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Kaposi's Sarcoma after Kidney Transplantation: a 21-Years Experience

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ABSTRACT

Introduction: The long-term use of immunosuppressive agents for prevention of allograft rejection increases the risk of malignancy approximately 100 times as high as that in the general population and Kaposi's sarcoma (KS) is a relatively common malignancy after kidney transplantation. The aim of present study was to investigate the frequency of KS in patients with kidney transplantation in 20 years period.

Material and methods: In this study Charts and pathology reports of 1487 recipients for kidney allografts treated at Imam Reza hospital between 1991 and 2012 were reviewed. The SPSS software package version 16 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis.

Results: There were 17 of 1487 incident cases of KS kidney transplant population at our hospital in period of study. There is no significant difference between age and gender of patients. The mean time between transplantation and non-KS malignant tumors was 34.4 ± 21.8 months (range 12–140 months), while in KS patients it was 18.7 ± 25.2 months, which was statistically significantly different ($P < 0.05$). After detection of KS in 12 patients, we perform serum antibody detection against HHV. Among them, 8 (66.6%) were seropositive.

Conclusion: KS is a common long-term complication in renal transplant recipients, with an increased incidence compared with the general population. Given that candidates for organ transplantation who are seropositive for HHV-8 -and thus at risk for KS- can now be identified, chemoprevention should be available in this high-risk population.

Key words: Kaposi's sarcoma, Immunosuppressive, Kidney transplantation

INTRODUCTION

The long-term use of immunosuppressive agents for prevention of allograft rejection increases the risk of malignancy approximately 100 times as high as that in the general population.[1] The prevalence rate of post-transplant malignancies in total differs between geographical areas; for example, in Europe, that rate is 1.6% and in Australia is 24%, with a mean of 6%. Skin cancers, mostly squamous cell carcinoma (SCC), are the most common tumors among persons have solid organ transplantation.[1] But, however, Iranian studies found that the most common malignancy after kidney transplantation was Kaposi Sarcoma (KS) among the Iranian

patients.[2] KS is a skin tumor of multicentre origin, characterized histologically by endothelium-lined vascular spaces and spindle-shaped cells.[3] KS presents as single or multiple lesions on mucosal surfaces, including the skin, lungs, gastrointestinal tract and lymphoid tissues.[4] The etiopathogenes of KS is complex and poorly understood, but is almost certainly dependent on human herpes virus type 8 (HHV -8) infection in immunosuppressed, immunogenetically susceptible individuals.[5-7] Although the treatment of KS is controversial, it should ideally address these pathogenic issues.[8, 9] The current guideline is reduction of immunosuppression as first-line treatment, but these recommendations are based on anecdotal experience or uncontrolled studies.[9, 10] Perhaps the most fundamental controversy that has implications for all aspects of the disease surrounds the nature of KS: i.e. whet her it is a true malignancy or reversible hyperplasia.[11, 12]

The aim of present study was to investigate the frequency of KS in patients with kidney transplantation in 21 years period.

MATERIALS AND METHODS

An observational prospective follow-up study with a retrospective component, carried out in the Imam Reza hospital from Kermanshah University of Medical Sciences (KUMS) during the period 1991–2012. Patients with pre-transplant neoplasm will be excluded from the analysis (n = 46). Patients who had received transplants were identified through the hospital's transplant registry. For each patient, information includes donor and recipient characteristics, patient and graft survival and cancer incidence after transplantation, data of serologic tests such as HIV were received.

The period of follow-up for each patient starts on the day of transplantation and continues until death or last reported contact. Following the methodology used in similar studies, patients will not be removed from the analysis at the time of graft failure for several reasons.

We usually suspect KS when a kidney recipient presents with multiple hyperpigmented cutaneous nodules that may be associated with gastrointestinal discomfort and pulmonary symptoms resistant to conventional therapies. Then a battery of endoscopic, bronchoscopic, radiologic and pathologic tests is used to diagnose KS. When KS were detected, serologic test for HHV were performed.

All patients in our study received cyclosporine based immunosuppressive agents. There were two main distinct periods of immunosuppressive regimen: the first period was from 1991- 2002 azathioprine, cyclosporine and prednisolone. The second period was from 2002 onwards during which the patients received triple immunosuppressive therapy consisting of cellcept, cyclosporine and prednisolone at the same dosages mentioned above. Induction therapy using anti-thymocyte globulin (ATG) or anti-lymphocyte globulin (ALG) was preserved to the high risk patients in the early phase of transplantation or treatment of acute rejection; OKT-3 was not used in any of the studied populations.

The doses of immunosuppressive agents were reduced, with changed drugs to sirolimus, or the agents were withdrawn upon diagnosis of KS. The method of reduction of immunosuppression and decision on which the agent to be reduced or withdrawn were dependent on the individual patient's health condition, response to treatment and his/her physician's judgment.

The SPSS software package version 16 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis. All statistical tests were considered significant at the level of $P<0.05$.

RESULTS

Frequency and Demographic Data

From March 1991 to December 2012, 1487 kidney transplantations were performed. Among them, 67 malignant diseases were diagnosed in 64 patients with an overall incidence of 4.5% and KS was diagnosed as more frequent malignancy in 17 (25.37%) patients (Table 1). Of these 17 KS patients, 10 were males and 7 were female with median age of 47.8 years old. There is no significant different between age and gender ($P> 0.05$). The mean time between transplantation and non-KS malignant tumors was 34.4 ± 21.8 months (range 12–140 months), while in KS patients it was 18.7 ± 25.2 months, which was statistically significantly

different (P < 0.05). All patients tested since 1991 were HIV- negative. After detection of KS in 12 patients, we perform serum antibody detection against HHV. Among them, 8 (66.6%) were seropositive. Data of Characteristics of transplant patients with Kaposi's sarcoma were summarized in the Table 2.

Table 1. Type and Frequency of Most Frequent post-Transplant Malignancies (n = 67)

Malignancy	Frequency (%)
KS	17 (25.3%)
Malignant lymphoma	14 (20.8%)
SCC	9 (13.4%)
Lung	5 (7.4)
Other malignancy	22 (32.8%)

Table 2. Characteristics of Transplant Patients with Kaposi's Sarcoma

Variables		KS patients (%)
Age of reception		47.8 ± 23.4
Gender	Male	10 (58.8%)
	Female	7 (41.1%)
Induction (ALG, ATG)		3 (17.6%)
Immunosuppressant (cellcept)		12 (70.5%)
Immunosuppressant (azathioprine)		5 (29.4%)
HHV serum antibody		8 (66.6%)

Clinical Feature

There was no significant increase in the number of KS patients under cellcept compared to azathioprine or in the interval to development of KS. Skin involvement was universal and visceral involvement occurred in five (29.4%) patients. The sites of cutaneous involvement were lower extremities in 9 (52.9%), followed by upper-limb involvement in 5 (29.41%) patients. Other KS lesions occurred on trunk in 4 (23.5%) and hard palate in 2 (11.7%) patients.

Treatments

Immunosuppression was reduced in 10 (58.8%) patients (that 8 (80%) patients of them received sirolimus) and thoroughly withdrawn in the remainder (including three cases of visceral involvement). In 2 (11.7%) patients Immunosuppression was discontinued. In 11 (91 .6%) of 12 patients, KS skin lesions improved with therapy (excluded are five patients who died soon after KS diagnosis). KS healed over several months with residual pigmented or hyperkeratotic lesions. Lesions improved when patients received additional local radiotherapy or chemotherapy. Patients received additional therapy arbitrarily if, in the opinion of the treating clinician, lesions were not improving. In the patients with HHV seropositive, ganciclovir were prescribed.

Renal Outcome

The renal prognosis of patients who did not succumb to disseminated disease was related to the management of immunosuppression. All two patients in whom immunosuppression was discontinued had functioning grafts when KS was diagnosed, but all grafts were acutely rejected. One patient had azathioprine and one patient had cellcept immunosuppressive therapy and there is no significant difference between these two regimens (P> 0.05). Dialysis was re-instituted in these patients a mean of 5 weeks after discontinuation of all immunosuppression. Other patients had good response to reducing Immunosuppression and remained their grafts in period of study.

DISCUSSION

Post-transplantation KS is a well-known complication after renal transplantation with a possible negative impact on the patient's and graft long term survival. The KS incidence peaks during the first year post-transplantation. In our study, 82.3% of all KS cases were diagnosed in the first 2 years after receiving a renal allograft, which is compatible with previous studies.[13, 14]

The results of this study showed lower incidence of KS (1.1%) in our transplant population than that reported from other regional countries.[15] Further, KS is frequent in African renal transplant recipients, where 13.3% of all transplanted patients developed KS.[16] We investigated the KS was the most frequent post-transplantation malignancies. In confirm to our study, Saudi Arabian[17] and Turkish[15] studies were

reported the most frequent post-transplantation malignancies were KS with 87.5% and 80.0%, respectively. Also, Nafar et al., found that the most common malignancy after kidney transplantation was KS among the Iranian patients.[2]

It is a difficult task to treat patients with a post-transplant malignancy. The risk of death from dissemination of malignancy should be weighed against the risk of graft rejection. According our results, in 11 patients (91.6%) KS skin lesions improved with reduction (including 6 patients with sirolimus therapy) or discontinued of immunosuppression with a graft loss rate of 11.7%. In compare to our study, Reduction of immunosuppression resulted in complete remission of KS in 28% of patients from Saudi Arabia,[17] and 61% of Italian patients.[18] Duman et al., report on complete remission after reduction of immunosuppressive drugs in all patients [12/12], with a graft loss rate of 20% in Turkey. [15] Reduction of immunosuppression allows for the immune system to reduce viral replication producing clinical remission of disease. New antiviral agents have recently been introduced as a promising therapeutic option in patients with KS.[19–21] However, prospective studies that will determine the efficacy of this approach are warranted. Sirolimus is a potent immunosuppressive drug that has been recently reported as an effective agent in the treatment of KS. Cutaneous KS lesions disappeared in all patients three months from the initiation of sirolimus therapy.[22] Sirolimus may become the first choice immunosuppressant in renal transplant recipients with KS for pro-viding optimal immunosuppression and inhibiting the progression of malignancy.

HHV-8 has been described in patients with HIV infection and KS.[23] The results of serologic studies support the notion that infection with HHV-8 is nearly universal in patients with KS, since specific antibodies are detectable in 70% to 90% of all patients with KS and almost 100% of immunocompetent patients with the disease. Also it's clear that Pre-transplantation HHV-8 seropositivity is found to be associated with an increased risk of post-transplant KS. Immunosuppressive treatment may induce reactivation of latent virus infection, playing an important role in the development of combined iatrogenic and endemic KS. It is also possible that HHV-8 may be transmitted from the donor to induce sarcoma development in the organ recipient.[24-26] We investigated that about 67% of our KS patients were seropositive for HHV after transplantation. Laboratory studies of the susceptibility of HHV-8 to antiviral drugs suggest that the virus is resistant to acyclovir and penciclovir, but sensitive to ganciclovir, foscarnet and cidofovir.[27] So, we treated our patients with ganciclovir.

CONCLUSION

KS is a common long-term complication in renal transplant recipients, with an increased incidence compared with the general population. Given that candidates for organ transplantation who are seropositive for HHV-8 -and thus at risk for KS- can now be identified, chemoprevention should be available in this high-risk population. Such strategies in HHV-8-seropositive candidates for organ transplantation should be directed against the virus itself, and the immunosuppressive regimen should be carefully monitored to avoid the possibility of rejection.

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