Concealed by veils

A 48-year-old woman of Moroccan origin presented in 1987 with renal failure of unknown origin. She received a cadaveric kidney transplant 1 year later. Four weeks after transplantation she had an acute, steroid responsive rejection. Her immunosuppressive maintenance therapy consisted of cyclosporin (trough level 150 ng/ml) and prednisone (7.5 mg daily).

Eight years post-transplantation (3 years ago) the immunosuppressive therapy was changed. Cyclosporin was replaced by mycophenolate mofetil (MMF) 2 g/day as part of a switch study in our hospital [1]. Prednisone dosage remained at 7.5 mg/day. The conversion was uncomplicated with an improvement in renal function and blood pressure. Serum creatinine decreased from 122 to 107 μmol/l and 24-h blood pressure decreased from 174/88 to 159/76 mmHg. No rejection occurred. Furthermore, cosmetic side effects of cyclosporin such as facial hair growth and gingival growth improved. After this conversion she continued with MMF and prednisone.

During her 3-monthly control she always presented herself in a long, body-covering dress, according to the traditional fashion of a female Berber. A year and a half ago, 18 months after the drug conversion, she started complaining about painful legs. After lifting the top of the veil, her legs appeared symmetrically oedematous and showed diffuse erythema.

Within a few weeks this clinical presentation changed into dark, blue-purplish intradermal nodules and plaques (Figures 1 and 2).

Question

What is your diagnosis? What would be your treatment?

Fig. 1. Anterior side of the lower legs of the patients with intradermal nodules and plaques (blue-purple) seen within a few weeks of presentation.

Fig. 2. Posterior side of the lower legs with intradermal nodules and plaques.
Histological examination of a skin lesion revealed typical nodular Kaposi’s sarcoma; a network of spindle cells and large vascular spaces with characteristic thin-walled ‘back to back’ capillaries. The lesions were confined to the skin; no visceral, conjunctival or oropharyngeal lesions were found. Therapy consisted of changing her immunosuppressive treatment. MMF was stopped after introduction of tacrolimus, while corticosteroids were slowly withdrawn. Thereafter the sarcoma lesions decreased in size and no new sites have appeared so far (Figure 3).

Kaposi’s sarcoma is highly prevalent after solid organ transplantation. The data from the Cincinnati Transplant Tumor Registry (CTTR) (1968–1998) presented a prevalence of Kaposi’s sarcoma of 4.3% (465 within a total of 10 787 patients) [2]. Another study from Saudi Arabia showed an incidence of 5% in renal transplant recipients, while in the general population from same ethnic origin the incidence for Kaposi’s sarcoma was about 0.3% [3]. Interestingly Kaposi’s sarcoma appeared to have a higher prevalence among kidney transplant recipients in comparison to recipients of other solid organs or bone marrow transplant recipients. The average age of presentation was 43 years (range 4.5–67), with a male:female ratio of 3:1. The average time of appearance was 21 months post-transplantation (range 1–226). Sixty per cent of patients had a non-visceral Kaposi’s sarcoma, while 40% had also visceral involvement. The majority of the patients were from Africa, Saudi Arabia, Israel, Greece and Italy [2]. This geographical variety suggests environmental triggers (viral infection, see further) and/or genetic susceptibility [4].

Kaposi’s sarcoma is a neoplasm of the skin and visceral organs composed of endothelium lined vascular spaces and spindle shaped cells [5]. The presentation is classified in several distinctive clinical forms: the classical form in older Mediterranean males, the endemic form in Africa, the epidemic form in HIV-infected persons and the ‘iatrogenic’ form in patients with immunosuppressive treatment like transplant recipients [6]. Recently an association between Kaposi’s sarcoma and the human herpes virus-8 (HHV8) has been found. It is detectable in the lesions of almost all patients with Kaposi’s sarcoma and its presence in the blood (identified by HHV-8 DNA-sequences in peripheral-blood mononuclear cells or antibodies to HHV-8) predicts the development of Kaposi’s sarcoma [7,8]. The route of transmission is not yet fully understood. HHV-8 virus may be present before transplantation or be transmitted through renal allografts. One study presented a seroconversion of HHV-8 in renal transplant recipients increasing the seroprevalence from 6.4 to 17.7%. Kaposi’s sarcoma developed in two of the 25 patients with a seroconversion [9]. From the data it seems likely that HHV-8, like other herpes viruses, can cause a primary infection with seroconversion in a HHV-8 positive donor to a HHV-8 negative recipient or it can be reactivated from a latent, dormant state in HHV-8 positive patients.

For the renal transplant recipient the risk for Kaposi’s sarcoma is associated with the risk of exposure to HHV-8 (endemic or by transmission of the donor graft) and the severity of immunosuppression. The (high) degree of immunosuppression results in increased frequency of virus infections or viral load in renal transplant recipients and/or diminished immuno-surveillance of virus-transformed cells [10]. Other comparable virus related cancers in transplant recipients are post-transplant lymphoproliferative disease (PTLD), associated with EBV and skin and cervical carcinoma associated with papillomaviruses [2]. Apart from the degree of immunosuppression also drug-specific associations with cancer exist, especially with Kaposi’s sarcoma. A recent study reported an increased incidence of Kaposi’s sarcoma concomitant with the use of MMF [11]. Kaposi’s sarcoma developed in 3/371 (0.8%) of the renal transplant recipients using MMF in comparison with 2/1464 (0.1%) recipients not using MMF. Besides the general immunosuppression, a yet unknown, drug-specific interaction seems to play a role. MMF is not only a T-cell inhibitor, like most other immunosuppressive drugs, but also a B-cell inhibitor. The trend towards more clinically relevant herpes and CMV infections in combination with a higher
incidence of HHV-8 related Kaposi’s sarcoma during the use of MMF suggests a reduction in the immunosurveillance of lymphocytes by MMF [11].

An important issue raising from the data is, should the donor and recipient be screened for seropositivity of HHV-8, especially in ethnic groups with a high prevalence? How great is the risk of developing Kaposi’s sarcoma when a HHV-8 negative donor is transplanted with a HHV-8 positive graft? Is there a reasonable prophylactic or therapeutic anti-viral treatment possible and/or necessary? Should the immunosuppressive treatment be different for these patients?

The first step in treatment in our patient was careful withdrawal of MMF, with the risk of occurrence of an acute rejection. In the earlier mentioned CTTR study reduction or cessation of immunosuppressive therapy accounted for 38% of the remissions, with non-visceral Kaposi’s sarcoma having a more favourable outcome [12].

However further observations and prospective studies must be awaited before the answers about aetiology, screening and treatment can be given. Until then it seems at least recommendable to have a closer look behind the veils in this group of patients possibly at higher risk for Kaposi’s sarcoma by ethnic origin strengthened by treatment of MMF.

Suggested reading


