Kaposi's sarcoma in renal transplant recipients

Experience at Johannesburg Hospital, 1966 - 1989

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Abstract **Between August 1966 and December 1989, 989 renal transplant recipients were followed up at the Renal Transplant Unit of Johannesburg Hospital. Seventy-five (7%) patients developed a total of 95 malignancies of which 5 (6%) were Kaposi's sarcoma. All patients received immunosuppressive agents; steroids, azathioprine and/or cyclosporin A. Clinical presentations included both limited skin involvement (1 patient) and disseminated forms of the disease: necrotic oral lesions (1 patient); disseminated skin involvement and lung metastases (1 patient); and widespread skin lesions with lymphadenopathy (2 patients). Four patients responded with complete tumour regression at all sites upon withdrawal of the immunosuppressive drugs. One patient suffered disease progression, and immunosuppression was continued, albeit at reduced dosages. These cases illustrate a relatively rare complication of immunosuppressive therapy. However, complete withdrawal of immunosuppressive drugs may result in sustained complete regression, despite the presence of advanced KS.**

S Afr Med J 1994; **84:** 16-17.

Kaposi's sarcoma (KS) is a relatively common malignancy in recipients of transplanted organs. It is estimated to occur in 0,4 - 0,6% of individuals with organ grafts, a frequency 150 - 200 times that of the general population.[1]

In renal transplant recipients, the incidence of KS is reported to be 3,4 - 6%, 400 - 500 times greater than that seen in the general population. The risk of KS following renal transplantation is the same as in patients with immunodeficiency states such as underlying malignant lymphoma, patients receiving long-term corticosteroid therapy and patients with AIDS.[2]

KS in renal transplant recipients is different from that in patients with classic KS. Although transplant-induced KS affects the skin, lymphadenopathy and visceral involvement are much more frequent. While the immunological abnormalities and presence of visceral disease make the condition resemble epidemic or AIDS-associated KS,[3,4] cessation of immunosuppressive therapy has been reported to facilitate regression of KS.[5] The rising incidence of solid organ transplantation is expected to lead to an increasing occurrence of KS in these patients.

The present study retrospectively reviews our experience with KS in renal transplant recipients followed up at the Renal Transplant Unit of Johannesburg Hospital over a period of 23 years.

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Accepted 24 Feb 1993.

Patients and methods

Nine hundred and eighty-nine renal transplant recipients were followed up in the Renal Transplant Unit of Johannesburg Hospital between August 1966 and December 1989. All patients received various schedules of immunosuppressive drugs such as azathioprine, cyclosporin-A and steroids. A review of the records of the Renal Transplant Unit and the Department of Medical Oncology/Haematology identified 75 renal transplant patients with a total of 95 malignancies. Five (6%) of these had KS. The medical records of these 5 patients were reviewed in detail.

The clinical course of KS and response to therapy were retrospectively analysed. When the histological diagnosis had been established, metastatic work-up consisting of blood chemistry analysis, chest radiography, gastro-intestinal studies, abdominal and pelvic sonography and/or computed tomography was performed.

Results

Five (0,5%) adult male renal transplant patients developed KS. Their mean age at the time of diagnosis was 47 years (range 43 - 53 years). Two patients were of Caucasian origin (Portuguese and Lebanese), 1 was Asian, 1 black and 1 'coloured' . The underlying renal diseases leading to haemodialysis, renal transplantation and immunosuppressive treatment included chronic glomerulonephritis (3 patients), diabetic renal failure (1 patient) and Alport's disease (1 patient).

Two patients were receiving therapy with azathioprine, cyclosporin A and corticosteroids, 2 received cyclosporin together with steroids, and 1 patient was treated with azathioprine and steroids.

The mean interval between transplantation and onset of KS was 18 months (range 8 - 38 months). Further clinical details are shown in Table I. Patient No. 1 had KS that was limited to the skin. The 4 other patients presented with advanced KS: disseminated skin involvement and lung metastases (No. 2), necrotic mouth ulcers (No. 3), disseminated skin lesions and inguinal lymphadenopathy (Nos 4 and 5 respectively).

Four patients were treated by means of withdrawal of the immunosuppressive drugs while 1 patient continued with the immunosuppressive regimen (cyclosporin A plus steroids) albeit at reduced dosages. Additional therapeutic approaches used included palliative radiotherapy and cyclophosphamide in patients 2 and 4 and interferon in patient 3.

The mean duration of follow-up of the KS patients was 18 months (range 15 - 24 months). Response to therapy is shown in Table I.

Outcome (Table I)

Only patient No. 2 suffered disease progression. In this instance immunosuppressive drugs had been continued. The patient died of disseminated KS. The other patients' lesions disappeared upon return to the chronic dialysis programme and discontinuation of immunosuppressive therapy. Patient No. 3 is alive, well and no longer receiving dialysis. The other three deaths were

TABLE I.
Clinical characteristics of renal transplant recipients with KS

Patient no.	Age/sex/ extraction	Immuno-suppressive drugs	Time from transplant to KS (months)	Category of KS	Management	Period of follow-up after KS (months)	Response to treatment	Outcome
1	53/M/white	Azathioprine; Prednisone	15	Local	Withdrawal of immuno-suppressive drugs	17	Complete remission	Died from sepsis; no KS at postmortem examination
2	44/M/white	Cyclosporin-A; steroids	21	Disseminated (skin, lungs)	Reduction of immune drugs; local radiotherapy; cyclophosphamide	15	Disease progression	Died of disseminated disease
3	48/M/coloured	Cyclosporin-A; steroids	8	Disseminated (skin, oral cavity)	Withdrawal of drugs; interferon	20	Spontaneous complete regression of lesions	Active, without KS; off dialysis
4	43/M/black	Azathioprine; Cyclosporin-A; steroids	8	Disseminated (skin, lymph nodes)	Withdrawal; local radiotherapy; cyclophosphamide	15	Complete remission	Died of sepsis; no tumour at postmortem examination
5	49/M/Indian	Cyclosporin-A; Azathioprine; steroids	38	Disseminated (skin, lymph nodes)	Withdrawal	24	Complete remission	Died of intracerebral haemorrhage; no tumour at autopsy

KS = Kaposi's sarcoma; M = male.

not tumour-related but resulted from sepsis (patients 1 and 4) and intracerebral haemorrhage (patient 5). Postmortem examination did not reveal any evidence of KS.

Discussion

The cause of the increased frequency of KS among renal transplant recipients is multifactorial: (*i*) genetic predisposition, i.e. increased incidence of specific HLA types; (*ii*) chronic immunostimulation in the presence of T-cell dysfunction; (*iii*) proliferation of suppressor cells with the production of specific growth factors; and (*iv*) direct neoplastic action of immunosuppressive drugs and the defective humoral and cell-mediated immunity of uraemia have all been implicated.[1,4,6,7]

The commonly used combination of azathioprine and steroids was believed initially to be of prime importance in the aetiology of transplant-related KS.[2,4] The majority of patients treated with this combination develop low helper (CD_4^+) lymphocyte counts, depressed helper/suppressor (CD_4^+:CD_8^+) ratios, low immunoglobulin levels and anergy to skin test. Following the discontinuation of these drugs, a partial restoration of immune function[2,8,9] can be demonstrated.

Cyclosporin A has an inhibitory effect on T-helper cells.[5,10] Engraftment is favoured and graft survival improved. An apparent increase in the incidence of lymphoma, skin cancer, multiple myeloma, mycosis fungoides and thymoma has followed the widespread usage of cyclosporin A for post-transplant immunosuppression.[10] Recently, KS has been described more frequently in patients treated with cyclosporin A than in patients treated with conventional immunosuppressive therapy (10% v. 3% of all neoplasms).[11-13] These patients have more aggressive disease, similar to that seen in AIDS-related KS.[4,11-13] A biological similarity to AIDS-associated KS is indicated in a recent ultrastructural study reporting the occurrence of abnormal intracytoplasmic structures in patients treated with cyclosporin A but not in azathioprine-steroid-treated cohorts. These structures are similar to those observed in the AIDS-related form of the disease.[14] The high incidence of disseminated KS in our series may be related to the use of cyclosporin A.

In conclusion, our small study provided further support for the role of immunosuppressive drugs in the pathogenesis of immunosuppression-induced KS. Due to the increased use of cyclosporin A in solid organ transplantation, a high incidence of the disseminated form of KS is to be expected. Withdrawal of immunosuppressive drugs can bring about complete regression, even in advanced KS. Unfortunately discontinuation of the drugs caused rejection of the transplanted kidney in 3 of our patients, necessitating a return to a chronic dialysis programme in each instance.

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