Case Report

Rapamycin-induced remission of Kaposi’s sarcoma is not associated with expansion of cytotoxic T-lymphocyte subsets

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Abstract
We present a case of post-transplantation Kaposi’s sarcoma (KS) successfully treated by conversion to rapamycin. Clinical and histological resolution was observed within 6 months of commencing rapamycin. Also, vascular endothelial growth factor (VEGF) staining in the biopsy samples resolved following rapamycin therapy. Interestingly there was no expansion in cytotoxic T-lymphocyte (CTL) subsets observed during this period, as might be expected if this remission was due to immune reconstitution following reduction in immunosuppression. These data suggest that the resolution of tumour with rapamycin could be the result of the antiangiogenic, antiproliferative effects of rapamycin.

Keywords: cytotoxic T-cells; Kaposi’s sarcoma; rapamycin; VEGF

Introduction
Kaposi’s sarcoma (KS) is a low-grade vascular tumour characterized by spindle cells, which are derived from human herpes virus 8 (HHV-8)-infected endothelial cells [1]. It is common in those with suppressed T-cell immunity, notably solid organ transplant recipients and HIV patients.

KS can cause significant morbidity and mortality in transplant recipients, and reducing the amount of immunosuppression is known to be at least partially effective in inducing remission of KS in these patients, although the risk of recurrence is high [2]. More recently, rapamycin, an immunosuppressant with antiangiogenic and antiproliferative properties, has been used with success in post-transplant KS [3]. However, whether it is due to a direct effect of the drug on the tumour or an overall reduction in T-cell immunosuppression is unclear.

Case
A 39-year-old HIV-seronegative Iraqi Arab male with end-stage renal failure (ESRF), secondary to tubulointerstitial disease, underwent a deceased donor renal transplant in August 2002.

Donor virology revealed positive CMV, but negative hepatitis B, C and HIV serology.

Initial immunosuppression consisted of tacrolimus (initially dosed to keep range between 10 and 15 ng/ml), mycophenolate mofetil (MMF) (750 mg given twice daily) and prednisolone (20 mg once daily).

Despite poor clinic attendance, progress was satisfactory until July 2003 when his serum creatinine rose from 1.69 to 3 mg/dl. Histology suggested calcineurin inhibitor toxicity; his tacrolimus dose was reduced and his renal function stabilized (2.1 mg/dl).

In May 2004 he developed lesions over his forearms and legs (Figure 1A). A skin biopsy was performed and KS confirmed (Figure 2A) which also had dense VEGF staining (Figure 2C) characteristic of KS lesions. Human herpes virus 8 (HHV8) was detected in spindle cells by in situ hybridization. At this time, immunosuppression consisted of prednisolone 5 mg/day, MMF 500 mg/day and tacrolimus 5 mg/day (level 6.2 ng/ml). Cutaneous KS was diagnosed after investigation revealed no visceral lesions. MMF and tacrolimus were discontinued and rapamycin was started on 8 June 2004 (target range of 6–10 ng/ml).

His Kaposi’s lesions regressed rapidly (Figure 1B); he underwent a second skin biopsy in January 2005, which showed histological resolution (Figure 2B) in just over 6 months of starting rapamycin therapy. The number of spindle cells had dramatically decreased, with a corresponding decrease in detectable HHV-8, and the previously dense VEGF staining had disappeared (Figure 2D). Flow cytometry of his T-cell subsets (using a FACScan flow cytometer...
Fig. 1. Panel A shows lesions at diagnosis on the patient’s fistula arm. Panel B shows the same arm after 12 months of rapamycin therapy. Panel C is a graph of T-cell subsets showing a late peak in the helper T-cell activity (CD25 and CD69), but no significant rise in either natural killer (NK) or T-cell CTL numbers (NK and T8+Dr, respectively). The x-axis denotes months after switching to rapamycin, and the arrows show the times of the two skin biopsies.

Discussion

Rapamycin inhibits the mammalian target of rapamycin (mTOR), which is emerging as a critical cell-signalling molecule that is commonly dysregulated in human cancers. It has direct antiproliferative effects on certain neoplasms, including endometrial carcinoma and mantle cell lymphoma, likely via the inhibition of mTOR-related cell signalling pathways. Rapamycin also inhibits VEGF expression of cancer cells in vitro and in animal models, again via mTOR inhibition (see [5] for review).

The mechanisms underlying Kaposi’s sarcomagenesis are becoming clearer. HHV-8 infection of vascular endothelial cells converts them into latently infected spindle cells. The expression of an early lytic cell cycle protein (vGPCR) in a few spindle cells is enough to activate a VEGF-dependent autocrine/paracrine loop, inducing proliferation in adjacent spindle cells and thus a proliferating angiogenic nodular KS lesion [6]. VEGF has also been shown to be abundantly present in KS lesions [3] and able to stimulate the migration and proliferation of spindle cells [7]. Thus, the anti-KS effect of rapamycin, if it is due to a direct rapamycin effect, may well be due to inhibition of VEGF expression rather than a direct antiproliferative effect. This would be consistent with our observation of the resolution of VEGF staining correlating closely with clinical and histological resolution of the KS lesions.

But is it simply due to a lessening of the immunosuppressive burden? CTLs have a central role in host immune responses controlling HHV-8 infection, highlighted by the high incidence of KS amongst individuals with impaired T-cell responses, HIV sufferers and transplant recipients. Furthermore, amongst transplant recipients, the incidence of KS was noted to increase after the introduction of calcineurin inhibitors, which act by T-cell inhibition. The importance of impaired CTL responses in HIV patients is well established where immune reconstitution, achieved by the
Rapamycin KS remission without T-cell response

use of highly active antiretroviral treatment (HAART), is accompanied by an expansion of the total CTL population [8]. Similarly, immune reconstitution in transplant recipients for other herpes virus-driven neoplasms has also been heralded by increases in the total CTL population [9,10].

Our case suggests that the anti-KS effect of rapamycin is not due to immune reconstitution. No expansion of the CTL or indeed the natural killer (NK) subsets was observed, whilst clinical and histological resolutions of the KS lesions occurred with complete disappearance of VEGF staining from the lesions. We believe this to be the first report showing that VEGF staining resolves and T-cell subsets do not change during disease improvement.

This finding would require further confirmation in wider studies, but the point is not merely a theoretical one. Post-transplantation KS is often fatal, and strategies to deal with it that rely on immune reconstitution may threaten the transplant itself. This is serious enough in the case of renal transplant recipients, but is even more vital in those whose transplant survival governs their own, such as liver, heart or lung transplants. This case demonstrates the effectiveness of rapamycin-induced KS regression and suggests that such a strategy does not put the transplant at unnecessary risk of rejection.

Conflict of interest statement. None of the authors have a conflict of interest to declare concerning this document. The results presented in this paper have not been published previously in whole or part.

References


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