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Donor Cancer Transmission in Kidney Transplantation

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INTRODUCTION

Despite careful donor selection, cancer transmission remains a rare but dramatic complication of renal transplantation. In the light of a case report, we first review recent evidence regarding the risk of cancer transmission in kidney recipients. Second, we discuss the difficult task of assessing the benefit–risk balance in the decision process of accepting organs from cancer patients.

CASE PRESENTATION

A 53-year-old man started hemodialysis in our center for an unspecified glomerulopathy. He had a history of hepatitis B, arterial hypertension, subclinical hypothyroidism, and hypercholesterolemia. He received a kidney from an unrelated brain-dead donor. Initial immunosuppression at the time of transplantation consisted of anti-interleukin-2 receptor, mycophenolate mofetil, tacrolimus, and corticoids. There was no complication during the immediate postoperative period. The patient was discharged on the eighth postoperative day and plasma creatinine continued to decrease progressively during the follow-up in our outpatient clinic to 1.5 mg/dl. After 100 days, the patient was admitted to the emergency department for rectal bleeding and abdominal discomfort. Plasma creatinine was slightly increased (2.2 mg/dl) as were lactate dehydrogenase levels (463 U/l, normal range <225). Chest radiography revealed multiple opacities suggestive of metastases. The patient was then subjected to an extensive work-up that included colonoscopy, bronchoscopy, full-body positron emission tomography scan, cholangio-magnetic resonance imaging, computed tomography of the abdomen and chest, gastroscopy, and computed tomography of the brain. The colonoscopy did not show any other pathologic lesion than hemorrhoids. CT revealed an infiltration of the renal graft, as well as several lesions in both lungs and adenopathies in multiple sites (mediastinum, retroperitoneum, and femoral) compatible with metastases. Plasma levels of cancer tumor markers were abnormal: carbohydrate antigen 19.9 was elevated (240 N < 19 kU/l) and carcinoembryonic antigen, carbohydrate antigen 125, and beta-HCG (human chorionic gonadotropin) were slightly elevated. Prostate-specific antigen and alpha-fetoprotein were in the normal range. A biopsy of the renal graft was performed 10 days after admission, leading to the histologic diagnosis of a low differentiated adenocarcinoma (Figure 1a). Immunohistologic characterization of the tumor cells showed a positivity for anti-cytokeratin 7 (Figure 1b), whereas other markers were negative (anti-cytokeratin 20, anti-p63, anti-cytokeratin 5.6, anti-thyroid transcription factor 1, anti-ER [estrogen receptor], PR [progesterone receptor], and gross cystic disease fluid protein 15), suggesting a primary tumor of upper gastric, pulmonary, or gynecologic origin.

We were later informed that 2 additional recipients from the same donor (kidney and liver) had also developed cancer. The liver recipient underwent a partial resection of the liver graft after confirmation of cancer lesion, and the second kidney recipient was explanted but already had liver metastases at the time of surgery. Finally, the donor origin of the tumor was confirmed by a caryotype and a polymerase chain reaction amplification of the microsatellite DNA region on the tumoral part of the biopsy (caryotype of the tumor was XX and the recipient was XY; polymerase chain reaction amplification: 79% of cells of donor origin). The patient was explanted,

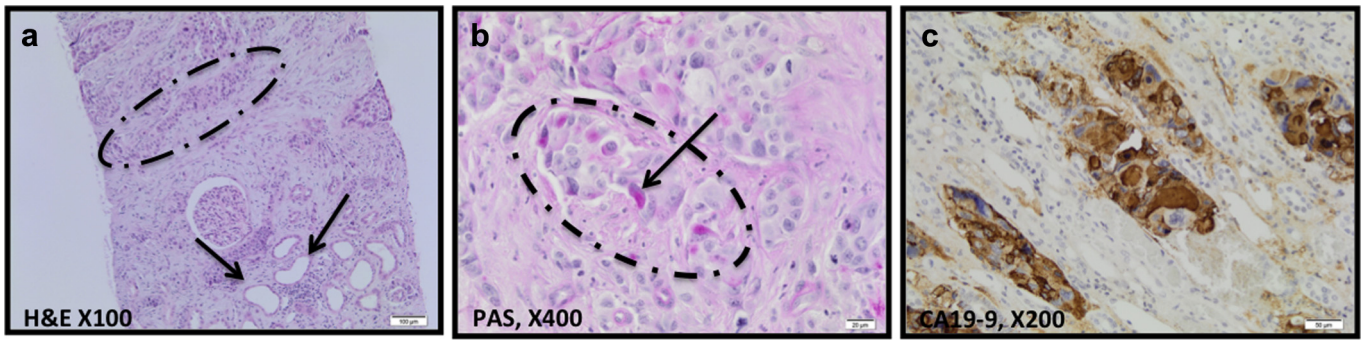

Figure 1. Histologic analysis of the kidney graft. (a) Atrophic tubules (arrows) and tumoral cells (dash-dotted line) are seen at low magnification (×100) on hematoxylin and eosin (H&E) stained section. (b) On high magnification (×400) and with periodic acid-Schiff coloration (PAS), mucine vacuole secretions are obvious (arrow) with tumoral cells (dash-dotted line). (c) On immunohistochemistry, tumoral cells are positive for carbohydrate antigen (CA) 19.9 staining.

immunosuppression was stopped, and iterative hemodialysis was resumed. Additional immunohistologic tests were performed on the surgical piece (Table 1). Chemotherapy consisting of cisplatin in association with 5-fluorouracil was started. After 5 cures of this regimen, positron emission tomography scan and computed tomography of the chest demonstrated a dramatic improvement of the metastatic lesions. Moreover, we observed the apparition of donor-specific anti-human leukocyte antigen antibodies, which had been impossible to detect before transplantation.

Table 1. Immunohistologic characterization of the tumor cells. Additional immunohistologic tests were performed on the graft biopsy and graft explant

Markers	Results
Antibody anti-CK7	+
Antibody anti-CK20	–
Antibody anti-p63	–
Antibody anti-CK5.6	–
Antibody anti-TTF1	–
Antibody anti-ER, PR, GCDFP15	–
Antibody anti-34BE12	+
Antibody anti-AE1-AE3	+
Antibody anti-CA19.9	+
Antibody anti-CA125	Locally +
Antibody anti-calretinin	–
Antibody anti-CEA	+
Antibody anti-cytokeratin 5.6.	–
Antibody anti-cytokeratin 7	+
Antibody anti-cytokeratin 20	–
Antibody anti-cytokeratin 14	Locally +
Antibody anti-cytokeratin 19	+
Antibody anti-EMA	+
Antibody anti-HMB45	–
Antibody anti-inhibin alpha	+
Antibody anti-p63	–
Antibody anti-S100	–
Antibody anti-TTF1	–
Antibody anti-vimentin	–

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; GCDFP, gross cystic disease fluid protein; HMB45, human melanoma black 45; PR, progesterone receptor; TTF, thyroid transcription factor.

Also, the blood level of carbohydrate antigen 19.9 marker had drastically decreased to 55 kU/l. As the evolution and/or patient's reaction proved better than expected, we suspected that the patient's immune system was able to control the disease. We therefore decided to stop chemotherapy and to carefully follow up any further development. Twenty months after chemotherapy was stopped, carbohydrate antigen 19.9 tumor marker remained in the normal range and no sign of cancer progression was found.

DISCUSSION

Inadvertent transmission of tumor remains a rare but dramatic complication in organ transplantation. The current recommendation for treatment of donor-transmitted tumors in kidney transplantation is cessation of immunosuppression, to allow rejection of the allograft and transplanted cancer cells.[1] After rejection has been established, the donor organ is removed. Chemotherapy and/or radiotherapy are usually performed depending on tumor characteristics. However, despite aggressive management prognosis remains poor. The survival rate was recently assessed.[2] Prognosis depends on the extension of cancer at diagnosis, tumor type (eg, 5-year survival rate is less than 30% for a melanoma and more than 70% for a renal carcinoma, respectively) and cancer differentiation. A series of strict donor selection criteria have been fixed to minimize the risk of cancer transmission in this context, thus limiting the number of organs available. However, patients remaining on dialysis also exhibit a bad survival rate. Indeed, according to the UK National Transplant List, up to 6% of patients awaiting kidney transplants die or are withdrawn before a graft becomes available.[3] Fifteen cases of donor-transmitted cancers were recorded in the UK between 2001 and 2010, whereas more than 4000 patients died on the waiting list spanning the same period.[4] Using organs from selected donors with

a history of cancer for transplantation could create an overall benefit in patients' survival. For nephrologists, balancing the risks and benefits in this context would thus inevitably represent an additional challenge. We discuss recently published data and try to highlight the critical points.

According to the literature, approximately 7% of deceased donors suffer from an unknown cancer at the time of organ removal, 60% of which have no apparent contraindication to organ donation.[5] This staggering number contrasts with the low frequency of tumor transmission from donors with no known tumor, which has been estimated at only 0.01% to 0.05% per transplanted organ.[1,6] In addition, only a limited number of cases have been described since the early years of renal transplantation. A recent review that systematically analyzed all case reports, case series, and registry studies reports 104 donor-transmitted cancer cases in which the outcomes of kidney transplant recipients were described.[2] The most common transmitted cancer types were renal cancer (19%), followed by melanoma (17%), lymphoma (14%), and lung cancer (9%).[2] Regarding deceased donors, there is no way to be absolutely sure that a specific donor has no hidden malignancy. One should argue that systematic donor autopsy could minimize risk of transmission. This procedure results in a significant human workload, is expensive, and not always feasible on a systematic basis. In addition, it may skip small malignant lesions. Several risk factors for cancer transmission were identified in donor patients with no known tumor. These factors included donor age above 45 years, the occurrence of nontraumatic cerebral hemorrhage that could mask brain or metastatic tumors and misdiagnosed primary central nervous system (CNS) tumors masking tumor metastases.[6–8] In addition, statistics showed that donors after circulatory death more frequently displayed a history of cancer as compared with donors after brain death (2.3% vs. 1.5%).[9] Donors with a previous history of cancer could represent an important source of organs considering that the risk of cancer transmission may be lower than previously estimated. Indeed, retrospective studies suggest that 1% to 2% of deceased donors have a previous history of cancer.[10,11] An analysis of Organ Procurement and Transplantation Network/United Network for Organ Sharing data identified 1069 donors with a previous cancer history, resulting in 2508 transplants (including 1236 kidneys).[10] Among these were 642 cases with CNS malignancies (including 175 with glioblastoma multiforme), 140 with melanoma, 10 with lung cancers, 51 with lymphoma or leukemia, 38 with colorectal cancers, and 75 with ovarian cancers. Approximately 30% of these patients had a cancer-free interval of less than 5 years. Only 1 donor with a glioblastoma multiforme transmitted fatal tumors to 3 recipients and 1 other donor with a melanoma transmitted his cancer to a single recipient. More recently, a study conducted in the UK among 17,639 donors found that 202 of them (1.1%) had a history of cancer (excluding patients with previous nonmelanoma skin cancer or those with extracranial cancers diagnosed on the day of donation).[9] Among these, 73.8% had a CNS malignancy and 61 had a cancer with an unacceptable or high risk of transmission according to the current guidelines. No cancer transmission was noted in the 133 recipients of these 61 donors. The authors conclude that an additional survival benefit of 944 life-years was gained by transplanting organs from these donors with an unacceptable and/or high risk of cancer 10 years after transplantation. In the same study, data from potential donors between 2009 and 2012 were analyzed, but only 6 of them presented a history of cancer classified as unacceptable and/or high risk with no other contraindication to donation. In another study conducted in the UK between 2003 and 2014, 61 donors with an active or previous history of cancer were identified among a total of 2546 kidney and liver transplantations resulting in 71 transplanted organs for 71 recipients.[12] Among these were 43 donors with CNS malignancy (including 9 with glioblastoma grade IV and 1 with glioblastoma grade III) and 18 with non-CNS malignancies (including 4 recipients transplanted from a donor with a previous history of lymphoma and 3 with a previous history of lung or breast cancer). One kidney recipient developed donor-transmitted lung cancer and one liver transplant recipient developed donor-transmitted lymphoma. In cases where the donor had a history of CNS cancer, contralateral renal cell carcinoma, or ipsilateral resected renal cell carcinoma however, none of the recipients developed cancer. Similar results were found in another study evaluating the risk-benefit ratio in kidney transplantation from a donor with a primary CNS cancer.[13] In this study, 179 donors were identified with a primary intracranial cancer, including 33 with high-grade malignancy (24 with grade IV gliomas and 9 with medulloblastomas). No transmission of malignancy occurred among the 448 recipients of 495 organs transplanted from these donors. Using these data, it was estimated that the use of kidneys from a donor with a primary CNS tumor provides a further 8 years of life compared with a recipient waiting for a donor with no primary CNS tumor.[14] Therefore, the previous assessment of donors with cancer as presenting an unacceptable and/or high risk has been re-evaluated by several authors. Notably, they suggest that selected donors with a previous history of melanoma, breast, ovarian, or colonic

cancer should be considered as donors at acceptable risk.[9] Others suggest that organs from donors with a history of intracranial malignancy, including those with high-grade tumors, should be considered and the balance of risks and benefits should be discussed with the patient accordingly.[13,15]

CONCLUSION

To conclude, it remains obvious that clinicians diagnosing a malignancy after solid organ transplantation that might be donor transmitted need to alert the organization in charge to take appropriate care of other potentially affected recipients.[16] Moreover, confirmation of the same type of cancer in other recipients from the same donor is another clue for donor cancer transmission diagnosis. Besides the mandatory reporting, investigations in related cases could confirm cancer transmission. If this is not the case, a careful surveillance could be considered as an alternative to organ removal. As most cases of transmitted cancer developed during 14 months after transplantation,[16] such screening and follow-up protocols should be designed at least for this critical period on an individual basis and after discussion within a multidisciplinary team. In this perspective, whole-body positron emission tomography scan has been recently reported to successfully detect transmitted lung cancer in an asymptomatic kidney recipient 7 months after donation.[17]

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Myron Kauffman H, McBride MA, Cherikh WS, et al. Transplant tumor registry: donor related malignancies. *Transplantation*. 2002;74:358–362.
2. Xiao D, Craig JC, Chapman JR, et al. Donor cancer transmission in kidney transplantation: a systematic review. *Am J Transplant*. 2013;13:2645–2652.
3. Kidney Activity, 2015. Available at: http://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/kidney_activity.pdf. Accessed August 19, 2015.
4. Lowe D, Daga S, Briggs D, et al. Meeting report: 3rd international transplant conference: how much risk can you take? *Int J Immunogenet*. 2015;42:59–68.
5. Sens MA, Zhou X, Weiland T, et al. Unexpected neoplasia in autopsies: potential implications for tissue and organ safety. *Arch Pathol Lab Med*. 2009;133:1923–1931.
6. Desai R, Collett D, Watson CJ, et al. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation*. 2012;94:1200–1207.
7. Garrido G, Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. *Transplantation*. 2008;85:S61–S63.
8. Buell JF, Gross T, Alloway RR, et al. Central nervous system tumors in donors: misdiagnosis carries a high morbidity and mortality. *Transplant Proc*. 2005;37:583–584.
9. Desai R, Collett D, Watson CJ, et al. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg*. 2014;101:768–774.
10. Kauffman HM, Cherikh WS, McBride MA, et al. Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. *Transplantation*. 2007;84:272–274.
11. Engels EA, Castenson D, Pfeiffer RM, et al. Cancers among US organ donors: a comparison of transplant and cancer registry diagnoses. *Am J Transplant*. 2014;14:1376–1382.
12. Pandanaboyana S, Longbotham D, Hostert L, et al. Transplantation of liver and kidney from donors with malignancy at the time of donation: an experience from a single centre. *Transpl Int*. 2016;29:73–80.
13. Watson CJ, Roberts R, Wright KA, et al. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK Registry data. *Am J Transplant*. 2010;10:1437–1444.
14. Warrens AN, Birch R, Collett D, et al. Advising potential recipients on the use of organs from donors with primary central nervous system tumors. *Transplantation*. 2012;93:348–353.
15. Transplantation of organs from deceased donors with cancer or a history of cancer, 2014. Available at: https://www.gov.uk/government/publications/transplantation-of-organs-from-donors-with-a-history-of-cancer. Accessed September 7, 2016.
16. NOTIFY, exploring vigilance notification for organs, tissues and cells, 2011. Available at: http://www.sohovs.org/soho/file.php/1/NOTIFY_-_report_Part_A.pdf. Accessed August 1, 2013.
17. Jaillard A, Baillet C, Beron A, et al. FDG PET/CT allowing detection and follow-up of tumor cell transplantation. *Ann Nucl Med*. 2016;30:250–254.