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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.

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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 sequence[3] in KS lesions, persistent immune system stimulation by antigenic presentation of the allograft,[2] and genetic factors[4] 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.

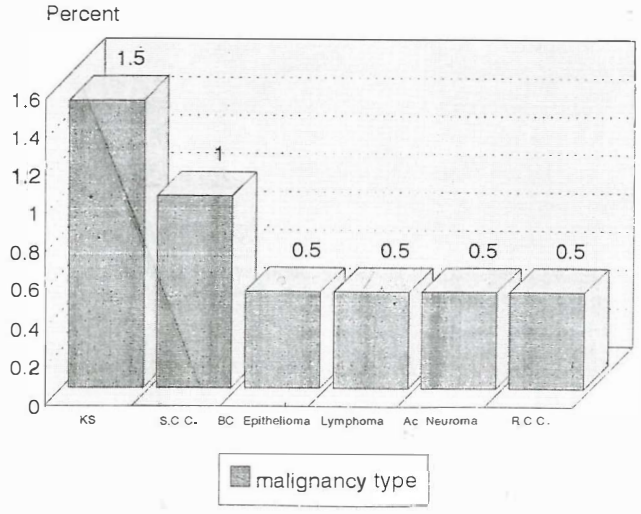

Fig. 1. Frequency of malignancies in 200 renal transplant recipients.

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[2] 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

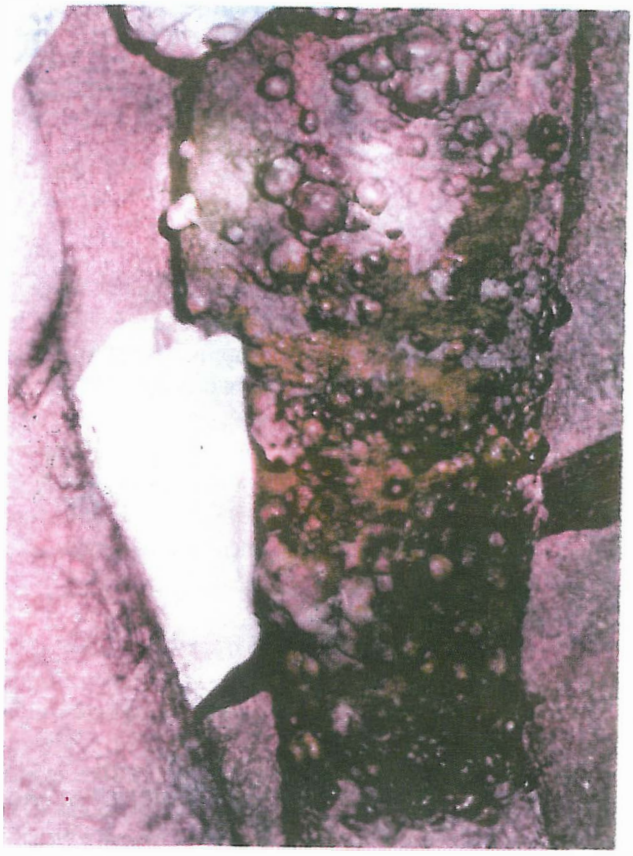

Fig. 2. Lesions of Kaposi's sarcoma in a renal transplant recipient.

of oncogen viruses, and oncogenicity of immunosuppressive drugs have been mentioned as predisposing factors for malignancy.

This study also reported the use of OKT_3 and ALG as 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,[4] 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 mesothelioma. 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.[4] 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_{19}, A_{23} and B_{49}, B_{18} and DR_5 and a decrease in the frequency of B_8 and DR_3. In another study[5] 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,[6] but other studies did not approve this.[7]

In one study[2] 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[8] 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[9] 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[10] 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[11] 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[12] 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[13] 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[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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