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Successful treatment of post-transplant Kaposi's sarcoma by reduction of immunosuppression†

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Abstract

Background. The aim of this study was to investigate retrospectively the clinical presentation, the efficacy of reducing immunosuppression and the consequences of this therapeutic approach in Kaposi's sarcoma (KS) developing after renal transplantation.

Methods. We reviewed the records of 502 patients who had been followed up at our transplantation unit between October 1, 1987 and December 30, 1998. Twelve patients (2.4%) with KS were included in the study.

Results. The mean age of KS patients was 38 ± 11 years (one female, 11 males). All were on prednisone, azathioprine (AZT) and cylcosporin treatment. KS was encountered at a mean of 18 ± 10 months post-renal transplantation. Typical Kaposi's lesions were present in the skin of 11 out of l2 patients. In the only patient without skin involvement, who died from haemophagocytic histiocytic syndrome caused by septicaemia, KS was diagnosed post-mortem in a lymph node. In five patients only skin involvement was present, while the others also had visceral involvement (oropharynx in two patients, trachea and lung in three, lymph node in two, stomach and duodenum in two). Cyclosporin was stopped within 1 month after KS diagnosis, and AZT was stopped in three patients. Both cutaneous and visceral KS manifestations disappeared and no patient was lost due to KS. During a follow-up period 46 ± 19 months, KS recurred in the lungs in one patient together with lung tuberculosis, while he was on prednisone and AZT. Two patients lost their graft due to chronic rejection. The remaining eight patients currently have a functioning graft with a mean creatinine level of 1.4 ± 0.5 mg/dl.

Conclusion. KS is the most frequent post-transplant neoplasia (80%) in our country. In the present study cohort, half of the patients had visceral involvement. Reduction or discontinuation of immunosuppression caused complete remission in all patients without surgical intervention, chemotherapy or radiotherapy.

Keywords: Kaposi's sarcoma; kidney transplantation; malignancy

Introduction

Moricz Kaposi first described Kaposi's sarcoma (KS) in 1872 [1]. Although its cellular origin is controversial, KS is generally regarded as a tumour of endothelial or spindle cell lineage origin, classically described as a pigmented multicentric angiosarcoma [2,3].

In 1969, the first case of KS in association with immunosuppression in a renal transplant patient was diagnosed. Since that time a number of renal and other organ allograft recipients receiving prednisone and azathioprine (AZT) have developed KS after the onset of immunosuppressive therapy [4]. The tumour is seen more commonly and earlier in cylcosporin (Cs)-treated patients than in patients on prednisone and AZT [5]. The incidence of KS in immunosuppressed renal transplant recipients was increased 400- to 500-fold over that seen in a control population of the same ethnic origin [6]. The tumour is more frequent among renal transplant recipients of Mediterranean, Arabic, Jewish and black origin [7]. The male : female ratio is 3 : 1. In 46% of cases, tumour occurs in the first year post-transplantation. Sixty per cent of patients who reported to the Cincinnati Transplant Tumor Registry (CTTR) had non-visceral KS confined to the skin, conjunctiva, or oropharingeal mucosa, and 40% had visceral disease that involved mainly the gastrointestinal tract, lungs and lymph nodes, but other organs were also affected [8].

Many treatment modalities have been used for post-transplant KS: surgical excision, radiation therapy,

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intralesional injection of chemotherapeutic agents, such as etoposide, bleomycin and vinblastin, reduction of immunosuppressive therapy, administration of α-interferon or cancer chemotherapy, or a combination of these various treatments. Most authorities agree that the first priority is to reduce immunosuppression. Clinical management of renal transplant patients who develop KS is difficult and requires a balance between the risk of death from generalized KS and the risk of graft rejection and complications of renal failure that may occur if immunosuppressive therapy is discontinued.

The aim of this study was to review the experience with KS in our renal transplant recipients and to analyse clinical presentation and response to treatment.

Subjects and methods

We retrospectively reviewed all patients who developed KS after renal transplantation in the Ege University Organ Transplantation Unit. The records of 502 patients who had been followed up at our unit between October 1, 1987 and March 30, 2001 were reviewed. Seventy per cent of all patients received transplant from a living related donor. Twelve patients with KS were included. Demographic data are given in Table 1.

KS was diagnosed in 11 patients by skin biopsy and in one by post-mortem lymph-node examination. Endoscopic examination of the upper gastrointestinal tract was used in four patients with gastrointestinal discomfort, bronchoscopy was used in three with pulmonary symptoms, chest X-ray was used in all patients, and thorax computed tomography (CT) was used in seven (one of them had positive chest X-ray findings). The tests were performed again when skin lesions had disappeared.

All patients received the following immunosuppressive regimen: methylprednisolone (500 mg i.v. before and after transplantation, and 250 mg i.v. every 12 h for three doses post-operation), AZT (2 mg/kg i.v. before transplantation, followed by 2 mg/kg/day orally, adjusted to maintain the white blood cell count at $>3.5\times10^9$/l), prednisone (1 mg/kg/day orally, tapered by 0.1 mg/kg every other day to 0.2–0.3 mg/kg/day, and reduced 0.1 mg/kg/day after 1 year) and Cs (5–8 mg/kg/day, adjusted to maintain the serum cylcosporin level within a specified target range). The Abbott TDx assay was used, with a target range of 180–220 ng/ml for the first year, 140–180 ng/ml for the second year, and 100–140 ng/ml for the third and subsequent years. Episodes of acute rejection were treated with a 1 g i.v. bolus of methylprednisolone on 3 consecutive days.

Immunosuppressive therapy was reduced or withdrawn once KS was diagnosed. First, cyclosporin dosage was reduced by 50% and then stopped within 1 month in all patients after diagnosis; AZT was also stopped in two patients. Neither chemotherapy nor radiotherapy was used. In five patients, an acute rejection episode occurred and was treated with pulse steroids before KS diagnosis. Anti-lymphocyte antibody treatment (ATG or OKT3) was not used. All patients were screened for anti-HIV ELISA. Tests for human herpes virus 8 (HHV-8) were not performed.

Results

The prevalence of KS was 2.4% (12/502) in our renal transplant population. Mean age was 38 ± 11 years (range 22–55 years). Male : female ratio was 11 : 1; this ratio was 1.7 in all renal transplant patients (317/185) (see Table 1). All but one (patient 5, cadaveric donor) received allograft from living related donors. Immunosuppressive therapy consisted of steroids, AZT and Cs in 11 patients at the time of KS diagnosis. One patient (patient 3) was on steroid and AZT, as Cs was stopped due to *de novo* haemolytic uraemic syndrome in the sixth month post-transplantation. Five patients had been treated with pulse steroids for acute rejection

Table 1. Demographic and clinical data

Patient no.	Age (years)/ sex	Primary kidney disease	Acute rejection episode	Time from RTx to KS (months)	Localization	Diagnosis
1	47/M	Unknown	–	26	Skin, lymph node	Skin and lymph node biopsy
2	22/M	Unknown	–	32	Skin	Skin biopsy
3	54/M	Chronic glomerulonephritis	At month 6	31	Skin	Skin biopsy
4	30/F	Chronic pyelonephritis	–	5	Lymph node	Post-mortem lymph node biopsy
5	46/M	Unknown	–	7	Skin	Skin biopsy
6	55/M	Unknown	–	20	Skin, oropharynx, lung, stomach, lymph node	Skin biopsy, gastroscopy and bronchoscopy
7	34/M	Chronic pyelonephritis	–	6	Skin	Skin biopsy
8	24/M	Chronic pyelonephritis	At month 9	25	Skin, lung, lymph node	Skin and lymph node biopsy, bronchoscopy, gastroscopy
9	38/M	Unknown	–	23	Skin, lymph node	Skin and lymph node biopsy
10	39/M	Unknown	At week 3	18	Skin	Skin biopsy
11	32/M	Amyloidosis due to FMF	At month 1	5	Skin, stomach	Skin biopsy, gastroscopy
12	37/M	Hypertensive nephropathy	At month 3	15	Skin, oropharynx, lung	Skin biopsy, bronchoscopy, gastroscopy

RTx, renal transplantation; FMF, familial mediterranean fever.

episodes before diagnosis of KS. No patients tested positive for HIV.

The average time to appearance of KS was 18 ± 10 months (range 9–32 months) after transplantation (see Table 1). Diagnosis was made by skin biopsy in 11 of 12 patients. In two of four patients in whom endoscopic examination of the upper gastrointestinal tract was performed, stomach and duodenum involvement was detected. Thorax CT was performed in seven patients and revealed lung involvement in three. With bronchoscopic examination of these three patients, KS-associated lesions were also seen in the trachea and bronchial system (Table 1).

In one patient (patient 4), KS was diagnosed on necropsy of the lymph node. She was admitted to hospital with fever and weight loss in the 10th month post-renal transplantation. Right posterior cervical lymph node enlargement, splenomegaly and pancytopenia were found under physical examination. Bone marrow examination revealed haemophagocytic histiocytic syndrome. The patient died due to multiple organ failure as a result of septicaemia.

Mean follow-up period was 46 ± 19 months (range 25–73 months). Immunosuppressive therapy was reduced or withdrawn in all of 11 patients after diagnosis (see Table 2). Once KS diagnosis was made, Cs was stopped in 10 patients on this treatment. The regression of KS lesions in skin and visceral organs occurred in eight patients and completely disappeared within 6 months (complete remission). In two patients (patients 8 and 11) whose KS lesions did not regress within 2 months after discontinuation of Cs, AZT was also stopped (see Table 2). In patient 11, KS lesions were widespread (he also had visceral involvement), one of which regressed within 6 months; the others were localized.

In two patients (patients 6 and 8), an acute rejection episode occurred after reduction of immunosuppression but was successfully treated by pulse steroids. KS reappeared in the lungs (without skin involvement), however, and patient 8 contracted tuberculosis following treatment for acute rejection. Immunosuppressive therapy was discontinued in this patient and he lost his graft due to chronic rejection. Another patient (patient 6) is now on prednisone and low-dose AZT, and has a good functioning graft.

During a mean 46 ± 19 months of follow-up, graft loss due to chronic rejection occurred in two patients (patients 8 and 9). Two patients were lost during follow-up: patient 1 died due to myocardial infarction 43 months after occurrence of KS, and the condition of the other, patient 4 (diagnosed post-mortem), is summarised above. All data are summarized in Tables 1 and 2.

Discussion

When non-melanoma skin cancers and *in situ* carcinomas of the uterine cervix were excluded, KS comprised 5.7% of neoplasms reported to the CTTR [9]. In our renal transplant patients, the prevalence of KS is 2.4% (12/502): KS constituted 80% of all post-transplant neoplasia, which is strikingly higher than that in CTTR. Ecder *et al.* also reported a high frequency of KS in Turkey. Genetic predisposition may be important in this area [10]. Similarly, the prevalence of KS was reported as being 5.3% in Saudi Arabia, comprising 87.5% of post-transplant neoplasia [7].

The mean age of our patients was 38 ± 11 years and did not differ significantly from that of CTTR. Male preponderance was more pronounced in our study. The time of occurrence of KS after renal transplantation in our study was 18 ± 10 months, as opposed to 21 months in CTTR.

In the Cincinnati Registry, visceral involvement was present in 40% of cases. Similarly, we detected visceral involvement in nearly half of all patients investigated for this.

In the Cincinnati Registry, 42% of patients with KS had complete remission after various treatments;

Table 2. Patient immunosuppressive therapy, management and outcome

Pt No	IS dose before KS Pr/AZT/Cs (mg/day)	Management	IS dose after KS Pr/AZT (mg/day)[a]	Follow-up after KS (months)	Outcome: last creatinine (mg/dl)
1	10/100/150	Cs stop; Pr–AZT	10/75	43	Died—myocardial infarction
2	10/100/125	Cs stop; Pr–AZT	10/125	59	1.2
3	10/150	AZT stop; Pr	7.5/125	55	1.2
4	15/100/250	Cs stop; Pr–AZT	–	–	Died—haemophagocytic syndrome
5	10/150/250	Cs stop; Pr–AZT	10/175	73	1.2
6	10/125/250	Cs stop; Pr–AZT	10/125	56	2.2—acute rejection episode 1 month later
7	10/100/300	Cs stop; Pr–AZT	7.5/150	65	1.1
8	10/50/200	Cs, AZT stop; Pr	10/75	19	Dialysis—acute rejection episode 2 months later
9	10/100/225	Cs stop; Pr–AZT	10/100	17	Dialysis
10	15/75/250	Cs stop; Pr–AZT	10/75	62	1
11	15/150/350	Cs, AZT stop; Pr	10/–	39	1.2
12	10/125/300	Cs stop; Pr–AZT	10/150	25	2.1

Pr, prednisolone; IS, immunosuppressive therapy; RTx, renal transplantation.
[a]Doses used for patients in March 2001.

38% of these were the result of reduction or cessation of immunosuppressive therapy [11]. In the Cincinnati Registry, after immunosuppression had been reduced, KS disappeared in 17% of 213 patients with mucocutaneous involvement and 16% of 143 patients with single or multiple visceral involvements [8]. Qunibi *et al*. [7] reported that in Saudi Arabia, complete remission following reduction or cessation of immunosuppression was achieved in 28% of cases. Only Ponticelli *et al*. [12] reported impressive results against Penn. Their complete remission rate following reduction or cessation of immunosuppression was 61% and graft loss rate was 31%. These were not higher than that reported in the literature. In our group, reduction or discontinuation of immunosuppression caused complete remission in all patients, with a graft loss rate of 20%. Our results were similar to, and probably better than those of Ponticelli.

Mortality rates vary widely from study to study. In the CTTR series, 57% of patients showing visceral involvement died. Moreover, 72% of deaths were accompanied by KS. In a French study, 21% of patients with KS died and all had visceral involvement. Despite the fact that nearly half of our patients had visceral involvement, no patient in our group was lost directly as a result of KS. All patients were treated with no other therapy. We think that our experience of KS is important in this respect, and our results are very impressive. Patients were shielded from the side effects of chemotherapy, radiotherapy or other therapies, and this approach was also cost effective.

An increased risk of post-transplant KS may be associated with serological evidence of HHV-8 infection (also known as Kaposi's sarcoma-associated herpes virus or KSHV), which has been described in patients with HIV infection and KS [13]. In a study of renal transplant recipients from Saudi Arabia, Qunibi *et al*. [14] found a markedly higher incidence of specific anti-HHV-8 antibodies in patients with KS compared with those without this malignancy (92 *vs* 28%; $P > 0.001$). Cattani *et al*. [15] and Diociaiuti *et al*. [16] reported pre-transplantation HHV-8 seropositivity as a risk factor for KS in kidney transplant recipients. In 400 consecutive renal transplant recipients, 32 had antibodies to HHV-8 at the time of transplantation. At 3 years post-surgery, 28% of antibody-positive patients had developed KS compared with no cases in antibody-negative patients [17]. Unfortunately we do not have the serological data for our group: HHV-8 testing was not performed due to technical difficulties.

The apparently higher risk of KS within a population of HHV-8-positive kidney transplant recipients is a strong argument in favour of systematic screening of HHV-8 serological features before transplantation. The challenge in the future will be to prevent the development of KS in these HHV-8-positive patients by avoiding overimmunosuppression.

It is well known that KS lesions may regress as a result of reduction or modulation of immunosuppressive therapy. However, clinical management of renal transplant patients who develop KS is difficult and requires a balance to be struck between the risk of death from generalized KS and the risk of graft rejection and renal failure complications that may occur if immunosuppressive therapy is discontinued.

Management of KS in our study consisted of progressively tapering immunosuppressive therapy, regardless of KS dissemination. Chemotherapy was prescribed only when a functional disability persisted, and polychemotherapy was prescribed for life-threatening disease. Barete *et al*. [18] reported that one (5%) of 20 patients died of KS progression. The rate of remission was 45% in their group, with a mean follow-up of 35 months. In our study we did not lose any patient due to KS progression.

In conclusion, KS is the most frequent post-transplant neoplasia (80%) in Turkey and half of our patients had visceral involvement. Reduction or discontinuation of immunosuppression caused complete remission in all patients without surgical intervention, chemotherapy or radiotherapy. Reduction of immunosuppressive therapy is sufficient, and also safer and cheaper than other therapies, for these patients.

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