Posttransplant Malignancies and Their Relationship With Human Leukocyte Antigens in Kidney Allograft Recipients

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Introduction. Kidney transplant recipients are at increased risk of cancers, most frequently skin cancers, and in some regions, Kaposi sarcoma and non-Hodgkin lymphoma. We sought to investigate the associate of the most frequent malignancies among our patients with human leukocyte antigens (HLAs).
Materials and Methods. We performed a retrospective study on 44 kidney allograft recipients who had posttransplant malignancy and 44 kidney allograft recipients without malignant lesions (control group). All of the patients had been treated by immunosuppressive regimens including cyclosporine plus prednisolone or cyclosporine, prednisolone, and mycophenolate mofetil. Data on HLA typing were achieved from their transplant records.
Results. There were 15 patients (34.1%) with Kaposi sarcoma; 13 (29.6%) with non-Hodgkin lymphoma, 6 (13.6%) with skin cancer, 2 (4.5%) with ovary cyst adenocarcinoma, and 8 (18.2%) with other tumors. The mean interval from transplantation to diagnosis of malignancy was 15.3 month. Twelve patients died of cancer during the follow-up (mean, 12.3 years). No significant difference was noted in the age, sex, and time of transplantation between these patients and those in the control group. Kaposi sarcoma was associated with HLA-CW4 (P = .03) with an odds ratio of 4.96 (95% confidence interval, 2.90 to 8.12).
Conclusions. We found HLA-CW4 as a risk factor of Kaposi sarcoma in kidney allograft recipients. Screening for malignancies after kidney transplantation sounds very important with special attention to the specific environmental and genetic factors in each population.

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INTRODUCTION

The risk of malignancies after kidney transplantation increases to a rate higher than that in general population. Kidney allograft recipients are at a high risk of cancers, especially skin basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) after a variable period of transplantation.[1-4] Cancer is the 4th most common cause of death in transplant patients after cardiovascular disease, infections, and liver failure.[3,5] There is not any definite clinical evidence about the direct effect of any of the immunosuppressive drugs on development of malignancy after kidney transplantation except for OKT3 or antilymphocyte globulin.[5] However, most researchers believe that the cumulative effect of immunosuppressive drugs is the cause of increasing incidence of malignancy after transplantation.[2,3,6] For the same reason, the treatment courses of rejection after kidney transplantation increase the risk of malignancy.[3,6,7]

In Contrast to the other countries, Kaposi sarcoma and non-Hodgkin lymphoma are of common malignant complications in the Middle Eastern Countries such as Iran and Saudi Arabia, partly attributed to human herpes virus-8 (HHV-8) infection.[8-12] At present, different studies have been done on risk factors of posttransplant malignancies with conflicting results. In transplant recipients with Kaposi sarcoma, a higher incidence of HHV-8 is documented compared with kidney recipients without malignancy.[10,11,13]

Genetic risk factors, mainly human leukocyte antigens (HLAs), have also been assessed in malignancy cases developing after kidney transplantation.[1,14-16] For instance, association of HLA-B27 and HLA-DR7 and reverse correlation of HLA-A11 with skin cancers in kidney allograft recipients have been suggested.[14,17] Concerning Kaposi sarcoma, HLA-A2 in the Arab kidney recipients was proposed.[9] In this study, we evaluated the results of HLA typing in our kidney allograft recipients with posttransplant malignancies and compared them with a control group of transplant recipients.

MATERIALS AND METHODS

We performed a retrospective study at Shaheed Labbafinejad Medical Center in Tehran, Iran, on a cohort of 44 kidney allograft recipients who had posttransplant malignancy and 44 kidney allograft recipients without malignant lesions (case group) who were living during the follow-up period. Kidney recipients in the case group were matched for age, sex, and time of transplantation. They were cancer free based on the regular follow-up screenings. All of the patients had been treated by immunosuppressive regimens including cyclosporine plus prednisolone or cyclosporine, prednisolone, and mycophenolate mofetil. Data on HLA typing were achieved from their transplant records.

We evaluated the frequency of different HLA antigens in the study and case groups. Quantitative variables were compared by the *t* test and for categorical variables, the chi-square test and Fisher exact test were applied. *P* values of less than .05 were considered significant.

RESULTS

Patients with posttransplant cancer consisted of 26 men (59.1%) and 18 women (40.9%). Fifteen patients (34.1%) had Kaposi sarcoma; 13 (29.6%), non-Hodgkin lymphoma; 6 (13.6%), SCC; 2 (4.5%), ovary cyst adenocarcinoma; and 8 (18.2%), other tumors. The mean interval from transplantation to diagnosis of malignancy was 15.3 month. Twelve patients died of cancer during the follow-up (mean, 12.3 years), of whom 7 had non-Hodgkin lymphoma, 2 had Kaposi sarcoma, and 3 had skin cancers.

No significant difference was noted in the age, sex, and time of transplantation between these patients and controls (Table 1). Results of HLA typing with regard to malignancy are shown in Table 2. Kaposi sarcoma was associated with HLA-CW4 ($P = .03$) with an odds ratio of 4.96 (95% confidence interval, 2.90 to 8.12).

Table 1. Clinical and demographic Characteristics of Kidney Recipients With and Without Posttransplant Malignancy*

Characteristics	Kidney Allograft Recipients	
	With Cancer	Without Cancer
Recipients' sex		
Male	26 (59.0)	26 (59.0)
Female	18 (40.9)	18 (40.9)
Mean age, y	43.50	43.00
Transplantation to diagnosis of malignancy, mo	15.3	…
Patients outcome		
Alive	31 (70.5)	33 (75.0)
Dead	12 (27.3)	0
Alive under dialysis)	1 (2.2)	11 (25.0)
Graft function		
Serum creatinine ≤ 2.5 mg/dL	27 (61.4)	28 (63.6)
Serum creatinine > 2.5 mg/dL	5 (11.4)	16 (36.4)

*Values in parentheses are percents.

DISCUSSION

Evidence has shown that the risk of cancers is 3- to 5-fold higher after kidney transplantation.[13,18] Moreover, the prognosis is poorer, especially for gastrointestinal cancers, in these patients compared to the general population.[13] Skin cancers, both SCC and BCC, are the most common malignancies in general population and so they are in kidney allograft recipients with a risk of development 3 times as high as that in general population. Mortality of cancers after transplantation depends on type and length of administration of immunosuppressive drugs.[18] For instance, it has been found that 35% of kidney

Table 2. Relationship Between HLA Antigens and Malignancy*

Malignancy	HLA			
	A	B	CW	DR
Kaposi Sarcoma	A1 (.28)	B7 (.39)	CW4 (.03)†	DR2 (.59)
	A3 (.24)	B21 (.28)		DR4 (.46)
	A9 (.16)	B35 (.22)		DR52 (.59)
	A26 (.71)			DR53 (.47)
	A28(.39)			DQ1 (.99)
NHL	A2 (.84)	B12 (.36)	…	…
	A3 (.20)	B35 (.55)		
	A11 (.44)	BW44 (.37)		
	A24 (.43)			
	A28 (.37)			
SCC	A3 (.23)	B8 (.63)	…	DR4 (.25)
	A11 (.63)			DR11 (.63)
				DR53 (.26)
				DQ1 (.63)
				DQ3 (.26)

*Values in parentheses are *Ps*. Ellipses indicate not examined. HLA indicates human leukocyte antigen; NHL, Non-Hodgkin Lymphoma; and SCC, squamous cell carcinoma.
†Odds ratio for CW4 in favor of Kaposi sarcoma was 4.96 (95% confidence interval, 2.90 to 8.12).

allograft recipients die of cardiovascular events or cancers by conventional immunosuppressives which can be reduced by the use of low-risk drugs and even anticancer immunosuppressives such as sirolimus.[19]

Prevalence of cancers in this group of patients has geographical patterns too; in Japan, gastrointestinal cancers (liver, stomach, colon, and rectum) constitute 50% of all malignancies, while in the United Kingdom, lymphoma, renal cell carcinoma, and lung cancer are the most common ones. In Saudi Arabia, Kaposi sarcoma and lymphoma (especially in children) are the leading malignancies, and finally, in southeast Asia with a high prevalence of hepatitis B and hepatitis C, liver cancer is the most frequently seen cancer among kidney recipients.[20]

As Kaposi sarcoma concerns, its incidence is high in the Middle East countries, affecting up to 5% of the transplant population.[21] Infection with the HHV-8 is linked with the neoplastic and nonneoplastic manifestations of Kaposi sarcoma.[12] Interestingly, the increased risk of Kaposi sarcoma in kidney transplant recipients surpasses the relative risks of other malignancies when compared with general population, and it is accompanied by 34% mortality within the first 3 years of diagnosis. Involvement of the visceral organs indicates the severity of Kaposi sarcoma and its aggressive form can be diagnosed with the help of endoscopy.

Reducing the strength of immunosuppression protocol can cause complete improvement in 30% of cases, and localized lesions can be treated with radiotherapy.[20] Moreover, knowledge of the predisposing factors and genetic risk factors can help us early diagnosis of cancers like Kaposi sarcoma in these patients and promote their survival and quality of life after transplantation, particularly in young patients.[1,14-16] Specific screening for non-Hodgkin lymphoma and Kaposi sarcoma seems to be crucial,[3,5,8] and assessment of HHV-8 infection can be of help.[10,11,13] Genetic screenings may be helpful too. For instance, association of HLA-B27 and HLA-DR7 and reverse correlation of HLA-A11 with skin cancers in kidney allograft recipients have been suggested.[14,17] Concerning Kaposi sarcoma, HLA-A2 in the Arab kidney recipients was proposed.[9] In line with the initial steps in this regard, we attempted to find the links between HLAs and prevalent cancers in Iran. Our fining about HLA-CW4 is in contrast with previous studies in which HLA-B27, HLA-DR7, HLA-DR1, and HLA-A2 were related to posttransplant malignancies.[9,14-17]

We failed to find relationships between other HLAs and Kaposi sarcoma, non-Hodgkin lymphoma, or SCC, but further investigation with more cases is warranted. Other risk factors including age, sex, and donor source should be studied along with immunosuppressive drugs and genetic factors in large-scale research. The future prospective can be promising by the ever-growing research in this field, bringing the hope

of betterment in graft and patient survival rates in kidney transplant patients.

CONCLUSIONS

Our Findings suggested HLA-CW4 as a risk factor of Kaposi sarcoma. Assessment of malignancy risk factors in kidney transplant recipients will increase the chance of a better quality of life and higher survival rates in these patients. Screening for malignancies after kidney transplantation in the Middle East countries sounds very important for prevention of prevalent cancers in the region. Further confirmation about HLAs needs evaluation of more cases, and it seems experiences about the risk factors of malignancy after transplantation is growing.

CONFLICT OF INTEREST

None declared.

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