

Study on Eight Patients with Malignant Tumors after Renal Transplantation

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ABSTRACT

The high incidence of cancer after renal transplantation is now a critical concern since the graft survival rate has been improved extensively. We experienced 9 malignancies in 8 patients out of 168 recipients up to December 31, 1999 in our hospital, consisting of a case of gastric plasmacytoma and cases of cancer in the liver (2), thyroid (2), prostate (1), breast (1), sigmoid colon (1) and gall-bladder (1). Two patients were diagnosed as having tumors within 3 months after transplantation, suggesting post-transplant acceleration of growth of the latent tumors. The other patients were diagnosed at an average of 128 months, ranging from 84 to 263 months after transplant. Two patients died of gastro-intestinal bleeding and acute heart failure. Four patients died directly of progressive neoplasm within 3 months after diagnosis. These results suggest that the course of malignancies developing in post-transplant recipients is more aggressive than that expected in non-transplant patients, and it is very important to intensively follow long-term surviving cases to detect the malignant tumors as early as possible.

Key words: Malignant Tumor, Renal Transplantation

The increasing incidence of certain cancers is a well recognized problem in organ transplant recipients^{10,13-15,18}. The largest number of transplants were performed in recipients of renal allografts and most of them have been followed up for long periods of as many as 20 to 30 years. In this article, we report 9 malignant tumors developing in 8 recipients after kidney transplantation.

PATIENTS AND METHODS

From September 1971 to December 1999, we experienced 168 cases of kidney transplantation, consisting of 138 cases of living related renal transplants and 30 cases of cadaveric renal transplants; 128 were male and 40 female. The median age at transplant was 31.6 years old, and 3.57% of the recipients were over 50. We studied the affected organs, the time of diagnosis, treatment and prognosis of malignancies after renal transplantation.

RESULTS

Eight patients (4.76%) developed 9 malignant tumors: two cases of hepatocellular carcinoma (HCC), two cases of thyroid cancer and one case each of gastric plasmacytoma, prostate carcinoma, breast carcinoma, sigmoid colon carcinoma and gall-bladder carcinoma, as shown in Table 1. In two of eight patients, tumors were found within 3 months after transplantation, suggesting post-transplant acceleration of latent tumors. The tumors of the remaining 6 patients appear to have newly developed after transplantation. These malignant tumors were diagnosed at an average of 128 months (range 84 to 263 months) after transplantation. The average age at the time of diagnosis of malignant tumor was 38.4 years (range, 18 years to 56 years). One patient (No. 7) was positive for HBs antigen, and three patients (No. 5, 6, 8) were positive for HCV antibody. Six out of eight patients died: four of malignant tumors and two of gastrointestinal bleeding and acute heart failure.

Table 1. Development of malignancy in renal transplant recipients

Case	Age	Gender	Donor	Immunosuppressant	Malignant tumor	Years after transplantation	Treatment	Prognosis
1	23	male	LD	PSL,AZ,AL	gastric cancer (plasmacytoma)	3 months	subtotal gastrectomy	died of acute heart failure one day after the operation
2	50	male	CD	PSL,AZ,AL	prostate carcinoma	7 years	orchiectomy	died of multiple bone metastasis 3 months after the operation
3	18	female	LD	PSL,AZ,CP,MI	thyroid carcinoma	0 month	hemithyroidectomy	died of upper gastro-intestinal bleeding 3 months after the operation
4	25	female	LD	PSL,AZ,MI	thyroid carcinoma	7 years and 2 months	hemithyroidectomy	surviving for 10 years and 8 months
5	38	female	CD	PSL,AZ,AL,MZ	breast carcinoma	8 years and 5 months	modified radical mastectomy	surviving for 7 years and 8 months
				PSL,AZ,AL,MZ	sigmoid colon carcinoma	10 years and 1 month	polypectomy	
6	37	male	LD	PSL,AZ,MI,CYA	gallbladder carcinoma	9 years and 5 months	chemotherapy	died of multiple liver metastasis and direct invasion to the stomach 3 months after the diagnosis
7	37	male	LD	PSL,AZ,MI	liver cancer (hepatocellular carcinoma)	18 years and 3 months	none	died of multiple liver metastasis 2 months after the diagnosis
8	14	female	LD	PSL,MZ	liver cancer (hepatocellular carcinoma)	21 years and 11 months	open microwave coagulation therapy	died of rupture of hepatocellular carcinoma 3 years and 11 months after the operation

Five out of 6 patients died within 3 months after diagnosis or the operation. We report here 3 interesting cases of malignant tumors found after kidney transplantation.

Patient No. 1 developed complications of pancytopenia and liver function disorder 2 months after transplantation, and we stopped administering azathioprine. One month later, the patient developed the complication of massive tarry stool due to bleeding from a gastric ulcer, then underwent subtotal gastrectomy. One day after surgery, however, he died of acute heart failure. The autopsy revealed plasmacytoma in the stomach.

Patient No. 5 was diagnosed as having early double cancers in the breast and sigmoid colon, as well as subdural and extramedullary meningioma, and huge hepatic cavernous hemangioma. She underwent modified radical mastectomy for the breast cancer, polypectomy for the sigmoid colon cancer, and extirpation of the extramedullary meningioma. Hepatic hemangioma was followed up in the out-patient clinics. The dose of azathioprine was decreased after the third operation.

Patient No. 8 was diagnosed as having HCC (S₅: 2 × 2 cm) 22 years after transplantation. She had a severe disorder in liver function (ICG R₁₅; 50%) and a mild bleeding tendency. Operative microwave coagulation therapy (MCT) was performed as a treatment for HCC and the patient was followed up in the out patient clinics. The tumor remained the same size 2 years after MCT,

but she was admitted because of hematemesis 3 years and 11 months after the MCT and died. An autopsy revealed rupture of HCC.

DISCUSSION

Renal transplantation is now established as the definitive treatment for end-stage chronic renal failure. Many years of clinical and laboratory research have improved the survival of patients and allografts. As renal allograft recipients survive longer, the focus of research has broadened to include the problems which arise as a result of prolonged immunosuppression. One significant cause of post-transplant morbidity is neoplastic disease, but little progress has been made towards understanding or reducing this risk. In different geographical areas, the incidence of cancer in transplant recipients varies considerably. In Europe¹⁸, de novo cancer occurred in 1.6% of transplant recipients compared with 3.3% in Scandinavia⁴. In an American series, an occurrence rate of 5.6%¹³, and in an Australian series of 24%¹⁸ are reported. A good deal of the variation is because of the high incidence of skin malignancy in those areas with a high risk for the development of those cancers. Data from several large kidney transplant programs showed an overall incidence of cancer ranging from 4% to 18%, with an average of 6%¹². Reports before 1990 in Japan showed an incidence of 1% or less¹¹, but this has increased to 6%¹⁹ in recent reports including our

results.

In 1993, Penn¹³ reported the incidence to be approximately 100 times greater than that of the age-matched general population. However, study showed that overall there was a 3 to 4-fold increased incidence of cancer in transplant patients compared with age-matched controls^{9,15}, and there was a markedly increased incidence of certain malignancies (skin and lip cancer)¹²⁻¹⁴. The Cincinnati Transplant Tumor Registry found no increase in the incidence of neoplasms that are commonly observed in the general population (carcinomas of lung, breast, prostate and colon)¹⁵. It is reported that the incidence of HCC was a 20 to 38-fold increase^{9,16}. In contrast with US and European reports, Japanese data revealed an increase in gastro-intestinal tract malignancy ranging from 45 to 57% in renal transplant recipients¹⁹.

The malignancies probably arise from a complex interplay of multiple factors. Several different mechanisms may contribute to the greater risk of cancer in immunosuppressed allograft recipients. The relative importance of these mechanisms varies with the type of cancer. Severely depressed immunity may hamper the ability of the body to destroy cancer cells induced by various carcinogens. Chronic antigenic stimulation by foreign antigens of transplanted organs, by repeated infections, or transfusions of blood or blood products may overstimulate a partially depressed immune system. Alternatively, defective feedback mechanisms may fail to control the extent of immune reactions and lead to unrestricted lymphoid proliferation and PTL¹⁸. Furthermore, once this loss of regulation occurs, the defective ability of the immune system is weakened and other malignant tumors may appear^{15,18}. Renal transplant recipients are susceptible to viral infections, some of which are potentially oncogenic in humans, including Epstein-Barr (EBV), herpes simplex, herpes zoster and polyoma viruses¹⁸. EBV is strongly implicated in causing lymphomas in primary immunodeficiency diseases and AIDS patients^{5,17}. EBV is also implicated in some leiomyosarcomas in pediatric AIDS patients and transplant recipients^{5,17}. Hepatitis B virus or Hepatitis C was implicated in causing HCC^{14,16}. Imanishi et al⁷ reported that the incidence of HCC was 11.7% by analyzing 204 cases of malignant tumors in renal transplant recipients in Japan, although European and US studies were only 2%¹³. This difference was probably caused by the increased complication in Hepatitis B virus and Hepatitis C in hemodialysis patients in Japan. Our previous study⁸ showed that 35% of renal transplant recipients were positive for HCV antibody, in which 28.5% were in a state of chronic active hepatitis. In this report, one patient (No. 7) was positive for HBs antigen and three patients

(No. 5, 6, 8) were positive for HCV antibody.

As well as contributing to oncogenesis through immune inhibition, immunosuppressive agents may be directly oncogenic¹⁸. The common immunosuppressants for renal transplantation are cyclosporine, azathioprine and corticosteroids. Of these common agents, cyclosporine did not show malignant potential in an extended toxicity experiment on animals and humans⁶. Prednisone has been shown to have no effect on chromosome numbers or morphology. Azathioprine, however, has been shown to cause chromosome breaks and nuclear abnormalities in humans and animals¹⁸. However, no direct oncogenic effect has yet been demonstrated. In this study, one patient was treated with cyclosporine and seven patients with azathioprine.

When treating tumors in renal transplant recipients, one must bear in mind that they frequently demonstrate more aggressive behavior than similar neoplasms in nontransplant patients³. It is noteworthy that 5 of 6 patients died within 3 months after diagnosis or the operation (Table 1). While treatment of many post-transplant malignant tumors is similar to that used in the general nontransplant population, there is as yet no widely accepted standardized protocol for the use of immunosuppression. When using chemotherapy, it is important to discontinue most immunosuppressive agents, except for prednisone. Otherwise the patients may be overimmunosuppressed and die of overwhelming infection^{3,13-15}. In our report, we stopped or decreased the immunosuppression (azathioprine) for two patients (No. 1 and No. 5). In our Department, MCT was used in the treatment of HCC^{1,2}. Our previous studies^{1,2} showed that MCT might be a new, less invasive option providing a cure for HCC in patients with advanced liver cirrhosis and severe complications. In the case of Patient No.8, no tumor growth had been observed for 2 years after the MCT.

Every effort should be made to detect tumors in their early stage after transplants. In our department, recipients longer than 5 years after renal transplantation or more than 50 years old are checked annually by

1. abdominal ultrasonography and computed tomography,
2. endoscopy in the upper gastrointestinal tract and colon-rectum,
3. tumor markers (carcino embryonic antigen, CA19-9, PIVKA-II, and α -feto protein), and
4. thyroid gland and breast examination.

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