Single-Center Case Series of Donor-Related Malignancies: Rare Cases With Tremendous Impact

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ABSTRACT

Background. Donor-related malignancy is a rare complication of organ transplantation.

Methods. In this case series, we discuss three cases of donor-related cancers in kidney transplant recipients who were registered in our center between 1979 and 2015. They account for an incidence of 0.29% of donor-related malignancies of a total of 1015 transplanted kidney grafts (deceased and living donors). The three cases that we describe presented in different ways and with different severity, although the response to the initiated treatment was comparable.

Results. All three patients not only survived their cancer episode but also had a complete oncological remission and underwent successful second kidney transplantation, accounting for a 100% survival rate in our small cohort.

Conclusions. Despite the very low incidence of this complication, transplant clinicians must be aware of the occurrence of donor-related malignancies when selecting a donor and should be able to diagnose and treat a case of donor-related cancer.

TRANSPLANT recipients are known to have a 3-fold excess risk of developing *de novo* cancer after solid-organ transplantation as a result of immunosuppression, as compared with the general population [1]. Besides, donor-related cancer may be transmitted with the graft (donor-transmitted cancer, DTC) or may develop later from the graft (donor-derived cancer, DDC) [2]. Donor-related malignancies, however, remain extremely rare [3–5]. An important study published in this field is a retrospective study of Kauffman et al [3], based on data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOSS), comprising a cohort of 34,933 deceased donors and 108,062 recipients between 1994 and 2001. This retrospective analysis reports an incidence rate of 0.04% for the deceased donor-related tumor rate. Of the total of 21 tumors reported, 15 were donor-transmitted and 6 were donor-derived. The overall mortality rate was 38%, with a mortality rate among the donor-derived group of 33% [3].

In this case series, we discuss three cases of donor-related malignancies in kidney transplant recipients who were registered in our center between 1979 and 2015. They account for an incidence of 0.29% donor-related malignancies of a total of 1015 transplanted kidney grafts (deceased and living donors). The three cases we describe here presented in different ways and with different severity, although the response to the initiated treatment was comparable. Fortunately, all three patients not only survived their cancer episode but also had a complete oncological remission and underwent a successful second kidney transplantation, accounting for a 100% survival rate in our small cohort.

Drs Georgieva and Gielis contributed equally to this work.

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Case 1: Malignant Meningioma

The first case of donor-related malignancy in our series occurred in a currently 69-year-old white man with autosomal dominant polycystic kidney disease (ADPKD) who underwent a first kidney transplantation in July 1994 at the age of 48 years. A bilateral nephrectomy was already performed 3 months before transplantation because of bilateral pyonephrosis. Polycystic kidney disease of the native kidneys was histologically confirmed without evidence of malignant degeneration of the cysts. Furthermore, there was no history of any other malignancy.

The patient received a kidney from a 35-year-old, heartbeating, male donor who remained comatose after a resection of a cerebral astrocytoma grade II, as diagnosed histologically at the donor center. In the initial surgical report, there was no evidence of meningeal invasion. The postoperative period was eventless, and the patient was soon discharged with a serum creatinine level of 1.5 mg/dL and a maintenance immunosuppressive therapy comprising steroids and cyclosporine.

Eight months after transplantation, the patient was readmitted to our department because of a biopsy-proven, antibody-mediated, acute rejection of the kidney. He was successfully treated with a high-dose steroid regimen of methylprednisolone 1 g intravenously daily for 4 days and Muromonab-CD3 (OKT3) for 12 days. Furthermore, azathioprine was added to the maintenance therapy as well as monthly infusions with intravenous immunoglobulins.

Five months after the episode of acute rejection, the patient's kidney function deteriorated once again to a serum creatinine level of 2.25 mg/dL (estimated glomerular filtration rate [eGFR] 32 mL/min/1.73 m^2 according to the abbreviated Modification of Diet in Renal Disease [MDRD] formula) as opposed to a previous value of 1.5 mg/dL (eGFR 50 mL/min/1.73 m^2 according to the abbreviated MDRD formula). A renal ultrasound examination revealed the presence of a grade II hydronephrosis and a more convex-shaped graft with a heterogeneous aspect of the parenchyma.

Because of the unsuccessful placement of a nephrostomy and ongoing renal insufficiency, a biopsy was performed. There were no histological signs of graft rejection, but, surprisingly, a diffuse infiltration of the kidney with malignant cells was seen.

Additional imaging with abdominal computed tomography (CT) and magnetic resonance imaging (MRI) revealed the presence of a nodular lesion at the transition zone of the pancreatic tail and the spleen, bilaterally enlarged adrenal glands, a small nodular lesion in hepatic segment VII, and no lymphadenopathy. Imaging of the neck and chest was negative for additional lesions.

On the basis of the hypothesis of a metastatic tumor in an immune-compromised patient, all immunosuppressive therapies were discontinued and a radical transplantectomy was performed 20 days after presentation with acute renal failure. During the surgical procedure, tumoral invasion of the iliac vein and diffuse peritoneal metastasis were observed. Hemodialysis was restarted, and chemotherapy with doxorubicin for the presumed sarcoma was given on a weekly basis.

Further characterization of the tumor's origin was made. All biopsy and autopsy material of the donor was retrieved from the donor center and re-assessed. Immunohistochemistry testing and the homologous appearance of the tumor cells in the donor as well as in the recipient, next to a DNA analysis of the tumor showing a common HLA-DR-genotype between the tumor and the donor's HLA typing, allowed us to state the diagnosis of a donor-related tumor [6]. Hence, the initial diagnosis of astrocytoma grade II in the donor was revised to malignant meningioma with meningeal invasion.

To summarize, the final diagnosis in this patient was a donor-transmitted metastasis of a malignant meningioma in the transplanted kidney. On the basis of the donor origin of the tumoral process, the therapy with doxorubicin was stopped and no new oncological treatment was initiated. Interferon-α was given for 6 weeks to increase the immunologic alloreactivity of the patient [6].

One month after transplantectomy, the patient was discharged. He remained in complete remission, and, 1.5 years later, the patient underwent a second, uncomplicated kidney transplantation. Twenty years after the donor-transmitted malignant meningioma, our patient remained alive without any oncological relapse. Furthermore, his second graft functioned well, with a serum creatinine level of 1.13 mg/dL (eGFR, 64 mL/min/1.73 m^2 according to the abbreviated MDRD formula) and under triple immunosuppressive therapy consisting of cyclosporine, mycophenolate sodium, and a low dose of prednisolone.

Medical information of the other transplant recipients of this donor was retrieved. The liver and heart recipients did not experience any donor-related problems after transplantation, and the transplanted organs remained well-functioning. The information on the recipient of the contralateral kidney is limited to 5 years after transplantation because of allocation outside of the Eurotransplant zone. Within this time period, there were no reported complications.

Case 2: Urothelial Carcinoma

The second case of donor-related cancer in our series occurred in a white man also with ADPKD who underwent a first kidney transplantation in 1999 at the age of 47 years. One year before the transplantation, a left nephrectomy was performed to increase available infradiaphragmatic space, and, simultaneously with the transplantation, a right kidney nephrectomy took place. Polycystic kidney disease of the native kidneys was histologically confirmed, without any evidence of malignant degeneration of the cysts.

The patient received a kidney from a 50-year-old, heartbeating, female donor who had cerebral edema after a

brain aneurysm embolization procedure. To our knowledge, she had an unremarkable medical history.

The post-transplantation period was uneventful, and the patient was soon discharged with a serum creatinine level of 1.5 mg/dL (eGFR, 50 mL/min/1.73 m^2 according to the abbreviated MDRD formula) and a maintenance immunosuppressive regimen consisting of cyclosporine microemulsion and prednisolone.

Two months later, the patient was re-admitted with a biopsy-proven Banff IA acute rejection, with complete recovery of graft function after treatment with intravenous methylprednisolone for 3 days. Because the renal biopsy also showed signs of calcineurin inhibitor nephrotoxicity, cyclosporine was converted to sirolimus, and azathioprine was associated with the maintenance therapy.

Seven years after transplantation, a surgical correction of a right testis hydrocoele was performed as well as a reimplantation of the transplant ureter to correct a distal stenosis of the transplant ureter resulting from a presumed ischemic stricture. No histological investigation of this lesion was performed at the time. Analysis of urine cytology showed no malignant cells.

Eleven years after his first transplantation, the patient presented with isolated macroscopic hematuria. An ultrasound of the transplant kidney did not reveal any abnormalities. A CT of the abdomen showed a small polyp in the bladder that was resected through cystoscopy. Histologic examination of the polyp revealed no malignant features. The hematuria resolved, and a control cystoscopy 5 months later was completely normal.

Three months later, however, the patient once again had macroscopic hematuria, this time complicated with an acute renal dysfunction (creatinine, 2.13 mg/dL; eGFR 35, mL/min/1.73 m^2, according to the abbreviated MDRD formula) and heavy pain in the suprapubic region and right iliac fossa. A renal ultrasound revealed a mild hydronephrosis with dilatation of the ureter, starting at the pre-vesical segment. An urgent cystoscopy only visualized a retracted bladder mucosa with a central redness at the tender point in the suprapubic region. An abdominal CT scan, revealed the presence of a mass in the right iliac fossa, probably originating from the ureter implantation site in the bladder, which was in close contact to the urinary bladder and the vascular structures in this region and was invading the rectus muscles.

A nephrostomy was placed, but, after this procedure, a rapidly progressive swelling at the right groin and testis was observed as well as the appearance of multiple skin nodes at the back, head, right arm, and left axillary of the patient. The kidney function deteriorated further.

Histological evaluation of both intravesical biopsies and a Tru-cut biopsy of the mass in the right groin pointed to the presence of a high-grade urothelial carcinoma.

An 18F-fludeoxyglucose–positron emission tomography (18F-FDG PET) scan further illustrated diffuse metastatic disease with invasion of the tumor in the abdominal wall, the urinary bladder, and the right scrotum (Fig 1A).

As the general condition of the patient rapidly deteriorated, the decision was made to perform a radical nephrectomy. The mass in the right testis and groin was not resected. A skin nodule at the back of the patient was

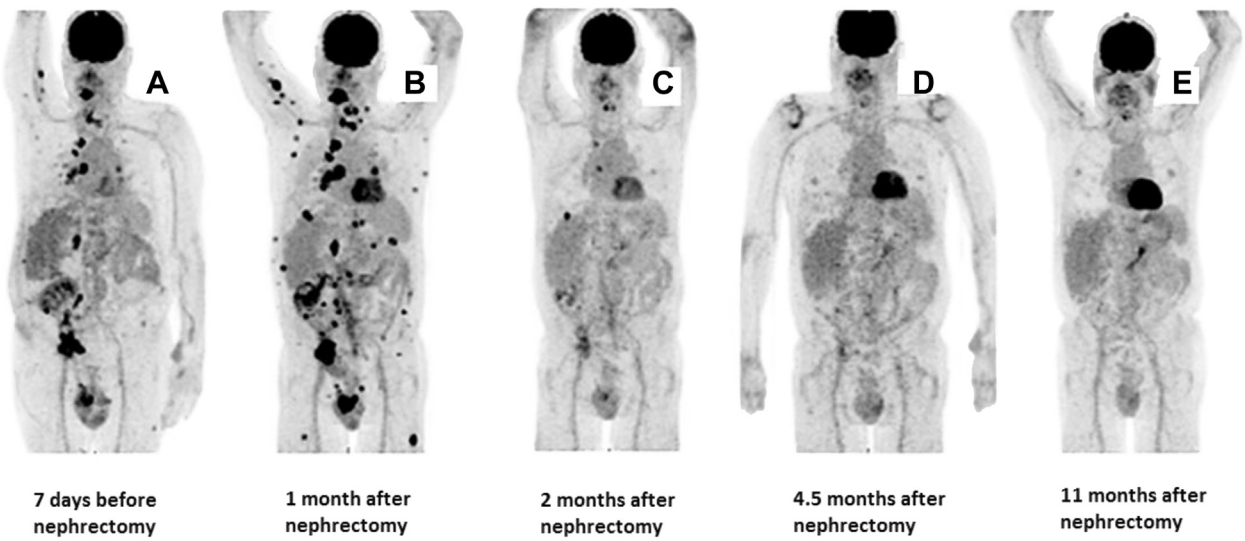

Fig 1. 18F-FDG PET scan over time. (**A**) Diffuse thoracic lymph node metastases (in the peri-cardiac lipoid tissue, at the hilus and mediastinum), multiple lesions in both lungs, and possibly a bone metastasis in the right scapula as well as hot spots in the oropharynx and thyroid gland. (**B**) Expansion of the tumor mass in the thorax, abdomen, upper and lower extremities, oropharynx, and mediastinum. New hot spots are seen in the para-iliac lymph nodes and liver. The mass in the testis and right groin remains stable. (**C**) Globally apparent but uncomplete therapy response with still-active tracer activity in the mediastinum, right liver lobe, adrenal glands, and groin. (**D**) Complete remission. (**E**) No evidence of tumor re-occurrence (special thanks to Maarten Boer for helping with imaging).

removed for oncological staging. On histologic examination, all specimens were invaded by a urothelial carcinoma. Further examination of the kidney graft revealed vascular invasion of the tumor with a secondary infarction of the renal parenchyma.

All immunosuppressive drugs were ceased, and hemodialysis was reinitiated. No additional chemotherapy was implemented, taking into consideration the donor origin of the cancer as well as the poor clinical condition of the patient, who at that point was admitted to the intensive care unit.

A control 18F-FDG PET scan, 1 month after the nephrectomy and after withdrawal of immunosuppression, showed further expansion of the tumor mass (Fig 1B). A clear clinical improvement became only apparent after 2 months, with involution of the testicular and groin mass as well of the skin lesions as confirmed by the 18F-FDG PET scan (Fig 1C).

During the next months, the patient impressively recovered. Four months after transplantectomy, the testis and groin mass as well as the skin lesions disappeared completely at clinical examination, and imaging accounted for a full remission (Fig 1D). The remission was reconfirmed 11 months after nephrectomy and cessation of immunosuppressive treatment (Fig 1E).

Genetic testing of the resected tissues showed overexpression of the female genotype at the chromosomic level. Hence, the unexpected diagnosis of donor-related, diffusely metastasized urothelial carcinoma 12 years after initial first renal transplantation was made.

Eight months after transplant nephrectomy, our patient underwent a second, uncomplicated kidney transplantation. At 3 years after his donor-related urothelial carcinoma, the patient was still alive and in good health. He had no evidence of tumor recurrence. At his latest visit, we observed a good kidney graft function with a serum creatinine level of 1.18 mg/dL (eGFR 53 mL/min/1.73 m^2 according to the abbreviated MDRD formula). His immunosuppression currently consists of cyclosporine, mycophenolate mofetil, and low-dose prednisolone.

Another patient in our center had received the contralateral kidney of the same donor without complications. At 16 years after transplantation, this recipient had a good graft function with a serum creatinine level of 1.55 mg/dL (eGFR, 48 mL/min/1.73 m^2 according to the abbreviated MDRD formula). The recipient of the heart had no donor-related problems.

Case 3: Adenocarcinoma

The third case of donor-related malignancy occurred in a white woman with biopsy-proven nephro-angiosclerosis who underwent a first kidney transplantation in 2012 at the age of 50 years.

The patient received a kidney from a 49-year-old, heart-beating, female donor who had cerebral edema after a cerebrovascular accident. To our knowledge, she had an unremarkable medical history.

In the immediate post-transplantation period, there were no significant complications, but, from the recipient's discharge onward, the kidney was functioning moderately, with a measured GFR of approximately 40 mL/min and under a maintenance immunosuppressive treatment comprising cyclosporine, mycophenolate mofetil, and prednisolone.

Four months after renal transplantation, the patient was admitted to the hospital with an acute renal failure (serum creatinine, 5.99 mg/dL; eGFR, 7 mL/min/1.73 m^2 according to the abbreviated MDRD formula). A renal biopsy was performed and showed normal histology of the kidney without any arguments for acute rejection. Because of the patient's history of persistent flank pain and anorexia, an unenhanced abdominal CT scan was performed. Surprisingly, this exam showed major abnormalities including infiltration of the perinephritic fat surrounding the transplant kidney, a dilatation of the transplant ureter, enlargement of para-aortic lymph nodes, and the presence of several hepatic lesions (Fig 2A). On the basis of this alarming picture, additional imaging with the 18F-FDG PET scan and MRI was performed. Diffuse hotspots were seen on the 18F-FDG PET scan (Fig 2B) and T2-weighted MRI images of the brain, and the spine showed the presence of multiple metastases (Fig 2C).

Blood screening for tumor markers showed increased levels of CA 19.9. Surprisingly, pancreas, liver, and bile enzymes of the patient were within the normal range. It was known that the recipient of the contralateral kidney had metastatic lung disease. Because both transplant recipients showed signs of a diffuse metastatic process, donor cancer origin was assumed. Therefore, immunosuppressive therapy with mycophenolate mofetil and cyclosporine was immediately stopped, and the prednisolone dose was tapered. Hemodialysis was restarted as the serum creatinine level increased to 7.56 mg/dL and uremia was present (213 mg/dL).

Four months after transplantation, the patient underwent a transplant nephrectomy. Macroscopic and microscopic evaluation of the removed donor kidney tissue revealed the presence of massive tumoral invasion in the entire kidney with total loss of renal architecture. Additional immunohistochemical stainings for CK7, CK19, CK20, and Ki67 pointed to the presence of a rapidly proliferating, poorly differentiated adenocarcinoma, probably from intrahepatic bile duct origin. However, no HLA immunohistochemistry was performed because this technique was not available.

As shown in Fig 3, after an initial increase in hotspots on the 18F FDG PET-CT and blood levels of CA 19.9, malignant lesions could no longer be detected on imaging 3 months after transplantectomy. Blood levels of the CA 19.9 decreased progressively to reference values 5 months after transplant nephrectomy. Because of this favorable evolution, no additional treatment with chemotherapy was initiated. However, a total of 5 sessions of radiotherapy, denosumab, calcium, and vitamin D were administered to treat an imminent cord injury.

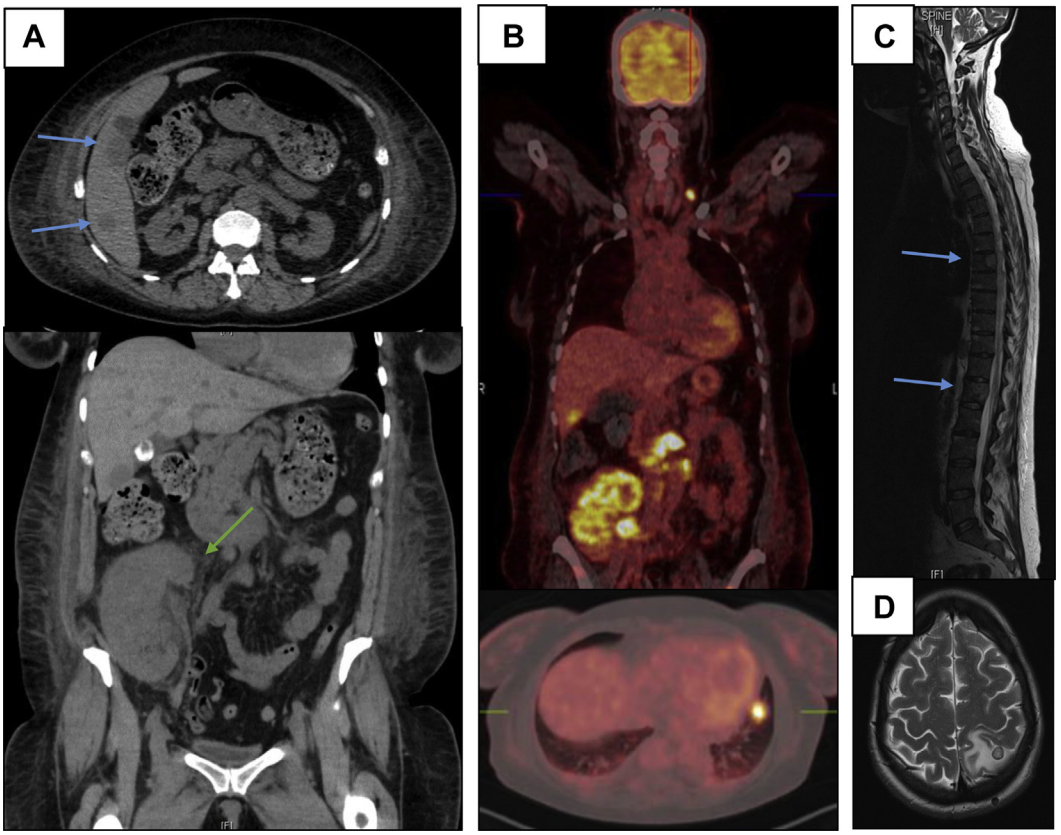

Fig 2. Medical imaging for case 3. (**A**) CT of the abdomen shows two lesions (blue arrows) in segments IV and V of the liver, enlargement of para-aortic lymph nodes, a slightly dilated ureter, and peri-renal fat infiltration of the kidney graft (green arrow). (**B**) 18F-FDG PET scan reveals increased tracer activity of the whole kidney graft and hilus with multiple hot spots in the liver, lung, and lymph nodes (retroperitoneal, left supraclavicular lymph node). (**C**) T2-weighted MRI of the spine shows bone metastases in the vertebral bodies of Th7, Th12, Th11, L1, L2, and L5. The most prominent lesions in Th7 and L1 are marked with blue arrows. (**D**) T2-weighted MRI of the brain shows a 9-mm nodular lesion in the left parietal subcortical region surrounded by vasogenic edema.

Complete tumor remission was confirmed through semi-annual PET scans, and, 1 year after the nephrectomy, the patient was listed for a second renal transplantation.

Twenty months after the transplant nephrectomy, the patient underwent a second renal transplantation. Despite the administration of high doses of induction immunosuppressive agents, there were no complications in the immediate postoperative phase. More than 1 year after this second transplantation, the transplanted kidney was functioning well.

Regarding the first donor of this kidney recipient, there was neither a history of malignancy mentioned in the Eurotransplant donor data nor macroscopic abnormalities during organ procurement registered in the donor quality reports.

Medical information of the other transplant recipients of this donor was retrieved. Besides the kidneys, also heart, liver, and pancreas islets had been transplanted from this donor. Unfortunately, the recipient of the liver died of donor cancer transmission, but the heart and pancreas islet recipients and their grafts still functioned well.

DISCUSSION

Donor-related malignancies are rare and can present in heterogeneous ways, depending on the underlying tumor [3–5,7]. Most donor-transmitted lesions occur within the first years after transplantation [8], whereas donor-derived tumors can develop in the graft only several years after transplantation [2]. We could reproduce this in our small cohort that comprised three donor-related malignancies of a total of 1015 kidney transplantations, accounting for an incidence of donor-related tumors of 0.29%. In our cohort, we equally observed three totally different clinical and pathological presentations with a different time of onset of the malignancy as well as severity of the clinical manifestations. The malignant meningioma of the first case as well as the adenocarcinoma of the third case occurred a few months after transplantation, as opposed to the late presentation of the urothelial carcinoma in the second case. The time line of

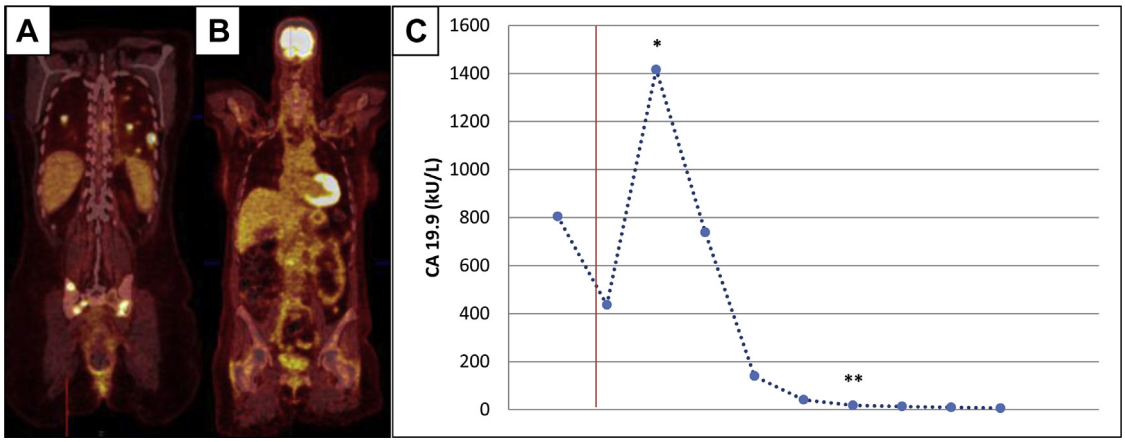

Fig 3. Clinical evolution after nephrectomy. (**A**) 18F-FDG PET image 1 month after transplant nephrectomy shows an increase of hot spots in the lungs, whereas (**B**) all lesions had disappeared 3 months after nephrectomy. (**C**) Blood levels of the tumor marker CA 19.9 increased after transplant nephrectomy (vertical red line) but decreased progressively to reference values (<37 IU/L) (*2 weeks and **5 months after transplant nephrectomy).

occurrence suggests donor-transmitted malignancies in the first and third cases, as opposed to a donor-derived origin of the tumor in the second case. For this latter case, extensive diagnostic work-up and vigilance were required to confirm a donor-derived origin of the tumor.

A common feature of all three cases was the favorable clinical response on withdrawal of immunosuppressive therapy and removal of the kidney graft, aiming at the rejection of the allogeneic tumor by the immune system of the recipient. In our series, additional therapy was given to two of the three patients. In the case of the malignant meningioma, therapy with interferon-α was initiated, aiming at a boost of the immunologic alloreactivity of the recipient [6]. In the case of the adenocarcinoma, radiotherapy and corticosteroids were used as treatment of an imminent cord lesion. In the case of our donor-derived urothelial carcinoma, no additional therapy was given. All three transplant recipients achieved a complete remission and were successfully re-transplanted within 18 months after the diagnosis of the donor-related tumor. All three patients were still alive at 20 years, 4 years, and 1 year, respectively, after re-transplantation, with no signs of oncological relapse after re-initiation of immunosuppressive therapy.

Recent literature shows a worldwide increasing awareness of the unavoidable risk of tumor transmission from donor to recipient, as seen in a number of reports commenting on the incidence rates of transmission (Table 1) [7].

Taking into account the increasing need for donor kidneys (the organ shortage, the increasing transplant waiting lists, and the increase of extended criteria donor donors),

Table 1. Epidemiologic Data on Donor-Related Malignancies

Country	Name Registry	Period	Prevalence of Tumors at Moment of Transplantation	Incidence of Donor Transmission of These Tumors
Spain	ONT Registry	16 years (1990–2006)	58/10,000 (unknown)	2.9/10,000
USA	UNOS Registry	6 years (1994–2000)	4/10,000 (known)	1.3/10,000
USA	OPT/DTAC	3 years (2005–2009)	No data	No data, 9 donor-derived malignancies
Denemark	Danish registry	27 years (not specified)	130/10,000 (total)	20/10,000
Italy	Italian National Transplant Center Registry (CNT)	1 year (2001–2002)	290/10,000 (total) 96/10,000 (unknown)	No data
Italy	Italian National Transplant Center Registry (CNT)	2 years (2006–2008)	0/10,000 (unknown)	No data
USA	IPITTR Registry (optional registry)	7 years (1994–2001)	No data (known)	7700/10,000 if melanoma, 9300/10,000 if choriocarcioma
Germany	MALORY	5 years (2006–2011)	282/10,000 (unknown)	100/10,000 (unknown) 1/10,000 (known)

Epidemiologic data on donor-related malignancies as adapted from the European Guidelines Guide to the Quality and Safety of Organs for Transplantation (5th edition 2013).

more and more guidelines are put forward to help us in the decision of accepting organs form a donor with a known malignancy.

The European guidelines on this topic are quite cautious [7]. As well as other guidelines, they consider as an absolute contraindication the transplantation of an organ from a donor with an active malignancy, lymphatic or distant metastases, or with a certain type of malignancy (including a melanoma or choriocarcinoma) [7]. In contrast, they suggest that a complete remission of 5 to 10 years should be achieved in cases of treated malignancies in the donor's medical history and that any newly diagnosed tumor in the donor should lead to the termination of organ transplantation. [7]. However, the time interval of remission varies between different countries, as well as between tumor types and stages.

The British SaBTO guidelines (Advisory Committee on the Safety of Blood Tissue and Organs) on accepting organs from donors known with malignancies have a slightly different approach to the topic [5]. The recommendation is brought forward that the risks of cancer transmission must be balanced against the risks of dying without transplantation [5]. In addition, these guidelines propose that the decision of acceptance of a risk donor should be made after discussion with peers and after an informed consent is given by the transplant recipient. The risk of cancer transmission is classified in six different categories, ranging from absolute contra-indication to low risk (Table 2) [5].

Table 2. Risk of Cancer Transmission by Known Malignancy in the Donor

Category	Risk of Tumor Transmission	Types of Tumors
Absolute contra-indications	–	Primary cerebral lymphoma
		All secondary cerebral tumors
		Active cancer with spread outside the organ
		Active haematological malignancy
High and intermediate risk	High risk >10%	Melanoma: without spread (except as below)
	Intermediate risk 2%–10%	Breast: cancer other than those identified below
		Colon: cancer other than those identified below
		Kidney: renal cell cancer >7 cm or stages 2–6
		Sarcoma: >5 years previously and resected
		Small cell cancer: lung/neuroendocrine
		Lung cancer: stage I to IV.
		WHO grade 4 tumors and equivalents
Low risk	0.1%–2%	All WHO grade 3 braintumors and equivalents
		Superficial melanoma + curative surgery and cancer free >5 years
		Breast tumors stage 1, hormone receptor negative + curative surgery + tumor free >5 years
		Ovary + curative surgery + >10 years
		Colon adenocarcinoma, cancer free >5 years
		Solitary renal cell carcinoma > 1 cm < 2.5 cm and Fuhrman grade ½
		Prostate Gleason >6
		Treated GI stromal cancers
		Thyroid:
		Solitary papillary carcinoma 0.5–2.0 cm
		Minimally invasive follicular carcinoma 1.0–2.0 cm
Minimal risk	<0.1%	Superficial skin tumors
		Prostate Gleason <6 or >6 with curative treatment + 3 years tumor free
		Uterine/cervix cancer in situ
		Superficial non-invasive papillary carcinoma of the bladder
		Resected solitary renal cell carcinoma <1 cm and Fuhrman grade 1/2
		Thyroid:
		Solitary papillary carcinoma (<0.5 cm)
		Minimally invasive follicular carcinoma (<1.0 cm)

Risk ratings as adapted from the European Guidelines Guide to the Quality and Safety of Organs for Transplantation (5th edition 2013).

A review of the literature in 2014 by Zhang et al [9], an Australian group, formulates comparable recommendations.

Sharing of information concerning reporting cases of donor-related tumors is extremely important in diagnosing and treating the recipients. The guidelines within Eurotransplant follow as of February 2015 the European Union requirements of Directive 2012/25/EU on reporting and handling of serious adverse events and reactions [10]. Taking into account our small series, we clearly observed an improvement of the reporting of donor-related cancers within Eurotransplant, such as more rapid communication of the pathology of the other recipients.

The treatment of donor-related malignancies after a kidney transplantation consists of cessation of immunosuppression and performing a transplantectomy [4,7]. Bruell et al [11], who looked at donor-related malignancies in different types of grafts and compared the survival between the group where explantation of the donor organ was achieved versus no explantation, report a 5-year survival of 59% in the explantation group versus 0% in the non-explantation group. Similar data are seen in the report of Kauffman et al [12] in a retrospective review of renal allografts in which a 2-year survival rate of 75% was seen in the explantation group versus 0% in the non-explantation group. In most of the published cases of donor-related malignancies, additional treatment with chemotherapy or radiotherapy was given. There are some reports in which the cessation of immunosuppression and transplantectomy alone were sufficient enough to eradicate the donor-related cancer [11,12].

There are still no consensus guidelines for the treatment of donor-related malignancies. On the basis of the current case reports and observations in the present cohort, a combination of nephrectomy and the definitive cessation of immunosuppression provides a great chance to achieve complete oncological remission [4,6,7,12,13]. As observed in our cases, patients can be successfully re-transplanted after an episode of donor-related malignancy, although no clear recommendations or guidelines exist on the time interval between the tumor episode and the second transplantation. In our cases, a median of 1 year after oncologic remission was noted.

To reduce the incidence of donor-related cancer transmission, a strict screening of the donor is imperative, especially in the current era of donor shortage and the use of older donors. The European guidelines give several recommendations for prevention of the transmission of tumors, including the acquisition of a complete medical history of the donor, clinical records of previously diagnosed and potentially treated neoplasms, and history of menstrual irregularities in the female donor [7]. Furthermore, an extensive clinical examination of the donor from head to toe and macroscopic organ evaluation during organ procurement are recommended. It is suggested to refuse organs from donors with intracranial hemorrhage with a history of intracranial tumors or metastases and without hypertension or arterio-venous malformations. The screening of tumor markers is only recommended in cases of confirmed malignancy in the history of the donor. The aim was to compare the values at donor assessment with the last known to evaluate the tumor activity. The use of CT scans of the chest and of the abdomen are recommended in the case of history of neoplastic disease [7].

Some authors suggest to perform, if possible, a limited or complete autopsy of the donor and a routine screening of tumor markers, when those are available, to help us diagnose an undiagnosed malignancy of the donor.

In case of detection of a malignancy after transplantation, a donor origin of the cancer must be considered, in addition to a *de novo* cancer in the recipient. If a donor origin of the tumor is likely, immediate reporting is required [7]. In the case of malignancy in the recipient, DNA-based techniques at the time of diagnosis could be used to help guide us in the diagnosis of donor-related malignancies [2,7,8].

When an organ of a high-risk donor is transplanted, a strict follow-up of the recipient is needed.

A nice illustration of the need for guidelines focusing on limiting tumor transmission is the first case in our series, in which a kidney from a patient with a grade II astrocytoma was accepted. However, at the time of diagnosis of donor-related malignancy, the histological findings were revised to malignant meningioma because of the presence of meningeal involvement, which represents an absolute contraindication for transplantation [4,5,7,9]. If that diagnosis had been made while procuring the organ, it would not have been accepted. Yet, again, the other recipients of the same donor did not develop any donor-related malignancies.

CONCLUSIONS

We presented in this report three cases of donor-related tumors diagnosed at our transplant center from 1979 until 2015. Despite the very low incidence, transplant clinicians must consider donor-related cancers if the transplant recipient has a tumoral episode after transplantation. In the case of a donor-related malignancy, adequate treatment should be initiated as discussed above.

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