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De novo undifferentiated pleomorphic sarcoma arising from a renal allograft: A case report

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Renal graft cancer;
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Abstract
To the best of our knowledge, this is the first report of an undifferentiated pleomorphic sarcoma arising from a renal graft. Transplantectomy was performed in a 47-year old woman presenting to the emergency room because of general weakness. Preoperative workup revealed a 5.5 cm malignant mass of the graft which was not present on routine ultrasound performed 12 months earlier. Following transplantectomy, local recurrence developed despite complete tumor resection and interruption of immunosuppression. Despite radiation therapy, the outcome was ultimately fatal. Genetic analysis revealed that the tumor had arisen from donor tissue. Annual ultrasound surveillance might not be enough effective to screen for these rare high grade neoplasms.
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1. Introduction

Renal transplant recipients (RTR) are at an increased risk of developing renal cancer [1,2]. *De novo* renal neoplasms develop after renal transplantation and they arise either from a native kidney or from the graft. This latter situation is much less frequent [1]. Less than 100 cases have been reported. Roupret evaluated a renal clear cell cancer (RCC) cumulative incidence of 0.24% among RTR population [3]. Most of these malignancies are RCC but papillary types 1 and 2, tubulopapillary, chromophobic, sarcomatoid, epidermoid and urothelial carcinomas and oncocytomas have been described [4-8].

Abbreviations: 18-FDG PET, 18-fluodeoxyglucose positron emission tomography; 99-Tc-HDP, Technetium 99 m-hydroxymethylene diphosphonate; CT, computed tomography; FNLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; LOH, loss of heterozygosity; MRI, magnetic resonance imaging; R0 resection, complete resection with no microscopic residual tumor (margins are microscopically negative according to the pathologist); RCC, renal clear cell carcinoma; RTR, renal transplant recipient; STR, short tandem repeat

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Kidney graft tumors represent a particular therapeutic dilemma. On the one hand, radical treatment requires allograft nephrectomy and return to dialysis. On the other hand, interruption of immunosuppression may conceptually favor the host's immune response. Current guidelines recommend that any solid renal tumor should be treated with partial or radical nephrectomy [9]. Percutaneous radiofrequency and cryoablation represent alternative treatments in specific cases [10-12].

Many uncertainties on allogenic tumors remain due to their rarity. In this context, we report the case of an undifferentiated pleomorphic sarcoma arising from a renal transplant. To the best of our knowledge, no such a case has been reported up to now.

2. Material and methods (molecular identification of the tumor's origin)

Extraction of DNA was performed from paraffin blocks by the phenol-chloroform technique. DNA extracts were quantified using a Nanodrop spectrophotometer ND-100. 0.5 ng of extracted DNA was amplified on a GeneAmp® 9700 PCR thermal cycler (Applied Biosystems), using the AmpF/STR® SMG Plus® PCR amplification kit (Applied Biosystems), according to the manufacturer's instructions. Amplified products were separated on a 3130XL Genetic Analyser (Applied Biosystems) and analysis of DNA profiles was undertaken using GeneMapper TM ID version 3.2 (Applied Biosystems).

3. Case report

A 43-year-old woman underwent deceased renal transplantation for terminal renal failure secondary to polycystic kidneys disease. She was placed on tacrolimus and mycophenolate and her evolution was unremarkable during 4 years. Then, she showed up at the Emergency Department of our institution with general weakness. Physical examination was normal. Laboratory studies revealed acute kidney failure. A non-enhanced abdominal CT-scan showed a suspicious 5.5 cm mass of the inferior pole of the grafted kidney compressing the excretory system and two enlarged right external iliac lymph nodes. Abdominal MRI confirmed a tissular heterogeneous mass responsible for hydronephrosis. Chest X-ray and 99 m-Tc-HDP bone scintigraphy were negative. The patient underwent ureteropyelography with double-J stenting and biopsies which revealed a malignant undifferentiated cancer with a distinct immunomarker pattern (Table 1). She underwent transplantectomy, iliac and ilio-obturator lymphadenectomy and segmental iliac artery resection. A 2-cm tumor thrombus was extracted from the iliac vein.

Gross findings of the surgical specimen consist of a whitish heterogeneous mass $5.5 \times 5.5 \times 5$ cm^3, studded with hemorrhagic areas, with a capsular effraction and perirenal adipose tissue infiltration. The tumor compresses the pyelocaliceal system and the proximal ureter. Large sampling of the tumor showed a diffuse highly cellular proliferation of pleomorphic and fusiform cells arranged often patternless. Mitosis were abundant (43 mitosis/10 high power fields; Mib1 was approximately 60%). Confluent necrosis was observed. Peritumoral parenchyma was atrophic. Immunohistochemical analysis shows diffusely or focally positive stainings for vimentin, NSE, and CD99. Epithelial (keratin, EMA), muscular (desmin, AML) and vascular (CD34) markers were all negative, as CD 57 and S-100 (see Table 1). Four iliac lymph nodes were invaded by the tumor. It could be explained by the local seeding of tumoral cells. We considered the surgical specimen as an undifferentiated renal pleomorphic sarcoma, grade 3 (FNCLCC classification). The TNM stage was pT2 pN1 cM0 pV1 pR0. The transplantectomy specimen and histology slides are shown in Figure 1.

Table 1 Immunomarker pattern.

Marker	Biopsy	Specimen
Vimentin	+	+
NSE	n.a.	+
CD99	+	+
VS38C	+	n.a.
t22q12	-	n.a.
EMA	-	-
Total keratin	-	-
CK 7	-	n.a.
CK 20	-	n.a.
CK 903	-	n.a.
Uroplakin	-	n.a.
LCA	-	n.a.
CD 3	-	n.a.
CD 20	-	n.a.
CD 34	n.a.	-
CD 56	-	n.a.
CD 57	n.a.	-
CD 128	-	n.a.
S-100	-	-
Melan A	-	n.a.
HMB 45	-	n.a.
AML	n.a.	-
Desmin	n.a.	-

We used STR loci analysis to determine the tumor's origin (graft versus host). The tumoral tissue showed LOH at the D3S1358, D16S539 and vWA loci. Microsatellite instability was seen with a new allele 13 at the vWA locus (Figure 2). No STR instability was observed at the other 7 loci analyzed. As the tumor mirrored the genetic instability of the donor's DNA and not that of the receiver's DNA, we concluded that the cancer originated from the donor's kidney.

Four weeks following surgery, an 18-FDG thoraco-abdominal PET-CT showed an intense hypermetabolic signal infiltrating the right psoas muscle and the iliac vessels with suspect retroperitoneal lymph nodes suggesting local recurrence and lymphatic spread. Ten weeks postoperatively, the patient underwent a local radiation therapy (60 Gy in 30 fractions). One year postoperatively, PET-CT showed persistent retroperitoneal infiltration with a differential diagnosis of actinic alteration or tumor persistence but no adenomegaly or distant metastases. The patient died abroad 18 months after transplantectomy. Unfortunately, it was not possible to obtain further details about the medical cause of death and a possible dissemination of the disease.

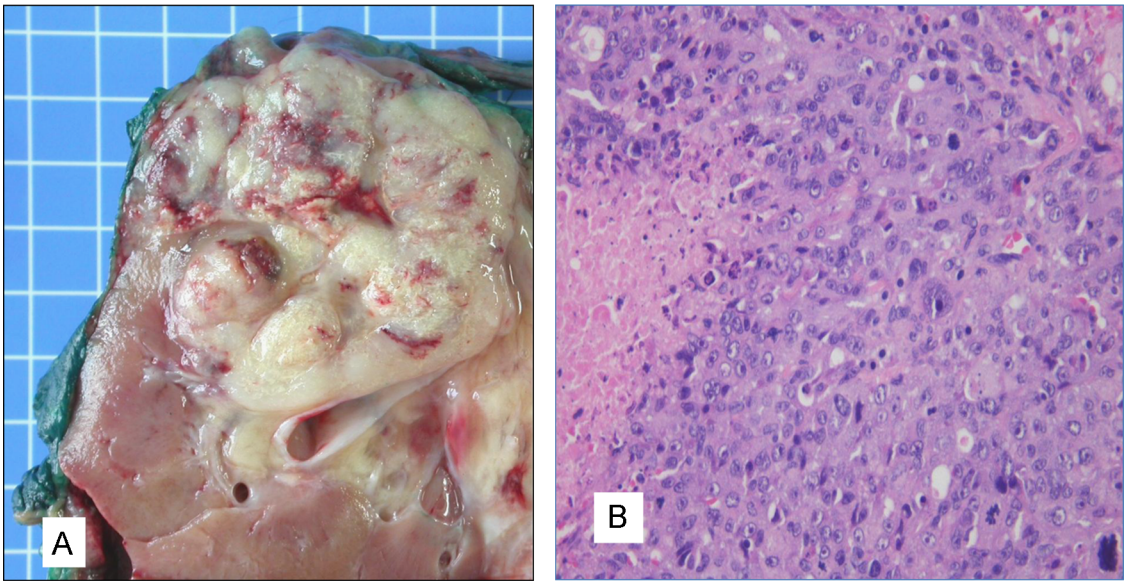

Figure 1 Undifferentiated pleomorphic sarcoma of the kidney. Soft lobulated and pale tumor bulging in the renal pelvis (A). Dense proliferation of pleomorphic cells with numerous atypia, high mitotic activity and necrosis (B: microscopy hematoxylin-eosin staining and loop magnification 100 ×).

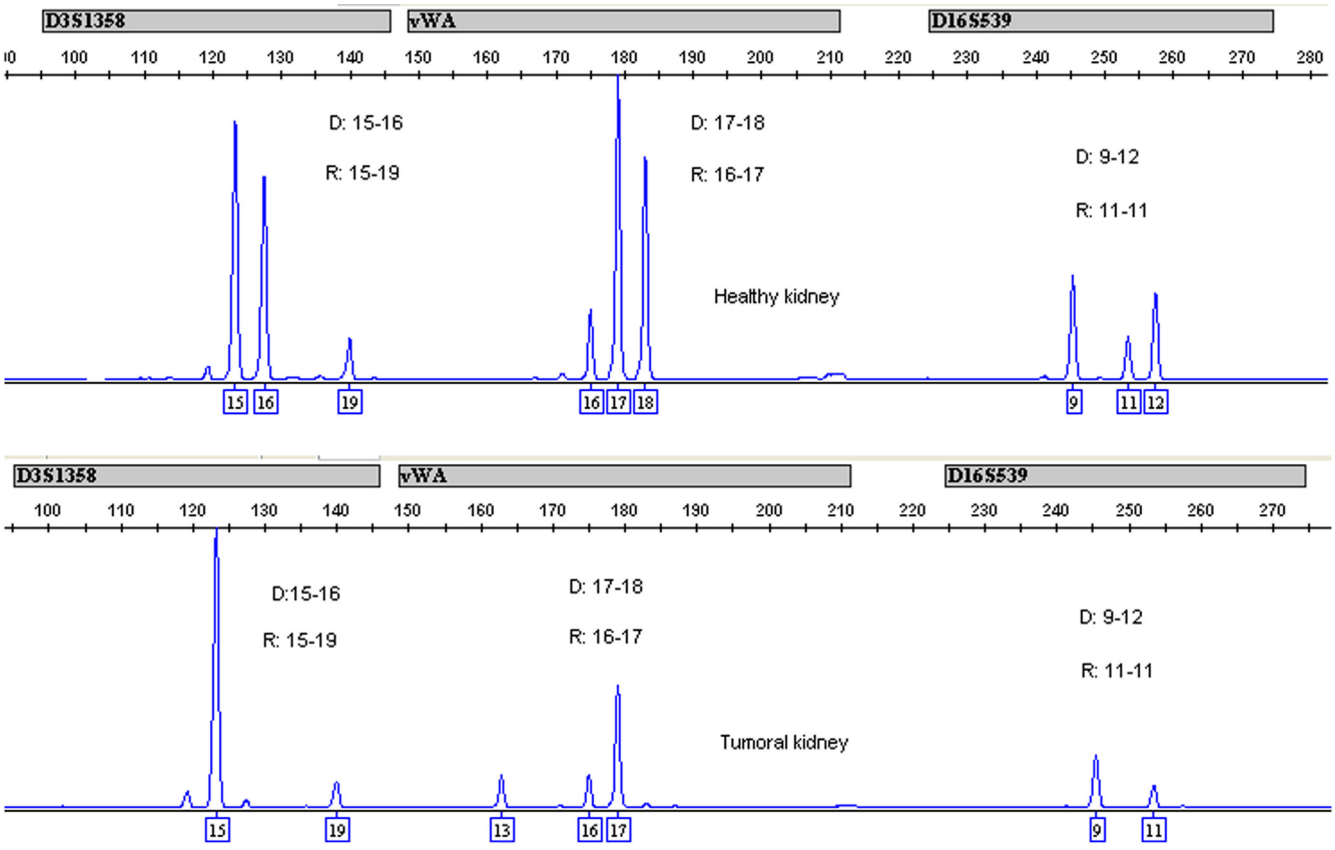

Figure 2 Electropherograms showing differences at 3 of the 10 STR loci (SGM Plus kit) between the DNA profiles of the healthy graft (upper part of the picture) and the tumoral graft (lower part of the picture). The major component of the mixed DNA profile of the healthy kidney is from the donor (D) and the minor component from the receiver (R) of the transplant. The tumoral tissue (lower part) shows a loss of heterozygosity at the D3S1358 locus (allele 16), at the D16S539 locus (allele 12) and at the vWa locus (allele 18). Microsatellite instability is seen with a new allele 13 at the vWA locus.

4. Discussion

To our knowledge, this is the first published case of primary sarcoma arising from a renal transplant. Despite its vast extension upon diagnosis, the tumor had not been detected during routine renal graft ultrasound 1 year before, suggesting rapid growth within short time. The EAU guidelines on renal transplantation recommend an annual echographic screening [9]. This case suggests that this surveillance might not be close enough to detect high-grade sarcomas because the tumor growth rate appeared to be about 10-times faster than the growth rate of renal cell carcinomas, which is estimated to be about 0.5 cm/year [13].

Because of the tumor's size, partial nephrectomy was not technically feasible and the patient returned to dialysis. Despite a R0 resection and the stop of immunosuppression, which might contribute to stop the growth of allogenic tumoral cells, there was a quick local recurrence. In our knowledge, there is no data about radiation therapy as treatment for local recurrence in renal transplant neoplasms. In regards with the 1 year follow-up, our case suggests a potential benefit for local tumor control within a short period of time.

5. Conclusion

Renal cancer prevalence in RTR might increase because of aging of RTR and older donors. Annual ultrasound surveillance might not be effective enough to screen for high-grade neoplasms. While radical surgery remains the only potentially curative treatment, adjuvant radiation therapy might be proposed for local recurrence.

Conflict of interest

All authors denied any conflict of interest.

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