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Malignant Lymphomas in Transplantation Patients: A Review of the World Experience[3,4,5]

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Malignant Lymphomas in Transplantation Patients: A Review of the World Experience[3,4,5]

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Summary (Übersetzung siehe Karteikarte)

Malignant lymphomas developed in 9 renal homograft recipients treated at widely separated transplantation centers. The development of these tumors appears to be an indirect complication of organ transplantation and/or the measures taken to prevent rejection. A further complication may be an increased incidence of epithelial tumors. It also seems likely that immune paralysis may accelerate the growth of metastases.

In our experience with a large series of renal transplantation patients who survived at least 6 months and were followed for periods as long as 6 years or more there has been approximately a 3 percent incidence of malignant tumors, particularly lymphomas [40]. In 1968 we reported [33] 5 cases of this type of tumor which occurred at 3 widely separated transplant centers. One of these cases was subsequently extensively restudied and was reclassified as an undifferented carcinoma [23]. Since then further cases have been described from several other transplant centers. At the present time there are 9 cases of lymphomas which developed in the more than 2,500 known renal homotransplant recipients.

Clinical Material

The salient features of these cases are summarized in Tables 1 and 2.

Case 1 (Denver) [33]

Before the transplant operation in May 1967 the patient complained of headaches, dizziness, blurred vision, nausea and vomiting. He also had two generalized epileptiform seizures. Neurologic examination was negative and his symptoms were attributed to severe hypertension.

Two months after the transplant operation he had a generalized seizure and was confused and incoherent for several days. At that time he had threatened rejection of the homograft, was hypertensive, and was found to be exceeding his restricted fluid allowance. Serum chemistries showed marked hemodilution. A diagnosis of water intoxication was made. This condition promptly improved with treatment consisting of fluid restriction and administration of sodium chloride and potassium supplements. No further neurologic symptoms occurred until 9 days before a diagnosis of reticulum cell sarcoma was made by craniotomy. This very extensive tumor of the brain caused the patient's death. Renal function was normal in the last months of life.

In this case, the possibility could not be excluded that the tumor was present at the time of transplantation and was the cause of his earlier neurologic symptoms.

Case 2 (Denver) [33]

In addition to the immunosuppressive agents mentioned in Table 1 the patient was treated with Actinomycin C and local homograft irradiation to control threatened rejection. After his transplant operation he had persistent

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[5] Presented at he Canadian Society of Chemotherapy Meeting, Toronto, Ontario, April 17 and 18, 1969.

Table 1. Lymphomas in Renal Transplant Recipients.

Number	Transplant-Center	Age	Sex	Donor	Immunosuppression: Splenectomy	Thymectomy	Imuran	Prednisone	ALG	Type of Tumor	Time after Transplantation	Organs Involved	Outcome
1	Denver	14	M	Mother	Yes	No	Yes	Yes	Yes	Retic. Cell Sarcoma	5 1/2 months	Brain	Fatal
2	Denver	23	M	Father	Yes	Yes	Yes	Yes	No	Retic. Cell Sarcoma	30 months	Thyroid; Liver Lung; Stomach; Prostate; Pituitary; Skin; Psoas Muscle	Fatal
3	Denver	20	F	Father	Yes	No	Yes	Yes	Yes	Possible Plasma-cytoma	7 months	Brain	Alive
4	Edinburgh, Scotland	26	F	Mother	No	No	Yes	Yes	Yes**	Retic. Cell Sarcoma	24 1/2 months	Mediastinal lymph nodes; Pleura	Fatal
5	Cleveland	32	M	Cadaver	No	No	Yes	Yes	Yes	Retic. Cell Sarcoma	22 months	Buttock	Alive
6	New York	35	F	Cadaver	No	No	Yes	Yes	No	Visceral Kaposi's Sarcoma*	10 months	Lungs; Esophagus; Stomach; Urinary bladder; Mediastinal and abdominal lymph nodes.	Fatal
7	Richmond	35	M	Cadaver	No	No	Yes	Yes	No	Retic. Cell Sarcoma	31 months	Lung	Fatal
8	Auckland, New Zealand	34	M	Cadaver	No	No	Yes	Yes	No	Retic. Cell Sarcoma	7 months	Tongue; Esophagus; Liver	Fatal
9	Auckland, New Zealand	46	F	Cadaver	No	No	Yes	Yes	No	Retic. Cell Sarcoma	9 months	Brain	Fatal

* A variety of lymphoma [31, 32].
** ALG Treatment post-dated for sl evidence of the neoplasm.

hypercalcemia which necessitated a parathyroidectomy on March 29, 1966. The thyroid gland was normal at this operation, but at autopsy on December 6, 1967 it was found to be enlarged and almost completely replaced by tumor. Up till the time of death renal function had been subnormal, but adequate.

Death occurred 6 days after emergency vagotomy and partial gastrectomy performed to control massive upper gastro-intestinal bleeding. The resected portion of stomach contained several ulcers, in the bases of which were small collections of tumor cells closely resembling those found in the brain in Case 1. At autopsy widespread tumor was found (Table 1).

Case 3 (Denver) [33]

In the early part of her post-transplant course threatened rejection required treatment with Actinomycin C and local homograft irradiation. Seven months after renal homotransplantation she developed a rapidly progressing left hemiparesis. A lesion in the right anterior and midthalamic areas was identified with pneumoencephalography and biopsied with a stereotaxic technique. The histologic findings were consistent with a tumor of lymphoid origin, possibly a plasmacytoma. Further studies revealed no evidence of tumor elsewhere in the body and no evidence of multiple myeloma.

Reduction in the dosage of prednisone and azathioprine combined with radiotherapy to the brain resulted in striking improvement in the patient's neurologic condition. At present, more than a year since the tumor was treated she is in good health apart from a moderate degree of residual hemiparesis.

Case 4 (Edinburgh) [45]

Several rejection episodes required increase of prednisone dosage. Later, ALG was used in an attempt to reduce the amount of steroid therapy. Right sided pleurisy developed 518 days after renal homotransplantation. A loculated effusion between the right upper lobe and mediastinum was seen in a radiograph of the chest. This

slowly diminished in size when antibiotics were given and could no longer be seen 2½ months later. A chest x-ray 725 days post-transplantation showed recurrence and extension of the aforementioned radiographic abnormalities. Operation revealed a reticulum cell sarcoma of the mediastinal lymph nodes and pleura. The patient died 760 days after transplantation. The kidney functioned throughout life.

Case 5 (Cleveland) [17]

The donor was a 7 year old girl who died following surgery for a medulloblastoma. Seven months after transplantation the patient was treated for threatened rejection of the kidney with intravenous Actinomycin C, local Cobalt 60 to the graft site and with 37 intramuscular injections of ALG, in addition to maintenance therapy with Imuran and prednisone. The ALG injections were administered over a period of 8 weeks, and were placed in the buttocks. Approximately 6 weeks after the first ALG injection the patient noted a small nodule in the left buttock at the site of an ALG injection. The mass persisted unchanged for 10 months and then started to enlarge. It was then widely excised and the residual defect was skin grafted. Histologic examination of the mass revealed a typical reticulum cell sarcoma.

Immunofluorescent techniques failed to show any horse gamma globulin in the tumor. Electron microscopy failed to show any virus particles.

Renal function has remained satisfactory up to the present time. The patient remains well but lymphangiography shows possible involvement of the aortic nodes by metastatic tumor.

Case 6 (Albert Einstein College of Medicine, New York) [38]

The transplant was from a cadaver donor who had no evidence of malignant disease. Several months following transplantation there were several episodes of threatened rejection which required treatment with Actinomycin C and local radiotherapy, as well as adjustment of the doses of azathioprine and prednisone. These episodes left the patient with impaired renal function. Seven months post-transplantation a right lower lobe infiltrate developed. This resolved with antibiotic therapy, but the patient was left with a cavitary lesion which persisted till her death 10 months post-transplantation.

Autopsy showed a chronic lung abscess and bilateral bronchopneumonia; evidence of progressive rejection in the transplanted kidney; and a widely disseminated tumor with the histologic features of the visceral form of Kaposi's sarcoma.

Table 2. Lymphomas In Renal Transplant Recipients.

Organs Mainly Affected	
Organ	Number of Patients
Brain	3
Lung	3
Skeletal Muscle	3
Liver	2
Esophagus	2
Stomach	2
Lymph Nodes	2

Case 7 (Richmond) [34]

Several rejection episodes required treatment with Actinomycin C in addition to routine therapy with azathioprine, prednisone and local irradiation of the kidney. Dyspnea and ascites developed 27 months following transplantation and he was treated for pneumonia, pulmonary insufficiency and congestive heart failure. Four months later a chest x-ray showed a nodule in the right lower lung field. Four days later the patient died of a cerebral hemorrhage. At autopsy there were two nodules in the right lower lobe which histologically were reticulum cell sarcoma.

There was no evidence of involvement of other organs.

Case 8 (Auckland, New Zealand) [18]

Four mild episodes of transplant rejection with temporary decline in renal function were treated with high doses of prednisone and with Actinomycin C. Thereafter renal function remained satisfactory till his death.

Five months following transplantation he developed extensive herpetic lesions on the lips and inside his mouth. Candida albicans was cultured from the oral swab. Despite appropriate therapy the tongue became ulcerated, the oral lesion spread to involve the esophagus and marked cervical adenopathy developed. His condition steadily deteriorated and he died. At autopsy there was severe ulceration of the lips, the right side of the face, both eyelids, the

tongue and the lower two thirds of the esophagus. Deep to the ulcers of the tongue and esophagus were areas of reticulum cell sarcoma. In addition, there were nodules of this tumor in the liver.

Case 9 (Auckland, New Zealand) [18]

During the first 3 months after transplantation the patients had three easily reversible episodes of decreased renal function. Three months after transplantation she developed severe labial herpes simplex infection, which spread to involve the nose. The labial lesions healed after 2 months, but the nasal lesions progressed and led to destructive rhinitis with septal perforation, which was still present at the time of death. For the month before death she was severely toxic with systemic staphylococcal infection, including a lung abscess.

At autopsy a reticulum cell sarcoma was found close to the surface of the right parietal cortex.

Discussion

Animal studies have shown that malignant tumors may develop in certain conditions characterized by disturbances of the host's immune defenses [36]. In man the same appears to be true. For example, patients with agammaglobulinemia and deficiences of cell mediated immunity have a high incidence of malignancy of lymphoid or other tissues [19, 20, 37].

An increased frequency of neoplasms has also been found in a variety of "auto-immune" disorders [20]. Iatrogenic alteration of the host's immune apparatus also appears to have caused an increased incidence of neoplasia [33].

So far the predominant tumor types encountered in renal homograft recipients have been lymphomas, although there have been reports of a variety of other tumors which appeared at varying intervals after transplantation. These include an ovarian dysgerminoma [20], a carcinoma of the cervix [28], a squamous cell carcinoma of the ear [33], and two cases of anaplastic carcinoma [23, 47].

In the present series there is a strong likelihood that the neoplasms began *de novo* at some time after the transplantation. Only in Case 1 was there any suggestion that the tumor might have antedated the transplant operation. In 4 cases the kidneys were obtained from related living donors who remained in good health for years after their nephrectomies [33]. In a further four cases the kidneys were obtained from cadavers who had no evidence of neoplasia. Although the donor of Case 5 had a medulloblastoma this tumor has little propensity to spread outside the central nervous system [43] and, further, it has no known relationship to reticulum cell sarcoma.

A number of the conditions present in the human recipients of renal homografts herein reported have been shown in experimental animals to be capable of inducing or influencing oncogenesis under the appropriate circumstances. Each of the main immunosuppressive agents, azathioprine [12, 13], prednisone [1, 2, 8, 9, 46] and ALG [4–7, 10, 15, 16, 22] has been shown in animals either to (a) increase a normally low incidence of spontaneous, virus-induced, or chemically-initiated tumors; (b) to facilitate the ease with which malignant cells can be transplanted; or (c) to accelerate metastatic growth. In addition, thymectomy [4, 15, 21, 26, 27, 30] or splenectomy [3] have a similar but less certain effect.

In the clinical situation, the relative contribution of any single factor is impossible to assess. All 9 of the patients received immunosuppressive therapy with azathioprine and prednisone, 4 received heterologous ALG, 3 underwent splenectomy and one had a thymectomy. Beside therapy with azathioprine and prednisone, the common feature in all cases was the continuous presence of antigen in the form of a homograft. All the patients had problems with rejection of varying severity and received increased immunosuppressive therapy to control this reaction. The development of reticulum cell sarcoma at the site of an ALG injection in Case 5 is of particular interest in view of the experimental work of Allison and Law [4] who injected mice with leukemogenic virus and ALS and found a remarkably high incidence of reticulum cell sarcoma in the subcutaneous tissues at the site of ALS injection.

There has been increasing acceptance of the concept that the immunologic system provides a "surveillance" function [11, 20, 25, 35] by which mutant neoplastic cells are identified and either eliminated or restricted in their growth potential. This point of view has been strongly supported by the ease with which neoplasms have been accidentally transplanted from cadaveric renal donors who died of cancer [24] and by the

subsequent disappearance of a transplanted malignant growth in at least one case after immunosuppression had been discontinued [44].

However, the foregoing sequence of events does not explain the peculiar predisposition to the development of lympho-reticular tumors. An additional factor was suggested in our reports [33, 39] to explain this high incidence. The possibility was raised that the chronic stimulation of the host reticulo-endothelial system by antigens of the homograft was responsible for the nature of the malignancies. The role of antigenic stimulation in increasing the incidence of experimental lymphomas has been well established [14, 29, 36, 41].

Further experience will be required to determine the frequency with which neoplastic growth will be a complication of clinical organ transplantation. At the moment, it appears that the incidence will be low enough so that the usefulness of such procedures will not be vitiated. In the meanwhile, it is important to be alert to this diagnostic possibility since only in this way can effective therapy be instituted as was accomplished in Case 3 and possibly in Case 5.

Further knowledge about the general effect of transplantation and immunosuppression on tumor growth will have an important bearing on the advisability of organ replacement for the treatment of primary malignancies of vital structures such as the kidney, liver and lung. There is already some evidence that such therapeutic efforts may not be as effective as might be hoped [40]. WILLIAMS et al. [42] performed renal homotransplantation in a child 6 months after excision of a Wilm's tumor. Sixteen months after transplantation, at a time when a cure of this kind of neoplasm would usually have been assured under normal conditions, metastases became apparent leading to death within a few weeks. In our series of orthotopic liver transplantations for hepatoma, there have been 4 long-term survivors. Three of these died of carcinomatosis 6 months, 11 months and 13 months respectively post-transplantation. One is alive 13 months since a first liver transplant and 2 weeks since a second liver was inserted to replace the first which had undergone chronic rejection. At the second operation the diaphragm and retroperitoneum contained recurrent tumor.

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