OVERVIEW OF THE NEPHROLOGY TRAINING PROGRAM AT DUKE UNIVERSITY MEDICAL CENTER

The nephrology training program at the Duke University School of Medicine provides comprehensive training in clinical nephrology, dialysis, renal transplantation, and hypertension. Fellowship options include a 3-yr clinical investigator pathway, a 3-yr basic science investigator pathway, and a 2-yr clinical training track. Of the 14 fellows completing training over the past 5 yr, 10 have pursued academic careers and 4 have entered private practice.

Each fellow completes a clinical program that includes rotations on three services: the transplant service, the acute nephrology service, and the VA consult service. During the transplant rotation, the fellow is involved in the evaluation of donor and recipient candidates for kidney and simultaneous kidney-pancreas transplant. Posttransplant care is primarily the responsibility of the nephrology division. The acute service provides interventional support to Duke University Medical Center's intensive care units, an inpatient renal ward, and a general renal consultation service. Outpatient activities include the longitudinal management of the fellow's own renal transplant, dialysis, chronic renal failure, and nephrology referral patients.

Clinical facilities include the 1,100-bed Duke University Medical Center and the 450-bed Durham Veterans Affairs Medical Center. The division directs five outpatient dialysis facilities, providing care for over 375 dialysis patients. Active peritoneal and home hemodialysis programs are included. The renal transplant program at Duke averages 70 kidney and simultaneous kidney-pancreas transplants per year. The Duke Hypertension Center provides the opportunity for clinical experience in refractory hypertension. An NIH-supported General Clinical Research Center is often used by the division.

The basic science investigator pathway includes 2 yr of research under the direction of a faculty sponsor. The division currently has a Transplantation Program Project Grant with three faculty members involved. NIH-funded basic science investigation is also ongoing in areas including metabolic bone disease, genetic predisposition for hypertension, signal transduction, and receptor regulation.

Advanced training in biostatistics, study design, and epidemiology (including the opportunity to pursue a Masters of Health Science degree) is available to fellows choosing the clinical investigator pathway. NIH- and industry-funded trials in the dietary modification of hypertension, morbidity and mortality in dialysis patients, hemodialysis vascular access, and cardiovascular disease in patients with renal failure are ongoing.

The straight clinical pathway includes 18 months of intensive clinical training that encompasses all areas of nephrology including the management of outpatient hemodialysis and significant outpatient transplant and hypertension experience with a brief exposure to clinical research. In addition, structured exposures to renal pathology and histocompatibility are available.

Transmission of Cancer With Cadaveric Donor Organs[1]

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ABSTRACT

A case is presented in which each of the recipients of a pair of cadaveric kidneys developed metastatic carcinoma. One of the recipients died, and the other demonstrated involution of metastatic deposits after graft nephrectomy and withdrawal of immunosuppression. By the use of polymerase chain reaction of minisatellite regions of donor and recipient DNA, the donor origin of the tumor was conclusively demonstrated. Although a relatively uncommon complication of cadaveric renal transplantation, the transmission of cancer with cadaveric organs may become

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more frequent as older donors are accepted for organ donation.

Key Words: *Renal transplant, transplated cancer*

It was not long after the dawn of the transplantation era that the problem of the transmission of malignancy from donors to recipients was recognized as a major problem. Since this first report by McPhaul and McIntosh (1) in 1965, more than 150 cases of donor-transmitted malignancy have been reported. A case of malignancy transmitted with each of a pair of cadaveric kidneys from the same donor is presented, the literature is reviewed, and suggestions are made on how the frequency of this devastating result of cadaveric transplantation might be lowered.

CASE REPORT

A 30-yr-old white man with end-stage diabetic nephropathy underwent cadaveric renal transplantation of a six antigen–matched kidney at Duke University Medical Center after 2 yr on peritoneal dialysis. He was initially treated with triple immunosuppression consisting of cyclosporine, azathioprine, and prednisone. No induction antilymphocyte preparation was used. The kidney functioned immediately, and he was discharged with a creatinine level of 2.1 mg/dL. His initial posttransplant course was complicated by two biopsy-confirmed episodes of acute cellular rejection, for which he received a total of nine daily pulses of 500 mg of methylprednisolone and one 10-day course of OKT3, 5 mg/day. He also subsequently developed a fever associated with cytomegalovirus seroconversion, for which he was treated with a 10-day course of ganciclovir. Over the subsequent 7 months, he developed slowly deteriorating renal transplant function. A transplant biopsy performed 9 months after transplantation demonstrated marked interstitial fibrosis and arteriolar thickening. There was no evidence of malignancy in any of the transplant biopsies.

Eleven months after transplantation, he developed shortness of breath and pain over the transplanted kidney. The serum creatinine was 4.8 mg/dL, and a chest x-ray demonstrated a reticulonodular pattern (Figure 1A). Pulmonary function tests demonstrated a restrictive pattern with a diffusing capacity of 35% of predicted. With the patient breathing room air, the arterial Po_2 was 53 mm Hg and the Pco_2 was 25 mm Hg. Bronchoscopy showed a grossly normal endobronchial tree; however, four out of four transbronchial biopsies demonstrated poorly differentiated non-small cell carcinoma with some squamous characteristics (Figure 2A). A computed tomography scan of the chest, abdomen, and pelvis demonstrated reticular/nodular parenchymal lung lesions, but no mediastinal adenopathy. There were mildly enlarged periaortic nodes, and the transplanted kidney was enlarged. A bone scan and brain magnetic resonance imaging scans were negative for metastatic disease. A transplant nephrectomy was performed, and immunosuppression was discontinued. A histologic examination of the excised transplanted kidney demon-

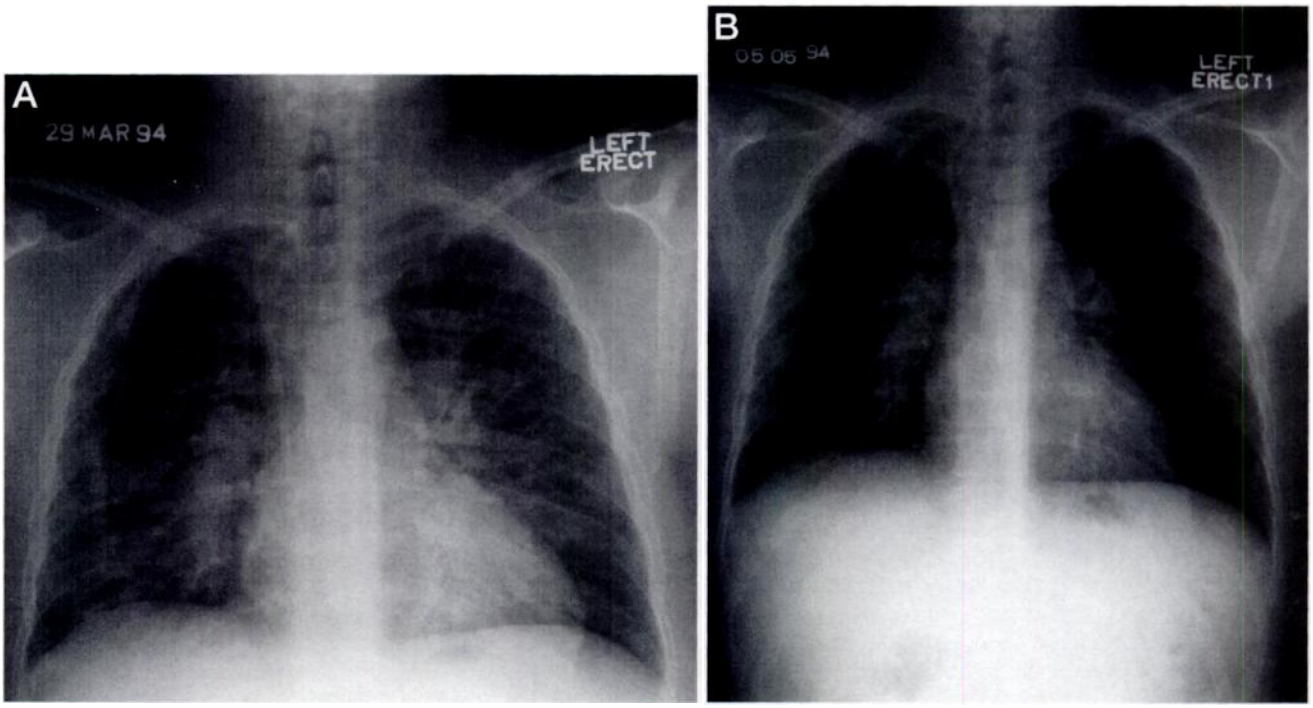

Figure 1. (A) Chest radiograph of Recipient A on presentation with dyspnea showing an interstitial reticulonodular pattern; (B) repeat radiograph 6 wk after transplant nephrectomy and the cessation of immunosuppressive therapy.

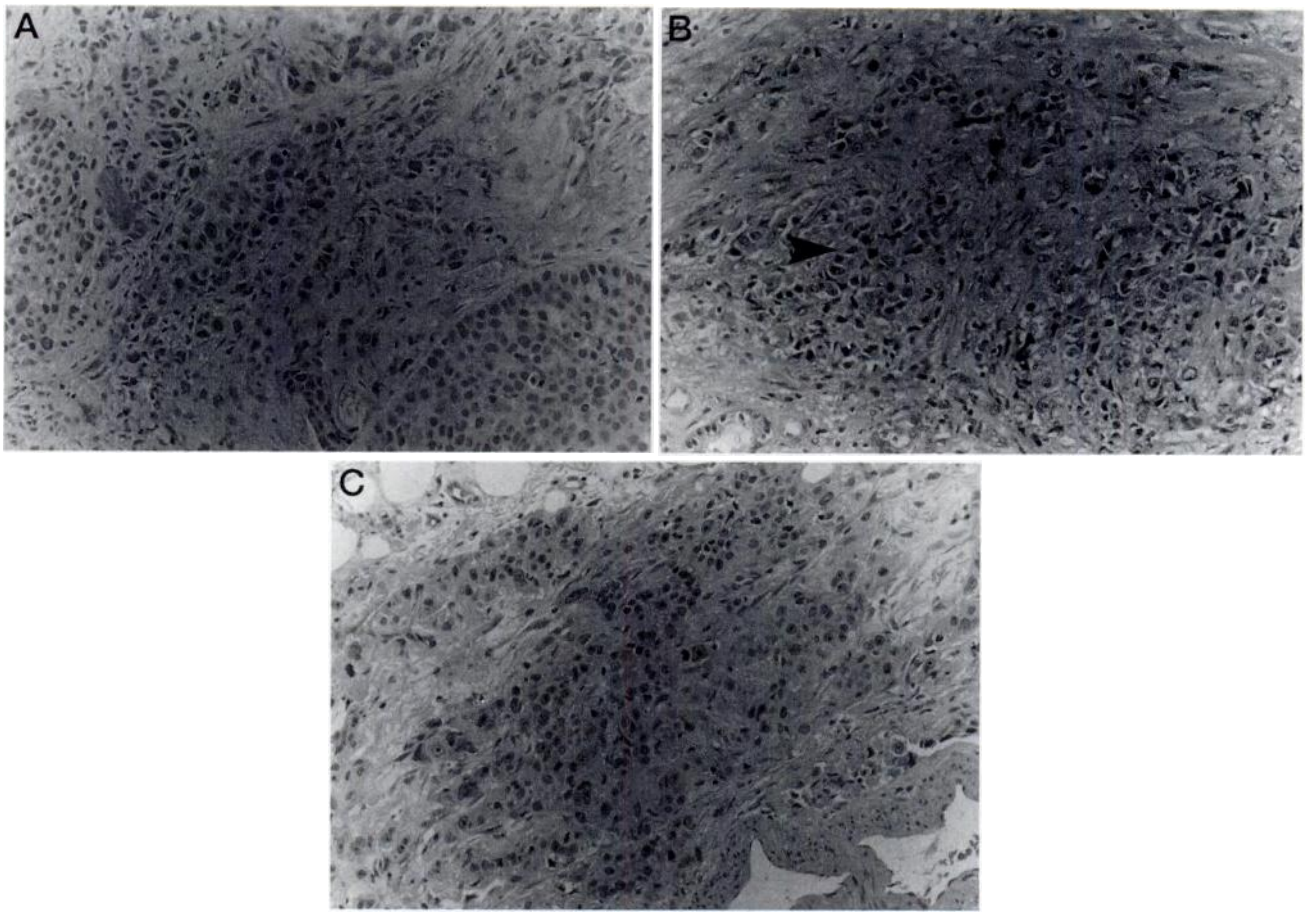

Figure 2. Photomicrograph (original magnification, ×250) of tissue obtained from: (A) transbronchial biopsy, Recipient A; (B) graft nephrectomy, Recipient A. Arrowhead demonstrates areas of tumor with similar appearance to transbronchial biopsy; (C) Tumor biopsy, Recipient B.

strated tumor present in small to medium-sized nests throughout the kidney, mainly in lymphatics and in areas adjacent to arteries. The tumor was quite pleomorphic (Figure 2B) in its appearance; some tumor nodules had a clear cell pattern, but the majority of the tumor was composed of poorly differentiated carcinoma and some areas had an appearance similar to that of the malignant cells from the transbronchial biopsies. By 6 wk after transplant nephrectomy, the dyspnea was markedly improved and the chest x-ray showed resolution of the interstitial changes (Figure 1B). He is now 6 months after transplant nephrectomy and has shown no evidence of recurrence of tumor. He continues to have a reduced diffusing capacity at 48% of predicted and a restrictive pattern on pulmonary function testing.

The kidney donor was a 64-yr-old man who was declared brain dead after an apparently spontaneous intracranial hemorrhage. Apart from some evidence of chronic obstructive airways disease, he had been in good health before his sudden death. A portable chest x-ray taken in the intensive care unit while the patient was on a ventilator showed bullous changes in the right lung, but no evidence of a mass lesion. At the time of organ harvesting, the kidneys appeared normal and there was no indication of any intra-abdominal malignancy. A subcapsular biopsy of the kidney at the time of transplantation surgery demonstrated changes of arterionephrosclerosis only. No autopsy was performed. The other kidney from the same donor was transplanted into a female recipient at another hospital (Recipient B). A needle biopsy of this graft performed because of a rise in creatinine 10 months after transplantation revealed malignant cells. A larger subsequent biopsy (Figure 2C) of the tumor was sent for karyotyping to determine if it was of donor or recipient origin. Karyotyping of this larger biopsy suggested that the tumor contained female cell types and, thus, was of recipient origin. In retrospect, the surgeon who performed the procedure noted that the tumor tissue was surrounded by fat and omental tissue, and thus, the sample that was karyotyped may have contained this uninvolved recipient tissue. The patient declined either graft nephrectomy or chemotherapy and died of metastatic carcinoma a few weeks later.

In order to confirm that the malignant tumor in our patient arose from the donor, we performed DNA "fingerprinting" on tissue taken from: the tumor in the transplanted graft in our patient (Recipient A), the cortex of the graft transplanted into Recipient A, a transbronchial biopsy of Recipient A, and peripheral blood of Recipient A. DNA was extracted, and six microsatellite loci were amplified by the polymerase chain reaction (PCR) in the presence of [^{32}P]dCTP, with primers obtained from Research Genetics, Inc. (Huntsville, AL). The PCR products were electrophoresed on 6% polyacrylamide–7.7 M urea gels. The dried gel was exposed to x-ray film for 16 h. The microsatellite loci are highly polymorphic, with genetic variability in the number of tandem repeats. Thus, DNA obtained from different individuals will yield PCR amplification products of different sizes. Analysis of multiple microsatellite loci produces a distinctive pattern of bands (corresponding to the varying sizes of DNA fragments) that can be used as a "DNA fingerprint" to distinguish individual samples. A comparison of the tumor DNA fingerprint with that of the recipient's lymphocyte DNA (Figure 3) allowed the unequivocal determination that the tumor was of donor origin.

Figure 3. DNA fingerprint analysis comparing: B, peripheral blood lymphocytes from Recipient A; C, cortex of transplanted kidney not involved with tumor; T, tumor from transplanted kidney; L, malignant cells from transbronchial lung biopsy. Tumor samples and kidney cortex show distinct differences from recipient blood lymphocytes, confirming that the tumor arose from the donor.

DISCUSSION

In this report, we have described the transmission of cancer from an apparently healthy organ donor to two recipients of renal transplants with devastating results for both recipients. Although the organ donor did not have an autopsy, with the use of DNA fingerprinting technology, we have been able to demonstrate unequivocally that the tumor arose from the organ donor, and we suspect arose from metastatic bronchial carcinoma. The recipient of one of the grafts was able to recover from histologically documented widespread metastatic cancer with withdrawal of immunosuppression and transplant nephrectomy.

The transmission of cancer from a donor to the recipient of a cadaveric organ is a catastrophic result of transplantation. In the early days of cadaveric transplantation, it was not uncommon for the organs of donors who died of cerebral metastases to be used for transplantation. After a series of reports of the development of metastatic cancer in the recipients of these organs (2), the use of organs from donors with recognized malignant disease was abandoned. Nonetheless, despite the modern practice of the exclusion of donors known to carry malignancy, there continue to be reports of unrecognized tumors in the donor being transmitted to graft recipients (3,4). A transplanted organ can transfer malignancy to the recipient in one of three ways. An unrecognized primary renal cell carcinoma in the graft may be transplanted. This appears to be the least common mode of transmission, perhaps because these tumors can often be recognized at the time of organ harvest. Second, the transplanted kidney may contain metastatic cells from a distant primary tumor that may subsequently metastasize further in the organ recipient, as was the case in the patients presented here. Table 1 summarizes the primary malignancies that have been reported to be transmitted with organ transplants. Third, the trans-

TABLE 1. Primary malignancies that have been reported by Penn to be transmitted with cadaveric organs (23)

Lung
Breast Carcinoma
Colorectal Carcinoma
Cutaneous Malignant Melanoma
Lymphoma
Bronchial Carcinoma
Renal Carcinoma
Choriocarcinoma
Glioma
Hepatocellular Carcinoma

planted organ may contain passenger leukocytes that may have already undergone malignant change or subsequently undergo malignant change to form a malignant lymphoma.

In 1926, Bailey and Cushing reported that primary central nervous system (CNS) malignancies never give rise to extracranial metastasis (5). Consequently, when clinical transplantation began, patients who died of primary CNS malignancies were considered suitable candidates for organ donation. Subsequently, it became apparent that primary CNS malignancies can rarely metastasize with an estimated frequency of between 0.4 and 2.3% (6,7). Although donors with primary brain tumors comprise up to 7% of the organ donors in some series, there have been only four reports of the development of a metastasis from a primary brain tumor in allograft recipients (8–11). Factors that traditionally have been associated with an increased risk of extraneural spread include a high grade of malignancy, a history of craniotomy, ventriculosystemic drainage, and a long duration of disease. Medulloblastoma and glioblastoma multiforme tumors together represent the vast majority of tumors that spread outside the CNS. Although there are anecdotal reports suggesting that ventriculoperitoneal shunting may increase the risk of extracranial metastasis, a recent review of 415 children with malignant CNS tumors found no difference in the occurrence of extracranial metastasis between children with or without a previous shunting procedure. Of the four previous cases of donor-transmitted CNS malignancy, three occurred in the absence of a shunt. Currently, the United Network for Organ Sharing (UNOS) standards exclude potential donors who died of a primary CNS malignancy if they have undergone a previous shunting procedure. Given the rarity of transmission of malignancy from patients with histologically confirmed primary CNS malignancies, it may be inappropriate to exclude these donors, whether or not they have had a shunting procedure previously.

It is important that donors with a suspected primary intracerebral neoplasm have a histologic diagnosis before organ donation because there are a number of case reports of tumors with the radiologic appearance of a primary brain tumor that later prove to be a metastatic deposit of a different primary tumor (12). Similarly, cases have been reported in which the donor died of what appeared to have been a spontaneous intracerebral hemorrhage that, on subsequent autopsy after the organs had been transplanted, turned out to be a hemorrhage into a cerebral metastasis (13,14). Choriocarcinoma with cerebral metastasis has been mistaken for a primary intracerebral hemorrhage, with the subsequent transmission of choriocarcinoma to organ recipients (15,16).

Renal transplantation is associated with the transfer of biologically active B lymphocytes, as demonstrated by cases of hemolytic anemia resulting from the production of antibodies against recipient blood group antigens by "passenger" lymphocytes from the donor. Recently, Starzl et al. have demonstrated the presence of donor-derived cells in skin and lymph node tissue more than 29 yr after patients received an allograft (17). It is well established that transplant recipients are at increased risk for the development of malignant lymphomas. HLA typing and DNA fingerprinting of tumor cells have been able to demonstrate that a number of these malignant lymphomas arise from lymphocytes derived from the organ donor (18–21). Just as the immunosuppressed state can induce recipient lymphocytes to undergo malignant transformation, so also can they similarly influence donor lymphocytes. Between 15 and 30% of lymphomas that occur after renal transplantation occur in the allograft itself; it is possible that many of these are derived from the donor (22).

The outcome of patients who receive a transplanted malignancy is not entirely clear. Penn has reported the development of malignancy in 78 (45%) of 142 patients who received a cadaveric graft from a donor who was subsequently found to have had a malignancy (23). The tumor was confined to the graft or surrounding tissue in 28 cases and became metastatic in 36. Figure 4 summarizes the experience in these 36 patients. Sixteen patients died without having received chemotherapy or discontinuance of immunosuppression. In the case of the 20 patients who had withdrawal of immunosuppression and or graft nephrectomy, 10 patients died of metastatic cancer, 9 went into complete remission, and 1 was alive at the time of the report with evidence of cancer. In addition to Penn's report, there are several case reports of the resolution of metastatic disease associated with the normalization of the patients' immune mechanisms by either cessation or reduction in immunosuppression and/or removal of the transplanted graft (24,25). How frequently a metastatic tumor will resolve after the discontinuation of immunosuppression is unclear, because undoubtedly, cases in which a good result is obtained from the cessation of immunosuppression are more likely to be reported. It has been apparent for more than 30 yr that when malignant cells are transplanted into nonimmunosuppressed subjects, they are frequently rejected completely (26). When, however, they are transplanted into an immu-

TABLE 2. Recommendations to reduce the occurrence of donor-transmitted malignancy

Exclude donors with known history of malignancy except histologically confirmed primary cerebral neoplasms and low-grade skin carcinoma.
Exclude women of child-bearing age who die of apparently spontaneous intracerebral hemorrhage if β-HCG is elevated, unless pregnancy can be confirmed by ultrasound.
Meticulous examination of abdominal viscera and lungs at the time of organ harvest with frozen section histology of any suspicious tissue.
Mandatory postmortem examination of older donors.

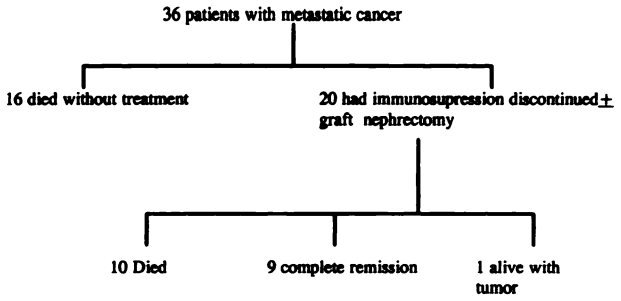

Figure 4. Outcome of 36 renal transplant recipients who developed metastatic cancer of donor origin, as reported by Penn (23).

nosuppressed patient, the tumor cells divide and spread rapidly. It has been suggested that if the donor and recipient are mismatched for HLA loci, the recipient is more likely to recover than if the graft is well matched, because there will be a more vigorous immunologic rejection of the transplanted malignancy (13). There are no clear guidelines on the use of chemotherapy or radiotherapy in this patient population. Although the discontinuation of immunosuppression and graft nephrectomy can frequently be achieved in a renal graft recipient, the situation is much more difficult with heart or liver graft recipients.

In modern practice, a single donor can provide organ tissue for as many as six different recipients, each of which could be potentially infected with malignant cells. Because older donors are increasingly being accepted for organ donation, it is to be expected that an increased number of clinically occult malignancies will be transplanted from them. It is essential therefore to intensify efforts to exclude patients with malignancy from the donor pool.

Penn and others (Table 2) have made a number of important recommendations to reduce the frequency of donor-transmitted malignancy (3,4,23). Patients with a history of any malignancy other than primary cerebral malignancies or low-grade cutaneous malignancy should be excluded. At the time of organ harvest, a rigorous laparotomy should be performed with meticulous abdominal examination and lung examination. A compulsory necropsy with frozen section examination of any suspicious tissue should be available within 24 h of death on older donors. Most potentially malignant tissue should be identified on gross examination of the organs. Even if an occult neoplasm is not discovered until some days later, when the paraffin-embedded tissues are examined histologically, this is important information for the clinician treating the transplant recipient. The harvesting team needs to be particularly suspicious of older donors and young women of child-bearing age who died of an apparently spontaneous intracerebral hemorrhage. When angiographic studies do not demonstrate a vascular malformation, every effort should be made to exclude a metastasis by screening ultrasound examinations of the abdominal organs and assay of human chorionic gonadotrophin (β-HCG) to exclude the possibility of metastatic chorionic carcinoma or other occult malignancies. Currently, UNOS does not require an autopsy on organ donors, nor does it keep data on the number of donors who subsequently have an autopsy, so it is difficult to judge what proportion of organ donors would be excluded if an autopsy was a mandatory requirement. When a kidney is transplanted from a cadaver donor in whom a later autopsy reveals a previously unsuspected cancer, the allograft should be promptly removed and immunosuppression should be discontinued, because registry data suggest that there is a greater than 45% chance that it contains tumor cells that will metastasize (23). If the patient refuses graft nephrectomy or it is technically impossible, close follow-up with appropriate radiologic investigations is necessary. If a tumor is subsequently discovered, the graft should be excised.

Twenty-nine years ago, McPhaul and McIntosh (1) wrote "Renal transplantation is an experiment in human immunology undertaken with the best interest of moribund patients in mind. That this experiment may have consequences far beyond technical hazards, personal discomfort and economic extravagance is quite clear." This statement has some truth even today. Only through careful selection of organ donors can this unexpected consequence of organ transplantation be minimized.

NOTE ADDED IN PROOF

Twelve months after transplant nephrectomy, Recipient A was found to have an isolated bony metastasis in the right acetabalum. He was treated with external beam radiation and is currently receiving therapy with interleukan-2, 14 months posttransplant nephrectomy.

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