

Kaposi's sarcoma in kidney transplantation: a 23-year experience

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■ ABSTRACT

Background: Kaposi's sarcoma is a cutaneous and extra-cutaneous multicentric malignancy first described by Moritz Kaposi in 1872. It is well recognised in renal transplant recipients and accounts for a significant portion of post-transplant neoplasms, with an overall average reported risk of 0.5 percent.

Aim: To assess the frequency of Kaposi's sarcoma in renal transplant recipients and determine demographic data, immunosuppression regimen, disease outcome and graft function after treatment.

Design: Retrospective study in a single centre in Portugal.

Subjects and Methods: Data from 1479 recipients treated at our institution July 1983 – September 2006 were reviewed.

Results: Six patients (0.4%) developed Kaposi's sarcoma. Pathological diagnosis was established early after transplantation (mean interval of 23 months). The ratio of male to female patients was 5 to 1 (with no correction for the differential transplant rates between genders) and the mean age at the time of diagnosis was 44 years. All patients had cutaneous or mucosal lesions and visceral involvement occurred in three cases (50%). All received calcineurin inhibitors; five ciclosporin and one tacrolimus.

Pretransplant recipient and donor human herpesvirus 8 serology was not performed and serostatus was known in only two after transplantation (one negative and one positive).

Two patients (33%) treated with Interferon alpha lost their grafts, returning to dialysis. Chemotherapy was added in four patients, and surgical excision performed in two. Since the advent of sirolimus, two patients have been converted to this agent, with inhibition of tumoral progression, while providing effective immunosuppression. No patient succumbed to Kaposi's sarcoma.

Conclusions: Kaposi's sarcoma in immunocompromised patients tends to be aggressive, with multi-organ involvement. In our patients conversion to sirolimus was a successful approach to its management. Chemotherapy is an effective option as an adjuvant or when disseminated disease fails to respond to immunosuppression changes.

■ Key-Words:

Kaposi's sarcoma; kidney transplant.

■ INTRODUCTION

First described in 1872¹, Kaposi's sarcoma (KS) has received renewed interest from the medical community over the past few decades because of its occurrence

in increasing numbers in patients with HIV or on immunosuppressive medication, such as organ transplant recipients. The incidence of KS is very much (84 to 500 times) higher in transplant recipients than in non-immunosuppressed populations².

The aetiopathogenesis of KS is complex, but a viral cause has long been suspected, and was confirmed in 1994 by the discovery of human herpesvirus 8 (HHV-8)³, an oncogenic gamma-herpesvirus known to cause infection in immunosuppressed, immunogenetically susceptible individuals⁴.

Skin involvement may be universal⁵, as in our series, with macular dark blue or purplish skin lesions. Visceral involvement, predominantly of lymph nodes, gastrointestinal tract and lungs⁶, occurs in 25 to 30 percent of kidney transplant recipients with KS⁷. Involvement of the renal allograft is unusual⁸. Post-transplantation KS is usually similar to the classic form, manifested as angiomatous lesions predominating on lower limbs twice as commonly as on the arms⁹.

KS in solid organ recipients usually has a benign course, but reports from the Arabian Peninsula describe an aggressive pattern in over a quarter of patients, characterised by rapid growth and widespread dissemination within a few weeks and a more frequent multicentric involvement^{10,11}.

The course of KS depends on the level of immunosuppression. Lesions usually regress with reduction/discontinuation of immunosuppressive therapy^{12,13}. Surgical excision, whenever possible, is a first line option. Additional treatment, required in cases of persistent functional disability or life-threatening disease, may include chemotherapy with liposomal anthracyclines or radiotherapy¹⁴. Interferon alpha may be effective, but should be used with caution, due to the risk of graft rejection¹⁵.

In this study, we report our experience with KS in a cohort of kidney transplant recipients.

■ SUBJECTS AND METHODS

Records of the 1479 kidney transplant recipients between July 1983 and September 2006 at our institution were retrospectively reviewed. All cases of KS were confirmed by pathological diagnosis. Data included

demographics, donor source (cadaveric or living-related), chronic kidney disease aetiology, immunosuppressive protocol, number of transplants, human leukocyte antigen (HLA) profile, human immunodeficiency virus (HIV) and HHV 8 status, therapeutic management, graft and patient survival rates and aetiology of graft loss.

■ RESULTS

Of 1479 kidney transplants performed at our centre, six patients (0.4%) were identified with KS. Demographic and clinical data of patients with KS are summarised in Table I. All patients were Caucasians. The male to female ratio was 5:1 compared with 1.4:1 in all renal transplant patients. Mean age at diagnosis was 44±13 years. They had all received kidneys from deceased donors; none of the 59 living donor recipients had KS. One patient had a second transplant. Pathological diagnosis of KS was established within 13 to 34 months (mean ± SD = 23±7) after transplantation. Aetiology of end stage renal disease was not known in four patients, one patient had chronic pyelonephritis and one had IgA nephropathy. All patients were HIV negative. Pretransplant antibody screening for HHV 8 was not performed. Serostatus for HHV 8 was known in only 2 after transplantation: one patient was IgG positive at one year, and another was IgG negative at two years after transplant. No data on donor HHV 8 serology were available.

All patients received calcineurin inhibitors (CNI). Basal CNI level was within the normal range in all patients. The immunosuppressive regimen consisted of prednisolone (Pred) and ciclosporin (CsA) in four patients; Pred, CsA and mycophenolate mofetil (MMF) in one and Pred, Tacrolimus and MMF in another. None of the patients were treated with polyclonal or monoclonal antibodies as induction immunosuppression, but therapy with polyclonal antilymphocyte globulin was needed in one due to acute rejection.

Skin involvement was universal and visceral involvement occurred in three (50%) patients. The sites of cutaneous involvement were lower limbs (five patients), followed by head (two patients), and trunk (one patient). One patient had cutaneous multicentric lesions of the lower limbs, head and trunk. KS affected the gastrointestinal tract (GI) in two patients, with lungs also affected in one and lymph nodes in another.

Table 1

Demographic and clinical data of post-transplant KS patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at diagnosis (yrs)	42	54	21	41	60	48
Gender	Male	Female	Male	Male	Male	Male
Time from Tx to diagnosis of KS (mths)	19	34	20	25	28	13
ESRD aetiology	Not known	Chronic pyelonephritis	Not known	IgA Nephropathy	Not known	Not known
HLA						
A	3.9	2.0	2.24	11.33	9.30	2.11
B	7.15	7.0	35.41	17.35	13.57	18.35
DR	2.0	7.11	12.15	4.6	4.7	1.3
Distribution of lesions	Skin, GI tract	Skin	Skin	Skin, lymph nodes	Skin	Skin, GI and lung
Treatment of KS	CsA withdrawn + anthracycline + surgery	Switch to SRL	CsA withdrawn + IFN	CsA reduced + IFN	CsA withdrawn	Switch to SRL + anthracycline + surgery
Follow up after KS (months)	49	175	191	205	106	41
Outcome Patient/kidney	Alive/functioning graft	Died/functioning graft	Alive/Dialysis	Alive/Dialysis	Alive/functioning graft	Alive/functioning graft

In all cases, treatment consisted of reduction/modification in immunosuppression, together with chemotherapy in four, which was combined with surgery in two. Details of treatment options were as follows. We stopped CNI therapy in three, reduced CsA dosage in one and switched from CNI to sirolimus (after this agent became available in our unit) in two transplant recipients (target trough levels of 10 ng/mL). Liposomal anthracycline (doxorubicin 20 mg/m², iv, every 2 weeks) was added in two patients, one with cutaneous and GI involvement, and another with KS affecting the skin, lungs and GI tract. Several years ago, two patients were managed with subcutaneous low-dose Interferon alpha (IFN) (3 million UI sc, 5 times a week, until remission, followed by 3 times a week). KS skin lesions improved with therapy, with tumour healing over several months with residual pigmented or hyperkeratotic lesions.

The renal outcome was good in four patients, whose grafts continued to function well. However, the two patients treated with IFN developed acute rejection, with loss of graft function; they subsequently required graft nephrectomy and returned to dialysis. One patient died from ischemic colitis over 14 years after developing KS. None succumbed to KS. At the present time, the other 5 patients are alive at 3 to 17 years after diagnosis, with no evidence of recurrence.

DISCUSSION

Owing to the use of immunosuppressive drugs, renal transplant recipients are at risk of malignancies including KS. In our treatment protocol for KS, withdrawal only of the most potent immunosuppressive agent, usually ciclosporin, was the mainstay option, although chemotherapy was also needed in more aggressive cases.

Our results are very impressive with regard to mortality. In the Cincinnati Transplant Tumor Registry (CTTR), 57% of patients with visceral involvement died¹⁶. Despite the fact that 50% of our patients had visceral disease, no patient was lost as a result of KS. Our epidemiological data were similar to those reported in the CTTR, in which there was a male preponderance, visceral involvement in 40% (higher than previously reported⁷) and a mean time from transplant to diagnosis of KS of 21 months.

We treated two patients with sirolimus. They showed progressive tumour regression without any apparent increased risk of rejection. More, one of these patients showed better graft function after conversion, which may be a result of the avoidance of a nephrotoxic drug. A recent work¹⁷ has shown that antineoplastic effects of sirolimus are primarily mediated by an antiangiogenic effect achieved through suppression

of vascular endothelial growth factor (VEGF), which induces growth of the tumour. In this study, Stallone *et al*, examined biopsy specimens for the presence of VEGF; Flk-1/KDR protein, the VEGF receptor; as well as phosphorylated Akt and p70S6, two enzymes in the signalling pathway targeted by sirolimus. Levels of the VEGF receptor and the latter enzymes were increased in the Kaposi's-sarcoma cells. VEGF was also increased in the Kaposi's-sarcoma cells and even more so in the normal skin cells immediately surrounding the lesions. This dual role of sirolimus may prove important in other situations in which transplant recipients are at high risk of tumour recurrence or primary cancer.

Several authors have reported that KS is seen more commonly and earlier in CsA treated patients¹⁸. In addition to its immunosuppressive action, a direct cancer promoting effect of ciclosporin by a cell-autonomous mechanism has been established¹⁹. In our series, KS was apparently more frequent with CsA, but there were too few patients to establish whether or not there is a real increase in risk with this agent. As reported by others^{20,21,22}, we had one patient with KS whose immunosuppression was Pred, tacrolimus and MMF.

In the early 1990s, when few therapeutic options were available, based on results in HIV patients, in whom Interferon-alpha (INF-alpha) has a capability to induce clinical remission (partial or complete) in 30-70%²³, we used this agent in two of our patients. Interferons are a family of proteins produced by nucleated cells that have anti-viral, anti-proliferative and immunomodulatory activity. Multiple effects have been detected, namely, antitumour activity with inhibition of cellular growth. The tumoral lesions disappeared in these two patients, but they developed severe acute rejection and lost their grafts.

KS can occur due to reactivation of HHV 8 infection in the recipient or due to the transmission of the virus from the donor³, consequently pretransplantation antibody screening is useful for identifying high-risk patients, especially in ethnic groups with a high prevalence. In this group the risk of post-transplantation KS is 23 to 28 percent²⁴, as compared with a risk of 0.7 percent²⁵ in patients who are seronegative before receiving a kidney transplant.

Iatrogenic KS shows extreme ethnogeographic associations, occurring in only about 0.4% of transplant

patients in the United States and Western Europe but in 5.3%²⁶ of renal transplant patients in Saudi Arabia and 2.4% in Turkey²⁷. The high frequency of iatrogenic KS in Saudi Arabia reflects the 7% endemic seroprevalence of HHV 8 in healthy Saudi donors. In our study, however, KS incidence was low (0.4%), which suggests that, along with viral infection, genetic predisposition may play a pathogenetic role. However, immunosuppression is the leading risk factor in transplant patients.

Conflict of interest statement. None declared.

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