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OCCULT NONHEMATOPOIETIC MALIGNANCIES PRESENT AT AUTOPSY IN SOLID ORGAN TRANSPLANT PATIENTS WHO DIED WITHIN 100 DAYS

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Background. **Patients are at an increased risk for developing malignancies after transplantation. Lymphomas, skin malignancies, Kaposi's sarcomas, and cervical/vulvar neoplasms are the most common, but visceral malignancies are also well documented, with a reported frequency ranging from 1% to 6%. These visceral tumors represent a mix of neoplasms that were clinically occult at the time of transplantation and those that arise de novo after transplantation. Little information, however, is available on the frequency of clinically occult malignancies at the time of transplantation and their contribution to the number of posttransplant malignancies.**

Methods. **A retrospective study was performed of all patients who received an organ transplant from January 1981 to June 1997 and died within 100 days, a time interval in which epithelial malignancies found at autopsy were presumed to have been present, but clinically occult, at the time of transplantation.**

Results. **A total of 375 patients were studied who received the following organ transplants: 231 liver, 52 heart, 26 heart and lung, 32 lung, and 34 kidney. Eleven malignancies were identified for an overall frequency of 2.9% and included three thyroid carcinomas, three carcinoids of the small bowel, two lung carcinomas, one laryngeal carcinoma, one renal cell carcinoma, and one seminoma.**

Conclusion. **The 2.9% frequency of malignancies seen in this study suggests that a small, but significant, number of patients have occult malignancies at the time of transplantation and that these occult tumors contribute substantially to the number of malignancies that present clinically after transplantation.**

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Malignancies after transplantation have been well described, with approximately two-thirds being lymphomas, skin malignancies, Kaposi's sarcomas, or cervical/vulvar neoplasms (*1*). The remaining third of the malignancies consist mostly of the types of neoplasms that are typically seen in the general adult population such as lung, prostate, colon, and breast carcinomas. Although the occurrence of visceral malignancies after transplantation is well documented, the extent of the risk remains unclear. Several studies have shown no increased risk (*2*, *3*), whereas others have shown an elevated risk above that of age-matched controls for carcinomas in general (*4*, *5*), as well as for specific carcinomas, such as oropharyngeal carcinomas (*6*), lung carcinomas (*6*), and bladder carcinomas (*7*). In addition, specific subpopulations may be at increased risk for certain tumors, such as renal carcinoma in renal transplant patients (*8*, *9*) and colon cancer in patients with inflammatory bowel disease (*10*). The contribution of immunosuppression as a pathogenic factor for these types of tumors remains unsettled, as these malignancies are likely to represent a combination of preexisting, occult tumors and de novo posttransplant tumors. Several clinical follow-up studies have attempted to address the issue of occult malignancies present at the time of transplantation by excluding patients who developed malignancies within a short period of time and have used time intervals that ranged from 30 days to 1 year (*4*, *11–14*). However, the true frequency of occult malignancies present at the time of transplantation remains unknown. The goal of this study was to determine the frequency and types of tumors that were present, but clinically occult, at the time of transplantation by examining autopsied patients who died shortly after transplantation with insufficient time to develop de novo epithelial malignancies. The results were compared to (1) a control group of nontransplant patients from the same hospital population and (2) the results of clinical follow-up studies from the literature, including reports from this institution.

PATIENTS AND METHODS

Autopsies were performed using the en masse ("Rokitansky") method, and sections were typically examined from all organ systems with additional sections examined depending on the clinical history and anatomic findings. A tumor was considered clinically occult if it was not diagnosed before death. In a few cases (four nontransplant control patients), tumors were strongly suspected clinically but an actual diagnosis was not made because of the patient's rapid demise; these cases were not considered as occult tumors. Only unequivocally malignant tumors were included in calculating the frequency of occult malignancies. Benign neoplasms, e.g., tubular adenomas of the colon, were not included. Occult neoplasms identified in explants were also excluded from this study. Finally, hematopoietic neoplasms, including posttransplant lymphoproliferative disorders, were excluded in order to focus on epithelial malignancies.

This study included all adult solid organ transplant patients at the University of Pittsburgh Medical Center who died within 100 days of their organ transplant and underwent postmortem examination during the 17-year time period from January 1, 1981 to January 1, 1998. Only autopsies with complete examination of the thorax and abdomen (n=375) were included in the study. In most of these cases, the neck organs were also examined (86%). A total of 52 patients were excluded because of autopsy limitations: 21 liver transplant patients, 15 heart transplant patients, 7 heart-lung transplant patients, 8 lung transplant patients, and 1 kidney transplant patient. Bone marrow transplant patients (n=50) were also excluded from the study. However, it is of interest to note that two of these bone marrow transplant patients had occult neoplasms including a thyroid carcinoma in a 61-year-old man who died on day 90 after transplantation and a clear cell renal carcinoma in a 74-year-old man who died on day 88 after transplantation. Although lymphomas are also not included in this study, one liver transplant patient, who died within less than 24 hr of transplantation, had a B-cell lymphoma.

Nontransplant autopsied patients were used as a control group to determine the frequency and type of occult malignancies present at the time of death in the University of Pittsburgh Medical Center hospital-based population. All autopsy reports were reviewed from the odd-numbered years, 1983 through 1997. The autopsies were performed in the same manner as for the transplant patients. Brain-only autopsies (n=162) were excluded, most of which were performed as part of a research protocol on Alzheimer's disease. Also excluded were autopsies with restrictions that did not permit full examination of the thoracic and abdominal organ systems (n=139), leaving a total of 1299 cases for study.

Mean ages of the various groups were examined by analysis of variance with post hoc Bonferroni tests used to compare each possible pair combination. The expected frequency of occult malignancies in the transplant population was calculated based on the frequencies of malignancies in the nontransplant patient population from the University of Pittsburgh Medical Center using 10-year intervals. Proportions were compared using chi-square tests. All statistical analysis was performed using SYSTAT, version 6.0.

RESULTS

The nontransplant patients included 758 males and 541 females with an average age at death of 59±16 (mean±SD) years. Most nontransplant patients were Caucasian (87%) and there was no significant difference in age at death between Caucasians and non-Caucasians (mostly African-American [94%], $P=0.91$). The control group had a lower frequency of Caucasians than the transplant group (87% vs. 93%, $P=0.007$). However, within the control group, the frequency of malignancies did not differ between Caucasians and non-Caucasians ($P=0.53$), and no corrections for race were made in subsequent analyses.

A total of 6.9% (n=90) of the nontransplant control patients had 93 occult malignancies that were present in 66 men and 24 women. Three individuals had two carcinomas each, including two males with both prostate and thyroid carcinomas and one male with a lung and thyroid carcinoma. Control patients with occult neoplasms were significantly older than control patients without neoplasms: 66±12 years for those with occult neoplasms and 58±17 years for those without tumors ($P=0.0001$). The types of neoplasms are shown in Table 1 and can be compared with the number and types of neoplasms seen in transplant patients who died within 100 days and with the number and type of clinically observed posttransplant neoplasms reported from the University of Pittsburgh. For the nontransplant hospital controls, prostate carcinomas made up a large percentage of the occult tumors (30%). Of the gastrointestinal neoplasms, 12 were adenocarcinomas, and 7 were carcinoids of the small bowel. Seven of the eight pancreatic carcinomas were islet cell tumors, and one was an adenocarcinoma.

For the transplant patients, a total of 375 autopsies were performed on 217 men and 158 women who received transplants and died within 100 days. The average age at death was 46 years. Additional demographics are shown in Table 2.

TABLE 1. Comparison of occult malignancies and clinical malignancies from the same institution

Tumor	Occult malignancies in transplant patients in this study (n)	Occult malignancies in hospital control patients in this study (n)	Malignancies in 2265 patients clinical follow-up studies from UPMC (*12, 18*)[a] (n)
Respiratory	3	11	16
Genitourinary (total)	2	34	12
Kidney	1	4	0
Bladder	0	2	2
Prostate	0	28	1
Testis/ovary	1	0	3
Cervix	0	0	3
Uterus	0	0	3
Gastrointestinal	3	18	5
Pancreas	0	8	0
Thyroid	3	10	0
Liver	0	8	1
Breast	0	1	4
Other	0	3	2
Total malignancies	11	93	46
Patients with malignancies	2.9%	6.9%	1.8%

TABLE 2. Demographics of patients included in study

Organ transplant	No.	Male:female	Caucasian (%)	Age at death (mean±SD)
Liver	231	1.4	92	47±13
Heart	52	2.1	92	45±13
Heart-lung	26	0.9	96	34±9
Lung	32	0.9	100	40±12
Kidney	34	1.4	94	48±13
Total	375	1.4	93	46±11
Nontransplanted control group	1299	1.4	87	59±16

TABLE 3. Occult malignancies in patients who died within 100 days of transplantation

Case	Sex	Organ transplant	Age	Survival (days)	Tumor	Size (cm)
1	Female	Liver	48	0	Jejunum, carcinoid	0.4
2	Male	Heart	51	8	Thyroid, papillary	0.3
3	Female	Kidney	62	9	Lung, adenocarcinoma	2.0
4	Male	Kidney	58	13	Renal clear cell	0.3
5	Female	Heart/lung	24	18	Thyroid, papillary	0.5
6	Female	Liver	45	24	Thyroid, papillary	0.5
7	Male	Liver	42	25	Seminoma	3.0
8	Male	Liver	73	33	Larynx, squamous	0.3
9	Male	Liver	51	51	Ileum, carcinoid	4.0
10	Male	Liver	45	52	Lung, adenosquamous	0.5
11	Male	Liver	48	78	Duodenum, carcinoid	0.5

Most patients were Caucasians (93%), and there was a slight male predominance overall. A total of 11 malignancies were seen in the transplant patients for an overall frequency of 2.9%. They were identified in seven males and four females with an average survival of 28 days (range, 0–78 days). There was no significant difference in average age at death between transplant patients with neoplasms (mean age, 50±12 years; median, 51 years) and those without neoplasms (mean age, 45±13 years; median, 48 years) (P=0.89). The malignancies included three thyroid carcinomas, three carcinoids of the small bowel, two lung carcinomas, one laryngeal carcinoma, one seminoma, and one renal cell carcinoma. All malignancies were stage I tumors, and none had metastasized (Table 3). The small total number of malignancies in the transplant group did not permit further analysis of any changes over time nor any potential relationship between the incidence of tumors and the types of organ transplantation.

The frequency of occult malignancies among nontransplant hospital controls from this institution (Table 1) was 3-fold higher than that of the autopsied transplant patients (P=0.004). However, this appeared to be principally the result of the control patients being significantly older in age at death (P=0.016). When an age-adjusted expected frequency of occult neoplasms was calculated for the transplant pa-

tients, the resulting expected frequency of 15 occult malignancies did not differ significantly from the observed 11 malignancies ($P=0.42$). Pretransplant screening for malignancies in transplant patients may also have contributed to the lower frequency of tumors in this patient population.

DISCUSSION

This study assumed that any occult tumor present at autopsy in a patient who died within 100 days of transplantation was present at the time of the transplant. Ideally, the shortest time interval possible would be used in this type of study, such as a single day. However, the time interval of 100 days was chosen for this study in order to provide a sufficiently large patient population. It is unlikely that any tumor present at autopsy in a patient who died within 100 days arose after the transplant. The average doubling time for even a rapidly growing carcinoma, such as an anaplastic lung carcinoma, is around 11 weeks (*15*).

The frequencies of malignancies were all quite similar in the autopsied transplant patients, nontransplant patients, and in the clinical follow-up studies from this institution. There were, however, differences in the types of malignancies. Prostate carcinomas made up 30% of the occult malignancies in the control patients, whereas no prostate carcinomas were found in transplant patients who died within 100 days, and only one prostate carcinoma was reported in clinical follow-up studies from this institution. In addition, thyroid neoplasms were common in both the hospital-based control group and in transplant patients who died within 100 days, but no thyroid neoplasms were detected clinically. These differences in the types of tumors may be a reflection of the differences in the ages of the various groups. In addition, transplant patients are carefully screened for malignancies before transplantation, and this may influence the number and types of occult tumors that are found at autopsy.

The 2.9% frequency of occult malignancies in the transplant patients who died within 100 days is similar to the frequencies of clinically detected posttransplant malignancies reported in representative studies from other institutions, Table 4. These studies report an overall frequency of 3.7% visceral malignancies in a total of 16,843 patients.

The results of this autopsy-based study and clinical follow-up studies in the literature can only be compared with a number of limitations in mind. First, several clinical studies report only the broad categories of tumors and not the specific organ of origin, making comparisons difficult (*16*, *17*). Second, some of the clinical follow-up studies have occasionally included neoplastic lesions that are generally not considered to be malignant, such as tubular adenomas (*18*). Third, a few clinical-follow-up studies appear to have included autopsy findings (*19*). Fourth, other studies report an admixture of data from child and adult transplant patients, and there is evidence that the types of posttransplant tumors are different in these two groups (*20*). Fifth, different lengths of follow-up time complicate direct comparisons of the various clinical follow-up studies, as do different immunosuppression regimens. Sixth, the autopsy procedure itself has certain limitations. Some types of malignancies will probably be under-represented in autopsy-based studies, particularly those of the oropharynx, breasts, anus, and in-situ lesions of the cervix (which often require colposcopy-directed biopsies for detection). Furthermore, it should be noted that the primary goal of an autopsy is almost always to determine the cause of death and the organs are not specifically examined to detect occult lesions. Because of this, a percentage of tumors that would likely declare themselves clinically, if given time, will not be detected at autopsy. Despite these limitations, autopsy-based data can be helpful in determining the contribution of occult malignancies to the number of neoplasms discovered in the posttransplant course.

TABLE 4. Representative frequencies of malignancies in clinical follow-up studies, excluding lymphomas, cutaneous malignancies, Kaposi's sarcoma, and cervical/vulvar malignancies

Organ transplant	n	Percent of patients with malignancies (n)	Mean length of follow-up (mo)
Liver			
Frezza et al. (*18*)[a]	1657	1.2% (20)	Not stated
Jain et al.(*6*)[a]	1000	2.6% (26)	78
Levy et al. (*31*)	556	1.1% (6)	35
Jonas et al. (*32*)	458	1.2% (33)	50 (median)
Heart			
Goldstein et al. (*11*)	633	3.3% (21)	Not stated
Pham et al. (*12*)[a]	608	3.3% (20)	52
Curtil et al. (*14*)	296	5.6% (15)	Not stated
Kidney			
Sheil et al. (*5*)	6596	5.6% (369)	79
Hiesse et al. (*33*)	1700	2.9% (49)	92 (group 1) 52 (group 2)
Frei et al. (*17*)	1352	3.2% (43)	53
Kim et al. (*21*)	1313	0.8% (10)	52
Mixed solid tumors			
Mihalov et al. (*34*)	674	1.8% (12)	37
Total	16843	3.7% (624)	

[a] Reports from the University of Pittsburgh Medical Center.

Several observations from this study support the idea that many of the visceral malignancies seen in the early posttransplantation course are clinically occult tumors that were present at the time of transplantation. First, there was no significant difference in the frequency of malignancies between nontransplant autopsy control patients and transplant patients who died within 100 days, after adjusting for age. Second, the frequencies of malignancies in this study and in clinical follow-up studies from this institution are very similar. Third, the types of occult neoplasms seen in the transplant patients who died within 100 days are well represented in both the nontransplant hospital control patients as well as in clinical follow-up studies from this institution. These observations suggest that patients undergoing transplantation have a small, but significant, frequency of malignancies that are not clinically detectable. These malignancies appear to contribute substantially to the clinical burden of visceral malignancies that develop during at least the early posttransplantation course. Furthermore, these results may partly explain the observation of no increased risk for malignancies seen in some studies (*2*), as the malignancies seen in the early transplant course may very well be those that were present to begin with and would thus present clinically with the same frequency as in nontransplant patients.

However, these data do not suggest that all visceral neoplasms that develop after organ transplantation arise from clinically occult tumors that were present at the time of transplantation, nor does it suggest that there is no increased risk for visceral malignancies after transplantation. Many clinical follow-up studies have shown an increase in the risk for at least some types of visceral neoplasms after transplantation (*5*, *12*, *14*, *21*, *22*). This risk clearly seems to increase with the length of clinical follow-up (*12*, *21*, *22*) and can be a major cause of morbidity and mortality in long-term transplant survivors (*5*, *14*). In renal transplant patients, the risk of malignancy begins to rise more rapidly around approximately year 4 after transplantation (*17*). These later malignancies probably arise de novo and account for the elevated risk documented in numerous clinical follow-up studies. This observation is further supported by data from our institution that suggests an increased risk for renal cortical neoplasms in those patients with long-term survival, but no increased risk in patients who died within 5 years of transplantation (*23*).

Risk factors for the development of posttransplant visceral malignancies have not been completely defined, and there is some discrepancy among the reports in the literature. Age appears to be the most commonly identified risk factor (*11*, *12*, *14*, *16*). Smoking is a particularly important risk factor, particularly for respiratory carcinomas, with several reports of clinically aggressive cancers in this setting (*14*, *24*, *25*). Other risk factors include male gender (*11*), analgesic nephropathy and acquired cystic renal disease in renal transplant patients (*8*, *9*), alcoholic cirrhosis in liver transplant patients (*26*, *27*), and ulcerative colitis (*10*, *28*). As for the effect of immunosuppression on preexisting malignancies, the bulk of the evidence suggests that immunosuppression enhances the growth of tumors, at least in some instances (*29*). For example, several studies have documented markedly accelerated clinical courses for patients with lung cancer (*12*, *14*, *24*). However, the precise role of immunosuppression in the origination of visceral tumors remains unclear. Interestingly, immunosuppression may even provide protection against the formation of some neoplasms (*30*).

In conclusion, clinically occult tumors that are present at the time of transplantation probably account for a significant proportion of visceral malignancies that develop in the very early posttransplant course. As for tumors that develop in the later posttransplantation course, the precise role for immunosuppression and other posttransplant factors remains unclear at this time. However, many clinical follow-up studies do indicate an increased risk for the development of epithelial malignancies.

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