of case of a de novo concurrent PRCC and AML developing in a renal allograft. Using FISH and microsatellite analysis, we have demonstrated that both PRCC and AML were tumors of donor origin.

Interestingly, recipients of other allografts from the same cadaveric donor did not develop tumors during their
follow-up. An extensive radiological workup of our patient did not reveal any other tumors, nor were profile metastasis of the PRCC found. This, taken in combination with the low grade and low stage of RCC and benign nature of the AML, indicates an excellent prognosis for our patient after her allograft nephrectomy. Fifteen months after the nephrectomy, she is doing well on maintenance hemodialysis with no tumor recurrence.

A review of all allograft nephrectomies (n = 25) at our center over the last 11 years did not reveal any other case of de novo RCC in allografts, confirming the rarity of this clinicopathologic complication.

References