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Case Report

Post-transplantation Kaposi's sarcoma appearing simultaneously in same cadaver donor renal transplant recipients

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Introduction

Organ transplant recipients have an increased long-term risk of developing a variety of malignancies, most of which are rarely found in the general population. Post-transplantation Kaposi sarcoma (KS) accounts for about 5.6% of these neoplasms, whereas KS prevalence in the general population, excluding HIV-infected patients, is only 0.02–0.07% of all cancers. The most common clinical form of post-transplantation KS is purely cutaneous (63%). It is an indolent sarcoma that usually occurs on the lower extremities, especially the ankles and plantar surfaces. It usually appears as multiple, irregular, reddish blue, purple to violaceous or reddish brown macules, nodules or plaques, most often in men (ratio male/female, 2.5:1 *vs* classic KS where the ratio is 8–17:1) of Mediterranean, Middle Eastern, or Eastern European ethnic origin. Other forms are not limited to skin (37%), involving conjunctiva, oropharyngeal mucosa, gastrointestinal tract, and lungs [1–4].

The first case of renal post-transplantation KS was reported in 1969 [5], and since then a number of reports have confirmed the high incidence of this cancer among immunosuppressed transplant recipients. No data exist about simultaneous appearance in the typical locations of cutaneous KS in HIV-negative renal transplant recipients who had received twin kidneys. We report two cases of cutaneous KS developing 20 months after successful renal transplantation in two HIV-negative recipients of grafts from the same cadaver donor.

Donor

A 53-year-old Italian male was admitted in August 1994 to an intensive care unit because of an irreversible cerebral vascular accident. He had a normal serum creatinine and no signs of generalized infections, malignant lesions and pre-existing disease which might affect the kidneys directly such as hypertension or diabetes. His HIV, HBV and HCV serology was negative; EBV, HSV and CMV serology was unknown. He was included as a potential multiorgan donor. His HLA typing was A2, -; B18 w6, B61(40) w6; DR4, DR11(5), DR52–53; DQ7(3).

Case 1

A 46-year-old Italian female received a cadaver renal allograft in our centre in August 1994 for end-stage renal disease secondary to reflux nephropathy. Her HLA typing was A1, A2; B18 w6, B58(17) w4; DR8, DR11(5), DR52; DQ7(3). She received a double immunosuppressive regimen including cyclosporin A (CsA) 10 mg/kg and methylprednisolone (MP). The graft functioned immediately and attained normal serum creatinine within 2 weeks. After 1 month, due to an increase of serum creatinine up to 2.6 mg/dl, she received MP pulses (8 mg/kg i.v. each) for 3 consecutive days, serum creatinine soon decreased to 2.0 mg/dl. Her immunosuppressive treatment was maintained by 3 mg/kg CsA and oral corticosteroid. After 1 year the glomerular filtration rate (GFR) was 45 ml/min. In April 1996 the patient presented two violaceous relevated papules: one on the medial aspect of the right leg and one on the left ankle, 2 cm and 0.5 cm in diameter respectively. The papules did not fade on pressure. Skin adnexial structure and mucosae were normal. She had one right inguinal lymphadenopathy. The physical examination was otherwise normal. Biopsy of the lesions confirmed the suspected KS. The patient's HIV antibody, repeated twice, was negative. Basal CsA level was within normal range. Abdominal and thoracic computerized tomography (CT) scan was negative. Gastrointestinal endoscopy and colonscopy were not able to find Kaposi-like mucosal lesions. Histological examination of inguinal lymph nodes revealed only a reactive lymphadenopathy. A diagnosis of purely cutaneous KS was made. CsA was decreased to 2 mg/kg, oral corticosteroids was continued. During the next 2

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months we saw an increase in dimension of the pre-existent lesions and the appearance of an other papule on the right leg, and three new papules on the medial aspect of left leg. At this time T cells subsets was: CD3 85%, CD4 54%, CD8 41% of a total of 6980 white cells/mm^3, and the CD4/CD8 ratio was 1.31. CsA was then decreased to 1.5 mg/kg, oral corticosteroids was continued, acyclovir 12 mg/kg was added. Two months later we saw no changes of number, colour and dimension in the lesions. The graft was functioning (GFR = 50 ml/min) and there was no other systemic involvement.

Case 2

A 45-year-old Italian female was transplanted, in our centre, from the same cadaver donor as the previous case. Her primary disease was unknown and her HLA typing was A1, A2; B44(12) w4, B39(16) w6; DR4, DR11(5), DR52–53; DQ7(3). She was immunosuppressed with CsA 10 mg/kg and MP. In the first week she had one episode of acute rejection treated with MP pulses (12.5 mg/kg i.v. each) for 2 consecutive days. Serum creatinine after 1 month was 2.0 mg/dl. Her immunosuppressive treatment was maintained by 5 mg/kg CsA and oral corticosteroid. In June 1995, because of an increase of serum creatinine, azathioprine (Aza) 1 mg/kg was added, CsA was reduced to 3 mg/kg; the corticosteroid was unchanged. After 1 year the GFR was 30 ml/min. In April 1996 the patient presented with three violaceous relevated papules: on the medial aspect of right forearm (2.0 cm), and on the medial aspects of right and left legs (0.5 cm and 0.7 cm respectively). The papules did not fade on pressure. Skin adnexial structure and mucosae were normal. Biopsy of the lesions confirmed KS. HIV antibody screening, repeated twice, was negative. Basal CsA level was within normal range. Abdominal and thoracic CT scan was negative. Gastrointestinal endoscopy suspected two mucosal KS-like lesions, but histological biopsy examination excluded gastrointestinal involvement of KS. Colonscopy was negative. A diagnosis of cutaneous KS was made. CsA was decreased to 2 mg/kg, Aza and oral corticosteroids were continued at the same dosage. During the next 2 months we saw an increase in dimension and in number of the pre-existent lesions. One new papule appeared on each leg. At this time T cell subsets were CD3 98%, CD4 60%, CD8 31% of a total of 4000 white cell/mm^3, and the CD4/CD8 ratio was 1.93. CsA was additionally decreased to 1 mg/kg, Aza and oral corticosteroids were continued; acyclovir 12 mg/kg was added. Two months later we saw no changes of number, colour and dimension in the lesions. The graft was functioning (GFR = 27 ml/min) and there was no systemic involvement.

Discussion

With the use of potent immunosuppressive agents, malignancies have arisen as an important factor of morbidity and mortality in transplant recipients. Of the immunosuppressives, CsA has been most frequently suspected as a cause of malignancy. In adult transplant patients the average latency period between starting the immunosuppressive therapy until the diagnosis of KS is 16.5 months, and the clinical initial presentation is usually a skin lesion [6]. The cause of post-transplant KS remains unknown. Besides immunosuppression, other factors such as genetic predisposition, environmental and geographic factors, and oncogenic viruses seem to be involved in a multifactorial pathogenic mechanism. There are epidemiological arguments for suspecting an infectious agent transmitted by tissue transplantation. Multiple independent studies have found herpesvirus-like DNA sequences, indicated as KS-associated herpesvirus or human herpesvirus 8 (KSHV/HHV-8), in nearly all KS tissues examined to date, including post-transplant KS lesions. These sequences, highly homologous to Epstein–Barr virus (EBV) and herpesvirus (HSV) Saimiri DNAs, could play a pathogenic role in post-transplant KS [7–9]. All these viruses are members of Gammaherpesvirinae, a subfamily of herpesvirus whose members are known to persist in lymphocytes and immortalize them. They infect a relatively large proportion of the host population and remain in a latent state as episomes through-

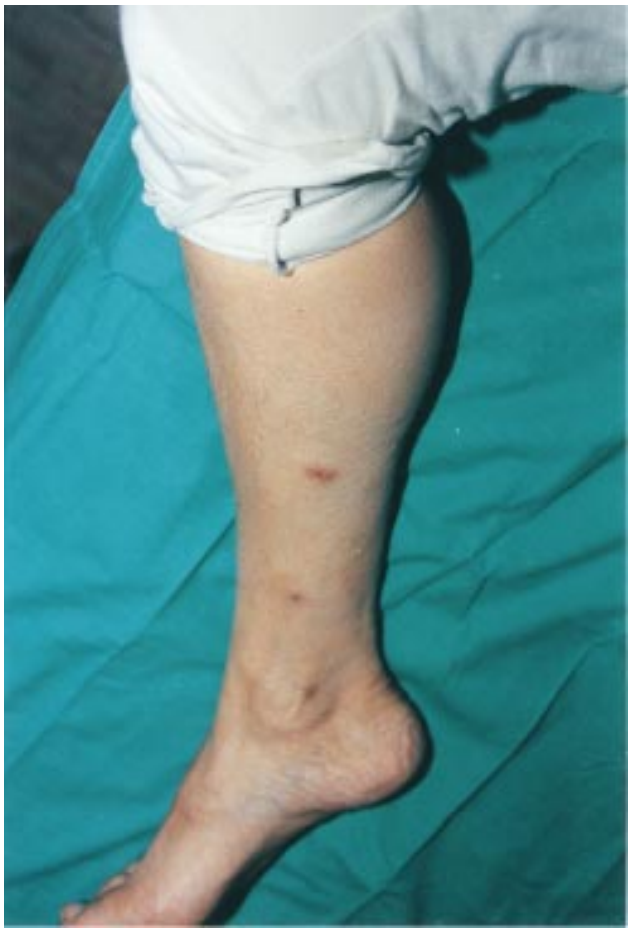

Fig. 1. Two Kaposi sarcoma lesions on the right leg of case 1.

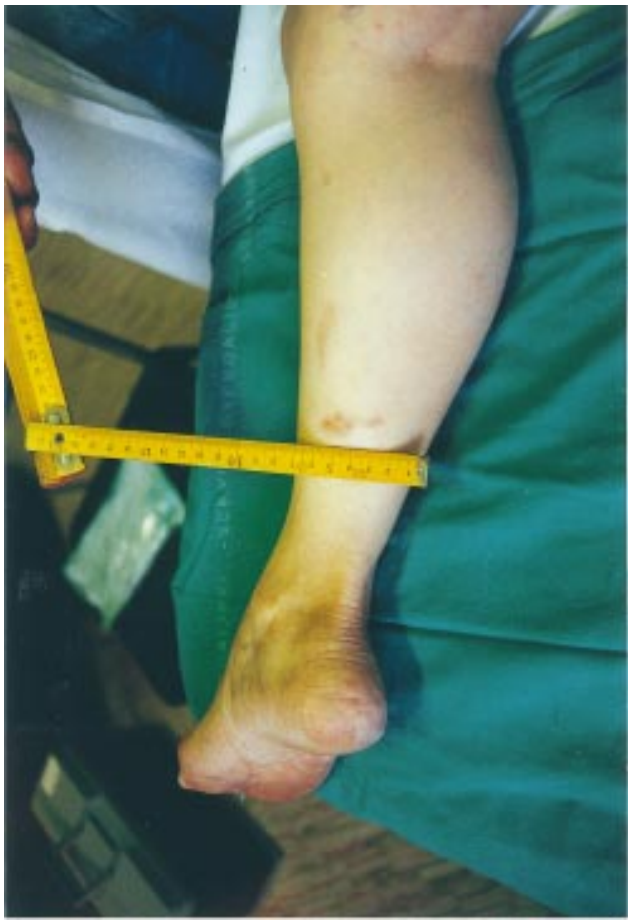

Fig. 2. Two Kaposi sarcoma lesions on the right leg of case 2.

out the life of the host. EBV is maintained in the latent state in B lymphocytes, and the infection is controlled by host defence mechanisms such as destruction of B lymphocytes that express specific subgroups of EBV genes, production of interferon and other lymphokines, and induction of T cell reactivity, natural killer cells, macrophages and antibody-dependent lymphocyte cytotoxicity. By analogy KSHV/HHV-8 could infect a large proportion of human population, making a latent home in some human cell and reactivating in order to spread in the population. Likewise, during tissue transplantation, KSHV/HHV-8 could be transmitted from the donor to the immunosuppressed host with an HLA antigenic predisposition [10]; the development of the neoplasm could reflect a decreased capacity of the host to destroy cells harbouring latent KSHV/HHV-8 because of continuous immunosuppression. In fact the simple reduction or cessation of immunosuppression, with or without antiviral therapy, may result in partial or complete remission of the disease in a significant number of these patients. In these two cases, control of the disease and maintenance of the functioning graft was achieved by decreasing only CsA and administering an antiviral drug. These two cases reinforce the hypothesis that an infectious agent is implicated in the pathogenesis of post-transplant Kaposi sarcoma.

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