NINE CASES OF MALIGNANCY AFTER KIDNEY TRANSPLANTATION

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ABSTRACT

Renal transplantation is considered one of the best long-term therapies for chronic renal failure, but unfortunately the incidence of malignancy significantly increases in renal transplant recipients. We analyzed nine cases of malignancy in 200 renal transplant recipients occurring in a 12-year follow-up in Imam hospital of Tehran University, Tehran, Iran. According to this study, the organ most commonly affected with malignancy in our series was the skin and the mean time of neoplasm occurrence after kidney transplantation was 2.9 years.

KEYWORDS: Kidney transplantation; malignancy; immunosuppression.

INTRODUCTION

It is well known that renal transplant recipients have an increased risk of developing malignancies. The immunosuppressed state, immunosuppressive drugs, viral roles such as the relation of cytomegalovirus (CMV) and Kaposi’s sarcoma (KS),1 Epstein-Barr virus (EBV)-associated lymphoproliferative disorders,2 herpes virus DNA sequence3 in KS lesions, persistent immune system stimulation by antigenic presentation of the allograft,2 and genetic factors4 are all contributing factors for cancer development after transplantation.

MATERIAL AND METHODS

Between 1985 and 1996, 200 patients received renal transplantation at the Imam hospital. We reviewed retrospectively the records of these patients. 140 recipients (70%) were male and 60 recipients (30%) were female. The mean age at the time of transplantation was 33.74±0.7 years. 164 patients (82%) received kidneys from living-unrelated donors, 35 patients (17.5%) from living-related donors and one (0.5%) from a cadaver donor. The observation period ranged from 1 to 108 months. The immunosuppressive regimens consisted of azathioprine, cyclosporine A and prednisolone and patients with acute rejection received methylprednisolone/ALG. The drug regimen of patients with malignancies will be discussed in the following section.

One-third of the malignancies in our series were Kaposi’s sarcomas. Since the study was retrospective, we didn’t search for any special viral genome, viral DNA assay, or HLA antigens in KS patients. Chi-square and Fisher’s exact test were used for statistical analysis. Significant findings were set at p<0.05. Data are expressed as mean values ± SD.

RESULTS

Nine cases of malignancy were detected in 8 patients (4.5%) after kidney transplantation. Of these, three patients (11.6%) were female and 5 (88.4%) were male. The mean age of patients at the time of kidney
transplantation was 48.5 years. All patients with malignancy were on chronic dialysis therapy before kidney transplantation and the mean period of dialysis was 2.8 years, the mean time of neoplasm diagnosis was 51.25 years and the mean serum creatinine at the time of neoplasm diagnosis was 1.9 mg/dL.

The kidney donor in 7 patients was live-unrelated and in one patient with two different kinds of cancer was from a live-related donor. Fisher's exact test showed that there was no significant relation between occurrence of cancer and type of donor (live related and unrelated) with $p=0.65$.

Acute clinical allograft rejection was diagnosed in 86 recipients and of these, three patients had histories of acute clinical rejection episodes before neoplasm detection; two of these patients had received methylprednisolone pulse and ALG therapy and one of these methylprednisolone pulse therapy. Using Fisher's exact test, there was no significant relation between history of rejection and neoplasm occurrence ($p=0.73$).

The immunosuppressive regimen in 7 patients consisted of azathioprine, cyclosporine and prednisolone and in one patient was cyclosporine and prednisolone before neoplasm detection.

In one patient, 2 months after successful treatment of squamous cell carcinoma (S.C.C.) on the nose, cheek and forehead area, Kaposi's sarcoma occurred in both calves. Neoplasms in our series included 6 cases of skin cancer, one case of lymphoma, one case of renal cell carcinoma of the native kidney and one case of acoustic neuroma.

Type of cancer and clinical presentation of patients at the time of cancer diagnosis as shown in Fig. 1 were:

1 - Kaposi's sarcoma: Violet red patchy lesions on the right anterior calf and pink and violet papules on the back of the right hand.
2 - Kaposi's sarcoma: Violet papular lesions on the hard palate, and macular lesions on both calves.
3 - Kaposi's sarcoma: Violet macular lesions with ecchymotic areas on both calves and edema (Fig. 2).
4 - Basal cell epithelioma: Fleshy nevus with ulcer on left cheek.
5 - S.C.C.: Ulcer of the skin of the left hand in the area of an A-V fistula.
6 - S.C.C.: Ulcer on the left cheek, forehead and nose.
7 - Renal cell carcinoma (R.C.C.): Presented with acceleration of hypertension, renal allograft dysfunction, bradycardia, and peripheral edema.
8 - Acoustic neuroma: Presented with headache, vomiting and renal allograft dysfunction in a patient with Alport's syndrome.
9 - Lymphoma: Presented with typhoid fever, renal allograft dysfunction, coagulation disorder, respiratory insufficiency and shock.

**DISCUSSION**

In one study in Japan the risk of de novo malignancies after kidney transplantation was estimated to be 100 times more than the general population. The most common cancer was skin cancer, followed by lymphoproliferative disorders which are 40 times higher than the general population.

The immune deficiency state, persistent stimulation of the immune system by external antigen allograft, activation...
of oncogen viruses, and oncogenicity of immunosuppressive
drugs have been mentioned as predisposing factors for
malignancy.

This study also reported the use of OKT, and ALG as
ded predisposing factors for non-Hodgkin lymphoma and has
studied the EBV genome in 2 cases of non-Hodgkin lymphoma after transplantation. In another excellent article, in
review of 8724 de novo malignancies that occurred in their
organ transplant recipients, sarcomas were 7.4% of
cancers and Kaposi’s sarcoma made up 5.7%, a much higher
proportion than in the general population. The major types
of sarcomas were fibrous histiocytoma, leiomyosarcoma,
hemangiosarcoma, undifferentiated sarcoma and
esothelioma. According to this study, theories that
explained the occurrence of sarcomas are as follows: during
the local “graft-versus-host” response, an angiogenesis factor
is liberated and causes intense proliferation of mesenchymal
and endothelial cells. Viral oncogens will produce malignant
transformation in cells. The Epstein-Barr virus (EBV),
which has been closely linked to the development of many
post-transplant lymphomas, has recently been found in a
clonal form in several smooth muscle tumors in organ
allograft recipients. KS is believed to arise from endothelial
cells. There are structural and functional interactions between
vascular and lymphatic endothelium and the immune system.
Endothelial cells play an important role in lymphocyte
traffic and participate in the immune response, acting as
antigen presenting cells. Other probable cancer etiologic
theories of KS as mentioned in this study are prolonged
exposure to foreign histocompatibility antigens of a
transplanted organ or repeated infection by viruses, fungi,
bacteria and protozoa, which may stimulate macrophages
and lymphocytes to liberate cytokines and growth factors
that cause proliferation of endothelial cells. This article also
has mentioned that genetic factors have a role in KS
development and stated an increase in frequencies of HLA-
A_{12}, A_{22}, and B_{w}, B_{s} and DR, and a decrease in the frequency
of B_{w} and DR. In another study oncostatin M and other
cytokines produced by human T-cell lymphotropic virus-1
(HTLV-1) infected CD_{4} cells showed a growth-promoting
effect for KS cells in culture, although this study was
performed on AIDS-associated KS cells. In another study
the combination of cyclosporine therapy, CMV reactivation,
and additional viral infection were pivotal in suppression of
the patient’s cellular immunity, allowing KS to appear.
Cytomegalovirus itself has been shown to be a strong
inhibitor of T-cell function, leading to severe opportunistic
infections that correlate with CMV burden. CMV has been
shown to code for growth factor-like substances which
might enhance all transformation. And in the KS cells
culture of a patient, CMV presence, as well as that of another
virus, has been visualized by electron microscopic study.

Concerning the role of cyclosporine therapy in the
production of lymphoproliferative disorders, some studies
showed an increased frequency of post-transplant lymphomas
in cyclosporine treated patients, but other studies did not
approve this.

In one study in 374 renal transplant patients, 5.9%
developed de novo cancers of which 45.8% were
gastrointestinal. This high incidence of gastrointestinal
cancers in this article may be due to geographic prevalence
or excellent screening of this cancer in this area.

In another study on 71 cancer cases in 274 kidney
transplant patients, skin tumors were the most common,
followed by lymphoma, renal, bladder, and bronchial
carcinoma. This study showed that the risk of tumor
occurrence may be less in patients treated with cyclosporine
and low-dose azathioprine than in those treated with
azathioprine and prednisolone after more than 5 years.
Another study on 6993 organ-transplant patients showed
that except for ovarian cancer, other cancers will increase
after transplantation and in a mean period of 4 years after
transplantation, cancers in which viruses have some role in
their production like non-Hodgkin lymphomas and KS are
more common, but after a mean of 8 years after
transplantation, cancers in these patients are as common as
other people. One study has mentioned the etiologic factors
of cancer after transplantation as follows: immune
insufficiency, cyclosporine, ALG, and ATG are factors
which change T-cell function and predispose patients to
oncogenic viral infections such as EBV, herpes simplex,
herpes zoster and human papilloma virus, with persistent
lymphoid stimulation, along with the direct effect of
azathioprine on chromosomal break. The study also
mentioned genetic factors and a history of chronic uremia
and dialysis therapy with interference with humoral and
cellular immunity. One study on 61 patients undergoing
chronic dialysis treatment showed EBV infection and serum
anti-EBV-VCA IgG titers were higher than the control
group. Detection of EBV with measurement of EBV-DNA
by southern blot hybridization after amplification by PCR in
peripheral leukocytes has been done. Persistence of EBV
infection and its relation to lymphoma needs further studies
in kidney transplant patients who have previously been on
chronic dialysis. Another study reported renal cell
carcinoma to have 4.6% incidence in a survey in the CTTR in
comparison with the 3% incidence of this cancer in the
general population. Among the causes of this cancer immune
deficiency, analgesic nephropathy and other diseases of
native kidneys have been mentioned, and urinalysis and
minute examination of the donor kidney at the time of
operation has been recommended.

Another article stated performing mammography and

*Measurement of serum antibody titer to VGA-IgG (Kayaku-
VCA slide, Wako Ltd., Osaka, Japan) was determined by indirect
immunofluorescence.

** CTTR: Cincinnati Transplant Tumor Registry.
measurement of specific prostatic antigen in aged recipients before transplantation. Opelz\textsuperscript{14} believes that transplantation from persons with complete HLA compatibility needs lower cumulative doses of immunosuppressive drugs and rarely needs monoclonal and polyclonal antilymphocyte antibodies and this will decrease malignancy incidence.

Education of symptoms of cancer to patients, prevention of risk factors and periodic thorough medical examination seems to be the optimal approach for early diagnosis of tumor development after kidney transplantation.

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