

CLINICAL FEATURES OF KAPOSI'S SARCOMA IN CROATIAN RENAL TRANSPLANT RECIPIENTS

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Abstract: *Aim:* To investigate the prevalence, clinical manifestations and outcome of Kaposi's sarcoma in Croatian renal transplant recipients.

Methods: The Department database was retrospectively analysed according to clinical presentation, immunosuppressive protocol, treatment, and outcome of patients with Kaposi's sarcoma.

Results: Kaposi's sarcoma occurred in four male patients (0.67% of all renal transplant recipients), with the onset of clinical presentation at 4 to 18 months of transplantation. HLA-B35 was present in all patients, whereas HLA-A2, -DR3 and -DR5 were present in three patients each. In all patients, the disease manifested with purple or bluish papules on the skin, without visceral organ or lymph node involvement. Immunosuppression was rapidly reduced in the first patient who rejected the graft. Three patients achieved complete remission upon reduction of immunosuppressive therapy and local irradiation, with preserved renal function.

Conclusion: Kaposi's sarcoma is rare in Croatian renal transplant recipients. It tends to occur in male patients, soon after transplantation and is associated with HLA-B35. Reduction of immunosuppression is recommended as the first choice method in patients with skin-limited disease, accompanied by radiotherapy in resistant cases.

Key words: Kaposi's sarcoma, kidney transplantation, tumour, immunosuppression.

Introduction

Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi, a Hungarian physician [1]. It was considered a rare tumour until the discovery of

the epidemic form of KS in patients with HIV disease [2]. Endemic KS occurs mostly in elderly men of the Mediterranean or East European Jewish origin, but also in native populations of equatorial Africa. The first case of KS associated with immunosuppressive therapy in a renal transplant recipient was described in 1969 [3]. The tumour appears more commonly after the introduction of cyclosporine in immunosuppressive regimens [4]. The incidence of KS in transplanted patients is 100- to 500-fold that seen in the general population of the same ethnic origin [5], showing a male predominance. Brunson *et al.* report on an increased frequency of HLA-B5, -B8, -B18, and DR5 in patients with KS arising after transplantation [6], suggesting combined ethnic and iatrogenic factors in the development of post-transplant KS. In the last decade, KS association with human herpes virus-8 (HHV-8) has been substantiated by strong evidence [7]. However, it is not clear whether post-transplant KS occurs due to HHV-8 reactivation as a consequence of immunosuppressive state, or due to primary HHV-8 infection transmitted *via* organ transplantation. A report of two KS cases in patients who received transplants from the same donor has suggested virus transmission from the donor [8]. On the contrary, in HHV-8 endemic regions KS occurs mainly in immunosuppressed individuals who were HHV-8 seropositive before transplantation [7, 9].

The aim of this study was to review our experience with KS, and to analyse clinical features, response to treatment and outcome of patients with KS in Croatia.

Patients and Methods

A database kept at the Dialysis Department, Zagreb University Hospital Centre, was retrospectively analysed to identify renal transplant recipients with KS. Records of 598 kidney transplant recipients operated on between December 1972 and December 2004 were reviewed. Eighty-five percent of all patients received a cadaveric transplant.

Until 1999, patients were treated with triple immunosuppressive therapy consisting of cyclosporin A (5 mg/kg/day, adjusted to maintain the serum level within a target range), azathioprine (2 mg/kg/day) and steroids (tapered to 0.1 mg/kg/day after 1 year). Since 1999, we have introduced mycophenolate mofetil (2 × 1 g, or 2 × 750 mg, according to body weight) instead of azathioprine. Episodes of acute rejections were treated with i.v. bolus of methylprednisolone (10 mg/kg) on 3 to 5 consecutive days. Cases of steroid-resistant rejections were treated with OKT3.

Patient characteristics, primary disease, virologic status, HLA typing, immunosuppressive regimen, disease dissemination, treatment and outcome were recorded. Tumour biopsy confirmed suspected diagnosis in all patients. Endoscopic examination of the gastrointestinal tract, and computed tomography of the thorax and abdomen were performed in all patients. Patients were screened for anti-HIV (ELISA), whereas tests for HHV-8 were not available.

Results

Case 1

A 41-year-old man of Albanian origin was started on haemodialysis in 1987 because of end-stage renal disease (ESRD) of unknown origin. He received a cadaveric renal transplant in December 1990. HLA typing was: HLA-A2, -A28, -B12, -B35, -DR3, -DR5. He received the transplant with 2 HLA mismatches. The patient was treated with azathioprine, cyclosporine and steroids. In August 1991, he developed macular dark blue lesions on the lower legs and forearms. Histopathologic diagnosis confirmed KS. There were no signs of visceral involvement. Serology testing CMV, EBV, HSV, VZV, hepatitis B, hepatitis C and HIV were negative. HHV-8 was not performed. Azathioprine was discontinued, and cyclosporine and steroids progressively reduced. The skin lesions disappeared completely after two months. However, graft function deteriorated, and the patient was started on haemodialysis in November 1993 due to chronic rejection. He died in April 2003 from heart failure without signs of sarcoma.

Case 2

A 16-year-old male was transplanted in October 1996. He was previously treated for 2 years with haemodialysis because of ESRD caused by membranoproliferative glomerulonephritis type I. The following tissue typing was obtained: HLA-A2, -A28, -B12, -B35, -DR3, and -DR5. He received a transplant with 3 HLA-mismatches. The patient was treated with azathioprine, cyclosporine and steroids. In April 1998, skin lesions on the arms and ears were noticed (Fig. 1), and Kaposi's sarcoma was diagnosed by biopsy.



Figure 1 – Kaposi's sarcoma of the earlobe
Слика 1 – Саркомой на Кароси на лобус од уво

The disease was localized to the skin. Serology tests for CMV, EBV, VZV, HSV and HBV were all positive. He was HIV and HCV negative. Immunosuppression therapy was reduced (cyclosporine 1 mg/kg/day, azathioprine 1 mg/kg/day), which resulted in incomplete remission. Local radiation therapy (800 cGy in 24 fractions) induced complete remission of sarcoma. He is currently without signs of KS with stable graft function (serum creatinine levels between 130 and 150 $\mu\text{mol/L}$), and is regularly followed-up.

Case 3

A 21-year-old male, an Albanian from Kosovo, resident in Croatia, received a renal transplant from a living-related donor in May 1998. The patient was started on ha emodialysis in July 1997, with ESRD caused by membranoproliferative glomerulonephritis. His HLA typing was: -A2, -A11, -B18, -B35, -DR3, -DR5. Immunosuppressive therapy consisted of cyclosporine, azathioprine and steroids. Postoperative oliguric acute tubular necrosis and histologically confirmed acute rejection (Banff borderline) complicated the post-transplantation course. Treatment with 5 boluses of methylprednisolone failed, and he received OKT3. The graft function stabilized later, with serum creatinine values around 280 $\mu\text{mol/l}$. In October 1998, a livid red exophytic tumour with a granulated surface developed in the left hard palate and maxillary palatal gingiva (Fig. 2).



Figure 2 – Infiltration of the hard palate and maxillary palatal gingival by Kaposi's sarcoma

*Слика 2 – Инфилтрација на тврдојоо нејце и на максјално-палајијалнајиа
џинџива со саркомоји на Кароси*

Computed tomography demonstrated osteolysis of the left alveolar ridge without penetration into the sinuses. Histology confirmed KS. Complete evaluation excluded disseminated disease. The patient had positive EBV, HHV-6, VZV, HSV-1 and HSV-2 serology. He was HIV, HCV and HBV negative. HHV-8 was not determined. Immunosuppression therapy was reduced. The tumour mass was reduced by approximately 50%, so he underwent local radiotherapy with 3000 cGy in 15 fractions, which resulted in complete remission. The current creatinine level is 195 $\mu\text{mol/L}$. The patient is under regular follow-up.

Case 4

A 60-year-old man of Croatian origin developed ESRD due to polycystic kidney disease in 1995 and started haemodialysis. In 1999 he underwent bilateral nephrectomy. The following HLA typing was obtained: -A9, -A31, -B22, -B35, -DR1, and -DR11. Cadaveric renal transplantation was performed in July 2004, and he received a transplant with 2 mismatches. The patient was treated with mycophenolate mofetil ($2 \times 1 \text{ g}$), cyclosporin A and steroids. His clinical course was uneventful during the follow-up period, with stable serum creatinine levels (95–110 $\mu\text{mol/L}$). In January 2005, the patient warned us of "strange skin changes" he had noticed two days before on his forearms. Violaceous papules were visible on both forearms as well as on lower legs, left sole and hard palate (Fig. 3).



Figure 3 – Typical violaceous papules on lower legs
Слика 3 – Типични виолетови папули на долније екстремитетии

There was no peripheral lymphadenopathy. Thorough evaluation excluded a disseminated form of disease. The patient's virologic status was negative. HHV-8 was not determined. Histology confirmed KS. Immunosuppressive therapy was reduced, and the patient currently receives cyclosporine 2 mg/kg, mycophenolate mofetil 2×500 mg and steroids. However, the skin lesions still progressed so the patient is currently receiving local radiotherapy with the planned dose of 2200 cGy in 20 fractions over 5 weeks. Renal function is relatively stable with a creatinine level between 130 and 146 $\mu\text{mol/l}$, and creatinine clearance 63 ml/min.

Discussion

Post-transplantation KS is a well-known complication after renal transplantation with a possible negative impact on the patient's and graft longterm survival. According to the Cincinnati Transplant Tumour Registry (CTTR), KS accounts for 5.7% of all neoplasms arising after renal transplantation [10]. However, in the Mediterranean countries KS is more common (Table 1).

Table 1 – Табела 1

Prevalence of patients with Kaposi's sarcoma in different countries expressed as percent of all transplanted patients and of patients with post-transplant neoplasia
Преваленца на пациенти со саркомой на Кароси во различни земји,
изразено како проценти од сите трансплантирани пациенти и пациенти
со посттрансплантациона неоплазија

Country	% of all patients	% of patients with neoplasia	Authors
Turkey	2.4	80.0	Duman S <i>et al.</i> (11)
Italy	1.6	Not done	Montagnino G <i>et al.</i> (12)
Egypt	1.7	48.0	El-Agroundy AE <i>et al.</i> (13)
Saudi Arabia	5.3	87.5	Qunibi W <i>et al.</i> (14)
Greece	1.7	24.0	Zavos G <i>et al.</i> (15)
Croatia	3.5	11.4	Basic-Jukic N <i>et al.</i> (present paper)

In our study, the prevalence of KS was 0.67%, accounting for 11.4% of all post-transplant malignancies. KS occurred in 3.5% of all transplanted patients, which is more often than in other populations, yet representing a relatively small percentage of all post-transplant malignancies (Table 1). KS is frequent in African renal transplant recipients, where 13.3% of all transplanted patients developed KS [16]. A male preponderance was pronounced in all studies. The mean time of KS occurrence after renal transplantation was 18–40 months in

different studies [11, 12], as opposed to our study where KS occurred 9.2 months after transplantation (range 4–18 months). In our patients, the mean age at KS onset was 34.5 (range 16–60) years. None of our patients had visceral involvement, in contrast to the mean of 40% reported in other studies [11–15].

Two of our patients (50%) were of Albanian origin, suggesting a possible ethnic background in the development of KS combined with iatrogenic stimuli. The Cincinnati Group investigated HLA typing of patients who developed post-transplant KS. They found an increased frequency of HLA-B5, -B8, B18, and -DR5, with 56% of patients of Italian, Greek, Jewish or Arabic ethnic background [6]. El-Agroundy *et al.* found a higher frequency of HLA-A1, A2 and -DR5 in KS patients in Egypt [13]. We found an increased frequency of HLA-A2 (75%), -B35 (100%), -DR3 (75%), and DR-5 (75%). Two patients had identical HLA-typing (HLA-A2, -A28, -B12, -B35, -DR3, -DR5).

HHV-8 has been described in patients with HIV infection and KS [17]. Pretransplantation HHV-8 seropositivity is found to be associated with an increased risk of post-transplant KS [18, 19]. Immunosuppressive treatment may induce reactivation of latent virus infection, playing an important role in the development of combined iatrogenic and endemic KS [20]. It is also possible that HHV-8 may be transmitted from the donor to induce sarcoma development in the organ recipient [8]. Unfortunately, we did not have the technical possibilities to perform HHV-8 testing.

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. Reduction of immunosuppression resulted in complete remission of KS in 17% of patients with the mucocutaneous form of the disease in the CCRT series [10], in 28% of patients from Saudi Arabia [14], and 61% of Italian patients [12]. 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 [11]. Reduction of immunosuppression allows for the immune system to reduce viral replication producing clinical remission of disease. None of our patients died from KS or suffered from side effects of radiotherapy. New antiviral agents have recently been introduced as a promising therapeutic option in patients with KS [21–23]. 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 [24]. Sirolimus may become the first choice immunosuppressant in renal transplant recipients with KS for providing optimal immunosuppression and inhibiting the progression of malignancy.

In our study, rapid and radical reduction of immunosuppression resulted in graft loss in the first patient. In subsequent patients we tapered immunosup-

pressive therapy slowly and incompletely. The patients received adjuvant radiotherapy localized to the malignant lesions. This approach resulted in complete remission with preservation of the graft function. None of our patients had achieved complete remission with reduction of immunosuppression only, in contrast to the other studies [11–15].

In conclusion, KS is not frequent in renal transplant recipients in Croatia. Considering Croatia as one of the Mediterranean countries, this figure is low. Outpatient controls at our Department are performed on a monthly basis, ensuring rapid detection of most problems in renal transplant recipients. Thus, all patients were diagnosed in the stage of limited mucocutaneous disease without visceral involvement, which resulted in excellent patient and graft survival. We recommend reduction of immunosuppression as the first-line treatment accompanied by radiotherapy in case of resistant lesions.

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Резиме

**КЛИНИЧКИ КАРАКТЕРИСТИКИ НА САРКОМОТ НА КАРОСИ
КАЈ ПАЦИЕНТИ СО ПРЕСАДЕН БУБРЕГ ВО ХРВАТСКА****Бубиќ-Филипи Љ.,¹ Башиќ-Јукиќ Н.,¹ Пасини Ј.,² Каштелан Ж.,² Кес П.²**¹Оддел за дијализа, Загреб, Универзитетски клинички центар, Загреб, Хрватска²Оддел за урологија, Загреб, Универзитетски клинички центар,
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Апстракт: *Цел:* Да се иследи преваленцијата, клиничките манифестации и исходот на саркомот на Кароси кај пациентите со пресаден бубрег во Хрватска.

Методи: Базата на податоци за саркомот на Кароси од Одделот беше ретроспективно анализирана според клиничката презентација, имуносупресивниот протокол, третманот и исходот на болните.

Резултати: Саркомот на Кароси се појавил кај четири мажи (0,67% од сите пациенти со пресаден бубрег), со започнувањето на клиничката презентација од 4 до 18 месеци по трансплантацијата на бубрег. HLA-B35 беше присутен кај сите пациенти, додека секој од HLA-A2, -DR3 и -DR5 беше присутен кај 3 пациенти. Кај сите пациенти, болеста се манифестираше со виолетови или модри папули на кожата, без да бидат зафатени вицералните органи или лимфните јазли. Имуносупресијата беше брзо редуцирана кај првиот пациент кој го отфрли пресадениот бубрег (графт). Три пациенти имаа комплетна ремисија по редукција на имуносупресивната терапија и локално зрачење, со зачувана бубрежна функција.

Заклучок: Саркомот на Кароси е редок кај пациентите со пресаден бубрег во Хрватска. Тој е со тенденција да се појави кај мажи брзо по трансплантацијата и е поврзан со HLA-B35. Редукцијата на имуносупресијата се препорачува како прв метод на избор кај пациенти кои имаат болест ограничена на кожата и придружена со радиотерапија при резистентните случаи.

Клучни зборови: Сарком на Кароси, трансплантација на бубрег, тумор, имуносупресија.

Работен наслов: Сарком на Кароси's по трансплантација.

Running Title: Post-transplant Kaposi's sarcoma.

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