Editorial

Transplant International

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Transpl Int (1993) 6: 1–3

Malignancy in transplanted organs

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Received June 18, 1992/Accepted June 24, 1992

"Primum non nocere". The first principle a physician learns is to do no harm. This is particularly important in organ transplantation, where the aim is to avoid transmission of disease, either infection, diseased organs, or cancer to the recipient(s). How well have transplant surgeons succeeded in this last goal? The answer is, surprisingly well. In the last 30 years or so, approximately 150,000 organs have been transplanted. By June 1991, the Cincinnati Transplant Tumor Registry reported that 64 of 142 recipients who had received organs from cadaver donors with malignancies had developed transmitted tumors [9]. Many of these donors had been used in the early era of transplantation, when the danger of transmission of cancer into immunosuppressed patients was not evident. Since then small numbers of cases have been reported [9], as borne out in the paper by Detry et al. [4] in this issue of *Transplant International*. The problem arises mainly when the cause of death of a cadaver donor is misdiagnosed. Cerebral metastases, particularly from choriocarcinomas, carcinomas of the bronchus or kidney, and malignant melanoma, may masquerade as a primary brain tumor or may bleed and mimic hemorrhage from a cerebral aneurysm or arteriovenous malformation. How can the organ procurement team avoid these pitfalls? Careful attention must be paid to the patient's history, such as treatment of a neoplasm in the past, or a history of menstrual irregularities following a pregnancy or abortion. Unfortunately, a detailed history of past illnesses is often not available to physicians caring for a suddenly stricken individual, and previous hospital records may not be available in the few precious hours, often late at night, that are available to procurement teams dealing with hemodynamically unstable donors. Every effort must be made to exclude a metastasis as the cause of intracranial bleeding when the donor has no evidence of hypertension and when no intracranial aneurysm or arteriovenous malformation can be documented. One should be particularly wary with a female donor in the childbearing years, with a history of menstrual irregularities, when a metastatic choriocarcinoma may be the underlying cause [1]. Measurement of beta-human chorionic gonadotropin (beta-HCG) levels is a major safeguard and, perhaps, is advisable in all female donors in the childbearing age group [1]. However, facilities for doing such testing may not be available in community hospitals or the test may not be done at night-time. A blood sample should be taken to the hospital at which the organ procurement team works and should be measured as expeditiously as possible.

Selection of donors is particularly important. Those who have cancer should not be used, with several exceptions: low-grade skin cancers, such as basal cell carcinomas and many squamous cell carcinomas; carcinoma in situ of organs such as the uterine cervix; or primary brain tumors that rarely spread outside the central nervous system [9]. However, one must be certain that brain malignancies originated there because, in some instances, autopsy examination performed after organ retrieval has shown that the apparent brain cancers were actually metastases from occult primary neoplasms [9]. We should also avoid using donors with brain tumors that have been treated with radiotherapy, chemotherapy, ventriculoperitoneal or ventriculoatrial shunts, or extensive craniotomies, as these may open pathways for neoplastic dissemination [6, 9]. If the potential donor has not been treated using any of these procedures, the risk of spontaneous spread of tumors outside the central nervous system is extremely small. Up until 1985, 282 cases of extrarenal spread had been reported in the world literature, only 24 of which had occurred spontaneously [6]. To put this figure in perspective, nearly 12,000 people in the United States alone die of primary brain tumors every year [2]. However, one transplant team had the extremely rare experience of transplanting a liver from a donor with a primary brain tumor that had spontaneously spread to the liver [8]. Although the liver appeared normal at the time of retrieval, the recipient subsequently developed a tumor that spread beyond the allograft and proved to be fatal. The authors advised against using donors with primary brain tumors for liver transplantation [8]. In contrast, another group reported the successful transplantation of

kidneys from a donor with a ventriculoperitoneal shunt [3]. However, this procedure is fraught with risk and the neurological and neurosurgical literature is replete with examples of metastatic spread via systemic shunts [6]. Furthermore, the transplant literature has an example of three patients who received grafts of the kidneys, pancreas, and heart from a donor with a cerebellar medulloblastoma who was treated with a ventriculoatrial shunt and who developed widespread metastases. This proved to be fatal in two of the recipients [7].

A much more difficult decision arises when a donor has a history of cancer treatment in the remote past. Most surgeons would accept a 5-year disease-free interval as evidence of "cure". However, it is well recognized that late metastases may occur from carcinomas of the breast or colon or from malignant melanomas. As Detry et al. [4] emphasize, these may be present as micrometastases at the time of organ retrieval and a diseased organ could be transplanted. The transplant surgeon has to evaluate each donor on an individual basis and weigh the small risk of transplanting cancer with organs from such a donor (none have been reported to date) against the hazard of discarding many potentially usable organs when there is a profound shortage of cadaver organs in most parts of the world.

During organ retrieval, surgeons should carefully examine all accessible intrathoracic and intra-abdominal organs for evidence of tumors. This has occasionally yielded positive findings, particularly with primary renal neoplasms [9], so that a particular organ or that particular donor was not used, as occurred with one donor reported by Detry et al. [4]. Unfortunately, micrometastases cannot be detected, and even macroscopic deposits may be missed if deeply imbedded in a large organ such as the liver or kidney. Detry et al. [4] recommend the use of intraoperative ultrasound to detect hidden macrometastases. Unfortunately, this is not available at most community hospitals. Perhaps, in the future, routine ultrasound examination may become feasible when organs are taken to the recipient hospital (often a university hospital that may have the necessary facilities). However, this test will fail to detect small metastases and micrometastases.

If a suspicious nodule is found while retrieving a kidney, it should be biopsied and a prompt frozen section examination obtained. If cancer is diagnosed, the neoplasm may be widely excised and the kidney transplanted, as was done successfully in several patients [9]. All such recipients must be carefully followed for long periods for signs of recurrence. However, the kidney should not be transplanted if the malignancy is large or excision gives inadequate margins.

Ideally, every cadaver donor should have an autopsy examination performed as expeditiously as possible and before any organs are transplanted, as was done with one of the donors described by Detry et al. [4]. In actual practice, permission for autopsy examination is seldom given, and if an autopsy is performed, this is usually done after the organs have been transplanted. Furthermore, with the pathologists' need to fix the brain in preservative for a week or more, the results of an autopsy are usually not available for several weeks. To complicate matters even further, even when an autopsy is performed at the donor hospital, the results may not be made available to the various recipient hospitals. Therefore, an added onus now falls on the procurement team to check with the donor hospital regarding any untoward autopsy findings.

When a kidney has been transplanted from a cadaver donor in whom a later autopsy reveals a previously unsuspected but widespread cancer, the surgeon should promptly remove the allograft because there is at least a 45% chance that it contains tumor cells [9]. However, the patient may refuse to have the allograft removed, or the surgeon may decide to leave it in situ. In such an event, the patient must be carefully evaluated at frequent intervals. Besides clinical examination, computerized axial tomography or magnetic resonance imaging may be performed and beta-HCG levels measured in cases where the donor had choriocarcinoma. If a transplanted cancer becomes apparent at a later date, the allograft should be removed, immunosuppressive therapy discontinued, and the patient placed on regular dialysis [9]. This gives the immune system a chance to recover and reject residual cancer cells. If necessary, a residual tumor can be treated with radiotherapy, chemotherapy, or immunotherapy with agents such as interferon or interleukin-2. If the tumor undergoes complete remission, further renal transplantation should be delayed until the patient has been free of cancer for at least 1 year [9].

A dilemma arises when a hepatic or cardiac allograft is involved by malignancy [9]. Theoretically, the graft can be removed and replaced with a healthy one. However, this may result in removal of a perfectly healthy organ, and the operation carries with it the risk of significant mortality and morbidity. On the other hand, despite retransplantation, there is a risk that residual cancer cells that have escaped from the first allograft may grow under the heavy immunosuppression necessary to sustain the replacement graft. This risk applies particularly to choriocarcinoma, where malignant cells may rapidly become blood-borne from a transplanted organ [5]. Possible alternatives are to reduce immunosuppressive therapy (risk of rejection); to resect a portion of the liver allograft if the tumor is favorably located; to reduce immunosuppressive therapy and treat the patient with chemotherapy if the neoplasm is likely to respond to such treatment (danger of overimmunosuppression); or, in cardiac allografts, to remove the allograft, stop immunosuppression, place the patient on an artificial heart device, and retransplant at a later date [9].

Fortunately, there has been very little litigation against transplant teams even though they work in a very high-risk arena. However, one's personal experience is that despite the small numbers of inadvertently transmitted malignancies, there has been a disproportionate amount of litigation against transplant teams in this particular area compared to the rest of the field of transplantation.

The essential message of the paper by Detry et al. [4] and of this editorial is, if one may slightly misquote the famous statement made on January 28, 1852 by Wendell Phillips, "Eternal vigilance is the price of life".

Acknowledgement. This work was supported in part by a grant from the Department of Veterans Affairs.

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