Kaposi's sarcoma in Sudanese renal transplant recipients: A report from a single center

Abdalla I. Sabeel, Wajeh Y. Qunibi, Osman A. Alfurayh, Khalid Al Meshari

Department of Medicine, Section of Nephrology, King Faisal Specialist Hospital & Research Center, Riyadh - Saudi Arabia

ABSTRACT: *Background:* **The incidence of Kaposi's sarcoma (KS) in Sudanese renal transplant recipients is not known.**
Methods: **We retrospectively assessed the prevalence of KS in 30 Sudanese renal transplant recipients followed for 16 years.**
Results: **Four patients (13.3%) developed KS within 4-36 months after transplantation. All patients were HIV negative.**
Conclusion: **The incidence of KS in Sudanese renal transplant recipients is very high, supporting the theory of racial or geographic factors in its genesis.**

Key words: *Kaposi's sarcoma, Sudanese, Renal transplant*

INTRODUCTION

Kaposi's sarcoma is a spindle-shaped vascular cell tumor that occurs in the skin, lymphoid, respiratory and gastrointestinal tissues. The classical KS is a rare cutaneous tumor of the lower limbs, usually affecting elderly men from Eastern Europe and the Mediterranean region, and runs a relatively benign course (1). The epidemic type of KS is a distinct and progressive form of the disease that affects patients with AIDS (2). Endemic KS is common in sub-Sahara Africa and progresses gradually, occurring predominantly on the legs and feet of young men (3). The prevalence of endemic KS is highest in equatorial Africa in a strip involving Uganda, Sudan and Zaire, accounting for 2-10% of adult malignancies (4).
Immunosuppressive therapy after renal transplantation is generally associated with a 200-fold increase in the incidence of KS (5). However, in certain ethnic groups, the incidence is 400-500 times greater than in normal controls (6). Among Saudi Arabian renal transplant recipients, KS is the most common tumor (7). Besides immunosuppression, environmental and genetic factors may play a permissive role and oncogenic viruses are also suspected in its pathogenesis. Kaposi's sarcoma-associated herpes virus (KSHV) was found in lesions from patients with all types of KS (8,9) and is now believed to be the causative agent.
The incidence of KS among Sudanese renal transplant recipients is not known. In this study we report our experience with KS in Sudanese renal transplant patients in our institution.

PATIENTS AND METHODS

Between 1984 and 2000, 30 adult Sudanese renal transplant recipients were followed at our hospital. One had had a cadaver kidney transplant abroad and the rest received living-related-donor kidneys at our institution. Twenty-six patients received triple immunosuppression with prednisolone, azathioprine and cyclosporine and four received only prednisolone and cyclosporine. The minimum transplant follow-up was two years.
The medical records of the Renal Transplant Unit and the Hospital Tumor Registry were reviewed and four of the 30 Sudanese patients were identified as having KS. Their medical records were reviewed in detail with special focus on the clinical course of KS, response to treatment and the allograft outcome. Sera of patients with KS were sent to test for KSHV antibodies. The specimens of KS lesions were formalin-fixed and paraffin-embedded, and studied later to detect KSHV DNA in these tissues.

RESULTS

Table I shows the main features of the four patients (13.3%) who developed KS. Their immunosuppressive regimen was similar to the other patients without neoplasia. HIV antibodies were negative in all cases.

Case 1

A 42-year-old woman received a cadaver renal transplant abroad in July 1984. Post-operatively she had 14 days' treatment with antithymocyte globulin. In the early post-transplant period she had an episode of rejection which was treated with pulse methylprednisone. Seven months after transplant her serum creatinine stabilized at 160 µmol/L with cyclosporine and prednisone. She returned to Saudi Arabia and was followed at our institution.

Three years post-transplant she developed cutaneous lesions on her legs and histological examination of one of the lesions showed KS. No visceral involvement of KS was detected by thoraco-abdominal CT or GI endoscopy. The dose of cyclosporine was halved and the tumor regressed completely but the allograft function deteriorated and serum creatinine reached 260 µmol/L. One year later she remained well with stable graft function and no clinical lesions of KS were detected. Then she had herpes zoster infection complicated by herpes encephalitis. Immunosuppression was discontinued and after treatment with intravenous acyclovir, she recovered from the herpes zoster infection but her allograft was lost due to chronic rejection and she returned to dialysis. She remained well on dialysis for six months but after that she was lost to follow-up.

Case 2

This 55-year-old man received a living-related-donor kidney transplant at our institution in December 1984. During the second week after transplant he received a five-day course of methylprednisone for rejection, and then was maintained on cyclosporine and prednisone with serum creatinine 120 µmol/L. Four months post-transplant he noticed multiple skin lesions in his upper and lower limbs, followed by two lesions on the tip of his nose. Biopsy of the left arm lesion was diagnostic for KS. Cyclosporine was discontinued and azathioprine 100 mg/day was introduced. The lesions on the nose were irradiated and the other lesions excised. CT and endoscopic studies showed no evidence of KS in internal organs. Graft function did not change, although cyclosporine was not reintroduced.

Ten years later, when he was taking 50 mg azathioprine and 10 mg prednisone per day, he had a recurrence of KS on the right foot. Clinical, radiological and endoscopic studies did not detect KS in other sites. Azathioprine was reduced to 25 mg and the lesions disappeared. Two years later he had another recurrence of cutaneous KS (the site of the previously healed KS) but there was no evidence of KS at other sites. HIV was negative and the lesions disappeared

TABLE I - CHARACTERISTICS OF SUDANESE RENAL TRANSPLANT RECIPIENTS WITH KAPOSI'S SARCOMA

Patient Age/Sex	Time from transplant to KS (months)	Type of KS lesions	CSA trough levels at the time of KS (µg/L)	Follow-up after KS (months)	Patient outcome	Allograft outcome (S-Cr)
1. 42/ F	36	Skin lesions on the leg	402	18	Cured. No recurrence	260 µmol/L (rejection, back to dialysis)
2. 55/ M	4	Multiple skin lesions on the limbs and nose	781	175	Cured. Had a recurrence and cured.	290 µmol/L
3. 32/ F	12	Lesions on the skin, GI tract and conjunctiva	492	100	Cured. No recurrence	96 µmol/L
4. 44/ M	5	Lesions on the nose	692	90	Cured. No recurrence	163 µmol/L

CSA = Cyclosporine, KS = Kaposi's sarcoma, S-Cr = Serum creatinine.

after irradiation. Four years later he was asymptomatic on daily doses of 25 mg azathioprine and 10 mg prednisone with serum creatinine 290 µmol/L.

Case 3

This 32-year-old woman received a living-related-donor kidney transplant at our hospital in December 1991. She was maintained on cyclosporine, azathioprine and prednisone, having normal graft function. In March 1992 she tested positive for HbsAg with antigenemia, and the azathioprine dose was reduced from 75 to 50 mg. One year post-transplant she developed KS involving the right thigh, left eye conjunctiva, stomach and rectosigmoid colon. Cyclosporine was reduced by 60% and the KS lesions disappeared within four months. Subsequent clinical, radiological and endoscopic investigations did not detect KS. Later, the cyclosporine dose was adjusted to achieve trough levels of 100-150 µg/L. At her latest visit, more than eight years after the initial diagnosis of KS, she was symptom-free and her kidney graft was functioning normally.

Case 4

This 44-year-old man received a living-related-donor renal transplant at our institution in May 1992. He received induction therapy with antilymphocyte globulin (ALG) for 14 days, then was maintained on cyclosporine, prednisone and azathioprine. He was discharged from the hospital with serum creatinine 140 µmol/L.

Five months after transplantation he noticed smooth brownish-purple nodules on both sides of his nose. Skin biopsy of the lesion on the right side confirmed KS. Cyclosporine and azathioprine doses were both reduced by 40 % and the lesions on the nose were treated by irradiation. Bronchoscopy showed suspected KS lesions on the trachea but bronchial brushing and biopsy from the trachea were negative. Upper GI endoscopy was normal. Colonoscopy showed a nodular polypoid mass in the transverse colon which was resected and its histology revealed tubulovillous adenoma. No lesions of KS were detected in other sites. The lesions on the nose resolved gradually and finally disappeared within three months.

Three years after transplantation, azathioprine was discontinued because of increased liver enzymes due to hepatitis C virus infection and he continued on cyclosporine and prednisone. One year later, he had bouts of rectal bleeding and colonoscopy showed internal hemorrhoids which responded to treatment and have not recurred. At his last visit, more than seven years after the initial diagnosis of KS, he is asymptomatic with serum creatinine 163 µmol/L.

Sera from these four patients were sent to Yale University (Professor Miller) and all tested positive for KSHV antibodies. The KS tissue samples from four cases were studied at George Washington University and the presence of KSHV-DNA was documented (9).

Discussion

Kaposi's sarcoma is a rare disease except in certain areas such as Equatorial Africa, Central Europe and in immigrants to North America who are of Jewish or Italian origin (1). Before the AIDS, epidemic KS was found in Europe and North America at the rate of 0.06% of tumors in the general population (6,10). The neoplasm occurred predominantly in men over the age of 50 years, affecting the lower limbs, with an indolent course and long-term survival (1,11).

In Africa, KS is common in sub-Saharan area where it is 200 times more frequent than in North America (6). It affects young men and presents distinct clinicopathological patterns that are clearly different from those seen in Europe or America, and usually pursues a more aggressive course (3). The tumor is endemic in most countries of Equatorial Africa with the highest prevalence in Uganda and Zaire where it accounts for up to 10% of adult malignancies. In Sudan, the incidence of KS is about 2% and the disease is more frequent in Southern Sudan (4).

KS is a serious complication after renal transplantation and its higher incidence among the transplant population has been repeatedly confirmed (6,7). The tumor tends to occur more commonly in certain geographic areas and racial groups. As a result, its incidence varies from 0.4% to 5.3% being more frequent in patients of Arabic, Jewish or black origin (5,7). In Canada, KS developed in 4% of renal transplant recipients of Jewish background, which is 400-500 times the risk for normal controls (6). In Saudi Arabia, KS is the commonest neoplasm developing after renal transplantation, occurring in 5.3% of renal transplant recipients, with more than half the cases from the South-Western region of the country (7). In South Africa, the frequency of KS is extremely high among black renal transplant recipients compared to whites (12). Our study found an incidence of 13.3% in Sudanese renal transplant recipients, which is the highest ever reported in the medical literature.

The differences in the incidence of KS between the various renal transplant populations suggests a role for genetic or environmental factors in addition to immunosuppression. It was claimed that environmental factors predispose to KS as the disease is endemic in Equatorial Africa but the environment alone is not sufficient since the disease is extremely rare in other countries with similar ecology (13). The observation that KS affects South African Bantus ten times more

than whites living in the same region (1) argues against the environment as the sole factor responsible for the disease. Racial factors might predispose to KS. This is supported by the high incidence in renal transplant recipients of Arabic, Jewish or Mediterranean ancestry (6,7). Also, endemic KS is confined to the indigenous black population (not infected with HIV) but is rare in North Africa (13,14). Recent studies supported a viral etiology, as KSHV was found in post-renal transplant KS and in African KS from both HIV-seronegative and HIV- positive patients (8,9). The presence of KSHV DNA in the KS tissue samples and KSHV antibodies in the sera of our patients implicates KSHV in the pathogenesis.

Penn (15) recognized the higher rate of KS in renal transplant recipients who received cyclosporine compared to those treated with azathioprine and prednisone. Our patients all developed KS while they were receiving this drug, with high cyclosporine trough levels when the tumor was first diagnosed (Tab. I). In many cases, reduction or withdrawal of immunosuppression halts the evolution of KS and results in complete remission, but graft function may deteriorate (16-18).

With reintroduction of immunosuppression (19) or retransplantation (18) the risk of recurrence is very high. KS recurred in one of our patients (20) after ten years of remission, thus highlighting the fact that these patients need life-long close follow-up for early detection and treatment of recurrence. The transmission of KSHV through transplantation (21) is a serious concern to the transplant community and it may prove advisable to screen potential kidney donors for the virus.

Patient 1 was transplanted abroad and we have no information about the donor. The other three received kidneys from living related donors but unfortunately it was not possible to trace the infective state of these donors. A sero-epidemiological study by our institution (22) showed the prevalence of human herpes virus-8 (HHV8) sero-reactivity in 28% of patients with end-stage renal disease (who were HIV negative and on the waiting list for their first renal transplant) and in 7% of healthy controls.

In view of the high prevalence of KS in our renal transplants and given the improvement of assays to detect HHV8 (23), it is time to insist on systematic screening of living kidney donors in our population. As HHV8 infection before and after kidney transplantation and the initial use of polyclonal antilymphocyte sera are independent risk factors for KS (24), transplanted patients need long-term close monitoring of HHV8 antibody titers so as to be able to reduce immunosuppression before KS develops and avoid - if possible - the use of polyclonal antilymphocyte sera. We should also consider using anti-viral agents of the acyclic nucleoside phosphonate analogues (cidofovir) to inhibit the replication of KSHV (23, 25).

Our study showed a high incidence of KS among Sudanese patients transplanted in a single center in Saudi Arabia but the patient sample is small and further larger-scale studies are needed. We believe that this high incidence results from several factors including racial and geographical and, more importantly, viral factors in the genesis of KS. If the incidence continues rising, it may have a negative impact on the results of renal transplantation among Sudanese patients.

Address for correspondence:
Abdalla Sabeel, M.D.
Consultant Nephrologist
Department of Medicine
Assir Central Hospital, Abha
P.O. Box 34 Abha
Saudi Arabia
sabeel01@yahoo.co.uk

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