

Transmission of Malignancy with Solid Organ Transplants

Christian Morath,^{1,3} Vedat Schwenger,¹ Jan Schmidt,² and Martin Zeier¹

Donor-derived malignancy is found in about 0.02-0.2% of allograft recipients. With an increasing number of older donors, this problem will gain more relevance in the future. We wish to review the current literature on tumor transmission with solid organ transplants and focus on the consequences of an extension of the donor pool, such as by the use of donors with a history of cancer. Finally, suggestions are made for screening regimens for living as well as cadaveric donors to minimize the risk of inadvertent tumor transmission.

Keywords: Tumor, Transmission, Donor derived, Transplantation, Allograft.

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Malignancy after transplantation can develop in three different ways: de novo occurrence (1–5), recurrent malignancy, or donor-derived malignancy in the allograft recipient. This overview will focus on donor-derived malignancies, which have a frequency of about 0.02-0.2% in transplant patients (6,7).

Donor-Derived Malignancies

Transmission of a tumor via (micro)metastases of an undiagnosed malignancy in the donor is rare, but this possibility must also be considered in the differential diagnosis of malignancy after transplantation. From 1968 to 1997, Penn found in 43% of transplant recipients who received their graft from a donor with malignancy evidence of transmitted cancer (8). According to data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (UNOS), a total of 21 donor related malignancies were reported in 108,062 transplant recipients from 1994 to 2001 (incidence of tumor transmission of 0.02%) (6). In this study, 15 tumors were donor transmitted (malignancies that existed in the donor at the time of transplantation; i.e., melanoma, lung carcinoma, small cell carcinoma) and six tumors were donor derived (de novo tumors that developed in transplanted donor cells; i.e., leukemia, PTLD). Mean time from transplantation to tumor diagnosis was 14.2 months and mortality rate among recipients was 38%. From a single center in Denmark, Birkeland and Storm reported on the risk of

tumor transmission with organ allografts from data collected throughout 27 years (1969-1996) (7). They found that 626 donors had 10 carcinoma in situ or dysplasia cervix uteri (nonmalignant) and 13 malignant tumors which were detected in the donor after organ procurement. This resulted in 17 recipients receiving a transplant from a donor with carcinoma in situ or dysplasia cervix uteri and 20 recipients receiving a transplant from a donor with a malignancy. One donor-to-recipient transmission of a melanoma was documented (incidence of tumor transmission of 0.2%). The risk for having a donor with an undetected malignancy was 1.3%. There are several other reports of tumor transmission, of note, in most of these cases malignancy had been identifiable in the allograft and tumor transmission could be directly traced to the transplanted organ (9–14). Two exceptions are leukemia and Kaposi's sarcoma. Bodo et al. described a case of acute promyelocyte leukemia which developed in a recipient of a liver allograft two years after transplantation (15). The leukemic clone bore the genetic and phenotypic markers of the donor. Barozzi et al. reported that donor-derived HHV-8-infected neoplastic cells gave rise to posttransplant Kaposi sarcoma in five of eight renal transplant recipients even when no Kaposi cells could be identified in the allograft (16). An observation from our department outlines that such transmission of isolated malignant cells also occurs with solid tumors (17). We reported on donor-to-recipient transmission of small-cell carcinoma cells with a renal transplant and no macroscopic or microscopic evidence of malignancy in the resected renal allograft.

Donors with a History of Cancer

To overcome the problem of organ shortage, several centers expanded their donor pool, such as by including donors with infectious hepatitis or a history of malignancy. Even patients with active malignancies such as low-grade skin cancer, carcinoma in situ of the cervix uteri, and primary central nervous system (CNS) tumors are considered as potential

¹ Department of Nephrology, University of Heidelberg, Heidelberg, Germany.

² Department of Surgery, University of Heidelberg, Heidelberg, Germany.

³ Address correspondence to: Christian Morath, M.D., Department of Medicine/Division of Nephrology, University of Heidelberg, Im Neuenheimer Feld 162, 69120 Heidelberg, Germany.

E-mail: christian_morath@med.uni-heidelberg.de.

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donors (18,19). For donors with selected tumors (after a cancer-free interval), this seems to be a safe maneuver whereas there are also numerous reports on fatal transmission of malignancy.

Donors with a History of Non-CNS Cancer

In a recent study, Kauffmann et al. (using data from UNOS) studied 14,705 cadaveric organ donors of which 257 had a known past history of cancer (i.e., nonmelanoma skin cancer) (19). A total of 650 organs were procured from the 257 donors. During a mean follow-up of 45 months, no donor derived malignancy was observed. However, there are also reports on donor-to-recipient transmission of malignancy even after a long apparent cancer-free interval of the donor. This is impressively shown in a case report of MacKie et al. (13). The authors reported on transmission of a melanoma from a donor to both recipients of the kidney allografts; one recipient died from metastatic secondary melanoma. The donor had melanoma surgery 16 years before organ donation and was apparently tumor-free during regular follow up. Several reports document that malignant melanoma is representing a common tumor responsible for donor derived post-transplantation malignancy (14,20). Other malignancies which possess a high risk of transmission, even after a long apparent cancer-free interval, include choriocarcinoma, lymphoma, carcinoma of the lung, breast, kidney and colon (19). Therefore, patients with a history of the above mentioned malignancies should be excluded as potential organ donors.

Donors with a History of Central Nervous System Cancer

According to a report from UNOS, a total of 1,220 recipients of organs from 397 donors with a history of CNS malignancy (2 medulloblastoma, 17 glioblastoma multiforme) were analyzed during a 96-month period (21). No donor derived CNS malignancy was observed in the transplant recipients and there was no difference in patient survival between recipients of organs from donors with a CNS tumor compared to recipients of organs from donors without such a tumor during a follow-up of 36 months. Similar observations were made by Chui et al. using the Australian and New Zealand Organ Donation Registry (22). Forty-six patients with primary CNS tumors (4 glioblastoma multiforme, 5 medulloblastoma) served as organ donors for 153 recipients. None of the recipients developed a donor derived CNS malignancy. However, there are also numerous reports on the transmission of CNS malignancy with a fatal outcome. Using the Israel Penn International Transplant Tumor Registry, Buell et al. analyzed the available data from 1970 to 2002 (23). Sixty-two organs were transplanted from 36 organ donors with CNS malignancy (16 astrocytomas, 15 gliomas or glioblastomas, 3 medulloblastomas, 2 cerebellar tumors). Of 25 patients receiving organs from donors with astrocytoma, one patient developed a donor derived astrocytoma. Eight tumor transmissions were identified in 26 patients receiving organs from donors with a glioblastoma (31%) and 3 out of 7 patients receiving organs from donors with medulloblastoma developed donor derived malignancy (43%). The high rate of donor-to-recipient transmission of glioblastoma or medulloblastoma is underlined by the high number of single case reports in the literature (24–26). Recommendations for the

use of organ donors with a history of CNS malignancy were made by a Committee of Experts of the Council of Europe in 1997 (18). Brain tumors were assigned to be of either lowest risk, moderate risk or highest risk for transmission according to their biological behavior. The use of organs from donors with glioblastoma multiforme, medulloblastoma and several other CNS malignancies is not recommended. Patients with malignant CNS tumors and ventriculoperitoneal or ventriculoatrial shunts, prior surgical manipulation of the tumor or radiation chemotherapy should also be excluded as potential organ donors.

Management of the Patient with a Donor Derived Malignancy

In patients with a donor derived malignancy and a kidney transplant, cessation of immunosuppression and (with exceptions) transplant nephrectomy with subsequent return of the patient to regular dialysis represents a substantial part of therapy. In some of these patients, cessation of immunosuppression leads to rejection of the donor derived malignancy by the recovering immune system (6,17). In most patients, however, to induce remission, specific antitumor therapy is necessary, such as surgery, chemotherapy, radiation (6,27). This regimen has considerable impact on the outcome of patients with donor derived malignancy and a kidney allograft compared to recipients of other solid organ transplants (i.e., heart, liver). From 1987 to 2004, eight case reports on CNS malignancy have been published with eleven patients developing a donor derived malignancy. Five of these eleven patients died, including all liver (n=3), heart transplant (n=1) and kidney-pancreas transplant recipients (n=1), while all 6 patients with a kidney transplant survived using the above mentioned regimen (25). Similar results were obtained by Kauffmann et al. in an earlier mentioned study (6). Three out of 8 liver transplant recipients (37.5%) and all heart transplant recipients (n=2, 100%) with donor derived malignancy died, whereas 8 out of 10 (80%) of patients with a kidney allograft and a tumor survived.

When a malignancy inadvertently is transplanted with a solid organ allograft (other than kidney), the regimen is less well defined. Emergency retransplantation was successful in some patients where the malignancy was diagnosed early after transplantation, i.e. at donor autopsy (12). There is also a report where a liver allograft harboring an adenocarcinoma was transplanted. The patient was retransplanted about one year after receiving the first allograft and is doing well on follow-up (28). In this patient, however, the tumor was localized to the liver transplant with no signs of systemic spreading. A report from Lipshutz et al. outlines the possible dramatic consequences of inadvertently transplanted tumors even when they are detected early after transplantation (11). The authors report on a patient who received a liver transplant from a donor who was found to have a large metastasized adenocarcinoma of the lung at autopsy. Despite emergency liver retransplantation within 7 days, the recipient died from metastatic pulmonary adenocarcinoma.

Strategies to Minimize the Risk of Tumor Transmission

Strategies to minimize the risk of tumor transmission with solid organ allografts are clearly indicated in view of an

TABLE 1. Strategies to minimize the risk of tumor transmission

Extensive history (history of malignancy, dangerous life style habits such as smoking)
Examination (scars, pigmented lesions, lymph nodes)
Laboratory investigation (in selected cases β -HCG, PSA)
Chest x-ray, abdominal ultrasound, CT scan in selected cases
Inspection of thoracic and abdominal organs during procurement, prompt biopsy if necessary
Routine autopsy

ageing donor population (for details see Table 1). One approach is the implementation of stringent organ donor screening protocols (18,29). Extensive history and laboratory investigation minimize the risk, however, this is often a difficult task to perform under urgent circumstances associated with cadaveric organ donation. As outlined above, organ donors with a history of cancer and a short cancer-free interval (i.e., less than 10 years, with exceptions) should not be considered for donation. In potential donors with brain hemorrhage of unknown etiology, metastasis as the cause of intracranial bleeding must be excluded, i.e., the serum level of β -HCG should be measured to exclude metastasized choriocarcinoma. Furthermore, several authors demand a thorough inspection of thoracic and abdominal organs as well as lymph node tissue for evidence of neoplasm during organ procurement by the transplant surgeon (6,29). Any suspicious mass should be biopsied and a prompt frozen section be examined. Finally, routine donor autopsy should be performed if possible. From the literature and our own experience, however, we know that less than 50% of donors are subjected to autopsy (7).

CONCLUSION

Donor-to-recipient transmission of cancer is a serious, though fortunately rare, complication of solid organ transplantation. A major task for the future is the reduction of accidentally transmitted tumors while a growing number of donors with advanced age are used. This task can only be achieved with the use of intensified screening procedures in both living and cadaveric donors.

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