Transplant International

Transplant International ISSN 0934-0874

REVIEW

Kaposi's sarcoma and mTOR: a crossroad between viral infection neoangiogenesis and immunosuppression

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Keywords
Kaposi's sarcoma, kidney transplant, mTOR, Sirolimus, viral infection.

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Received: 30 August 2007
Revision requested: 17 September 2007
Accepted: 21 April 2008

doi:10.1111/j.1432-2277.2008.00697.x

Summary

The incidence of Kaposi's sarcoma (KS) among the recipients of solid organ transplants is about 500 times the rate in the general population, suggesting a role for immunosuppression in the development of the disease. The drugs used for the induction and maintenance of immunosuppression and the length of treatment with these agents influence both the incidence and the type of cancer development. The clinical presentation of KS in transplant recipients is often limited to the skin. The risk of death from KS is related to the form and extent of the lesions. The main approach to managing transplant-associated KS is to reduce or even discontinue immunosuppressive therapy; this strategy carries a risk of acute rejection of the graft. KS is a multicentric tumor composed of endothelium-lined vascular spaces and spindle-shaped cells. Its pathogenesis is unclear. Recent evidence suggests that vascular endothelial growth factor (VEGF) is likely to be a growth factor for KS cells: blocking the interaction between VEGF and Flk-1/KDR can abolish VEGF-induced growth of the tumor. Recently, Sirolimus, a drug used in kidney-transplant recipients, has been suggested to reduce KS progression in transplant recipients. This unexpected effect of the drug confirms previous experimental information on KS pathogenesis and may shed light on an array of molecular mechanisms, modulated by Sirolimus, of potential clinical interest in the transplantation scenario.

In 1872, Moritz Kohn, an Austro-Hungarian dermatologist, who changed his name to Moritz Kaposi after converting from Judaism to Catholicism, described five men with aggressive 'idiopathic multiple-pigmented sarcomas of the skin' [1]. In 1894, Kaposi himself changed the term 'pigmented' to 'hemorrhagic' ('idiopathic multiple hemorrhagic sarcoma of the skin'), and in 1912, the eponym 'Kaposi's angiosarcoma' was introduced by Sternberg [2,3].

Although originally defined as a sarcoma, the neoplastic nature of KS is still a controversial issue. Duprez *et al.* in a series of 139 biopsies from 98 patients observed that individual KS-disseminated tumor skin lesions represented distinct expansions of HHV-8-infected spindle cells. Thus, their results suggest that KS lesions, especially in patients with advanced skin tumors, are reactive proliferations rather than true malignancies with metastatic dissemination. [4]. On the other hand, Rabkin *et al.* [5], in order to determine whether KS is a monoclonal disorder, assessed the methylation patterns of the androgen-receptor gene in multiple lesions from women with the acquired immunodeficiency syndrome. In polyclonal tissues, about half the copies of each allele are methylated, whereas in cells derived from a single clone all the copies of only one allele are methylated. To minimize contamination by normal DNA, they used microdissection to isolate areas composed primarily of putative tumor cells. In eight patients with a total of 32 tumors they observed a highly unbalanced methylation patterns in 28 tumors. In all the tumors that had unbalanced methylation from a

given patient, the same allele predominated. Thus, they suggested that KS is a disseminated monoclonal cancer and that the changes that permit the clonal outgrowth of spindle cells occur before the disease spreads. Both these reports were somehow confirmed by Gill *et al.* [6]. These authors examined 24 biopsies from the 12 patients. Five cases were consistent with individual KS lesions being clonal. In two cases, multiple KS specimens derived from the individual patients had different androgen-receptor alleles inactivated, proving unequivocally that these KS lesions arose independently from distinct transformed cells. In seven cases, only a polyclonal pattern of inactivation was observed, whereas two others had tumor areas of both clonal and polyclonal inactivation patterns. These findings suggest that KS can be a clonal neoplasm, and in some of the cases multiple KS lesions in a given patient can arise from independent cellular origins and acquire clonal characteristics.

Different investigators described four clinical types of Kaposi's sarcoma (KS) based not only on clinical features, but also on geographic, and epidemiologic considerations.

Classification of Kaposi's sarcoma

Classic Kaposi's sarcoma

The classic type of KS primarily affects elderly men of East European and Mediterranean origin. Classic KS is significantly more common in men than in women, with a ratio as high as 15:1. Multiple firm, purple-blue or reddish-brown plaques and nodules typically appear initially on the hands and feet and progress up to the arms and legs over a period of years or decades A visceral localization is present in approximately 10% of patients. Lymphedema may precede or follow the appearance of skin lesions. Characteristic histologic features include spindle-shaped tumor cells surrounding hyperemic vascular slits, often in association with extravasated erythrocytes, hemosiderin deposits and dermal fibrosis. The median age at histologic diagnosis in one study reporting a population of 80 patients, 67 men and 23 women, was 64 years (range, 26–90) [7]. Homosexual men may be at increased risk for classic KS, even in the absence of clinically detectable immunosuppression.

Endemic Kaposi's sarcoma

In the 1950s, KS was recognized as being common in different geographical areas of Africa. Kaposi's sarcoma accounted for 3–9% of cancers reported in Uganda in 1971 [8]. In 1983, Bayley noted an abrupt increase in the incidence of KS in Zambia. In addition to the usual number of patients with typical endemic KS, he documented an increasing number of patients with an aggressive atypical variant that responded poorly to conventional treatment [9]. Once the acquired immunodeficiency syndrome (AIDS) could be diagnosed reliably and patients could be classified as having human immunodeficiency virus (HIV)-negative endemic KS or HIV-positive epidemic KS, African centers distinguished between the two in reporting treatment results. In a retrospective analysis of 47 HIV-negative black South African patients treated in the Johannesburg General Hospital between 1980 and 1990, 29 presented with localized disease [10]. Four of the 47 had concurrent lymphoma [10]. Typical findings in 10 Zambian men (median age, 41 years) with indolent disease were nodules or plaques on edematous limbs [9]. None died of the disease in the short follow-up period. KS in HIV-negative and HIV-positive patients is now the most frequently occurring tumor in central Africa, accounting for 50% of tumors reported in men in some countries [11]. In eastern and southern Africa, KS makes up 25–50% of soft-tissue sarcomas in children and 2–10% of all cancers in children [12].

Immunosuppression-associated or transplantation-associated Kaposi's sarcoma

Another group at increased risk for KS are organ-transplant recipients and patients receiving immunosuppressive therapy, particularly members of ethnic groups at increased risk for classic KS [13–22].

The median interval from organ transplantation to the diagnosis of KS is 29–31 months (range, 3–124 months) [18,19]. In three series with a total of 35 cases of KS, the percentage of men presenting KS ranged from 67% to 80%, with a male to female ratio ranging from 2:1 to 4:1 [13,18,19]. This type of KS tends to be aggressive, involving lymph nodes, mucosa, and visceral organs in about half of patients, sometimes even in the absence of skin lesions.

Epidemic or AIDS-associated Kaposi's sarcoma

In 1981, Friedman-Kien *et al.* described more than 50 previously healthy, young homosexual men with KS involving skin, lymph nodes, viscera and mucosa [23]. Concurrent life-threatening opportunistic infections were associated with a significant defect in cell-mediated immunity, a syndrome now recognized as AIDS. This aggressive and frequently fatal epidemic variant of KS affected homosexual men with AIDS 20 times more often than male patients with hemophilia and other AIDS patients with a similar degree of immunosuppression [24]. Although the incidence of KS in American men with AIDS decreased from 40% in 1981 to less than 20% in

1992 [25], it remains the most common AIDS-associated cancer in the United States.

Kaposi's sarcoma-associated herpesvirus

Compelling epidemiologic evidence, including the peculiar geographic distribution of KS, prompted speculation about an infectious cause [24]. In 1994, Chang *et al.* identified DNA fragments of a previously unrecognized herpesvirus, called Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 or HHV8), in a KS skin lesion from a patient with AIDS [26]. Over 95% of KS lesions, regardless of their source or clinical type, have been found to be infected with KSHV. Although several studies suggested the contribution of cytokines as well as HIV tat protein to the pathogenesis of KS lesions, it is clear that the presence of KSHV is the primary and necessary factor in the development of this tumor. In addition, immunosuppression in the host appears to be an important cofactor in the clinical expression of KS in some KSHV-infected patients. The relation between clinical lesions and immunosuppression underscores the unusual pathology and clinical course of this proliferative disease and suggests that KS may not be a conventional neoplasm. Most human herpesviruses are associated with disease in immunocompromised hosts, as a result of either the reactivation of latent virus or the proliferation of growth-transformed cells. Herpesviruses are divided into three subfamilies, and KSHV together with Epstein–Barr virus (EBV) are members of the gammaherpesvirus subfamily [27]. Gammaherpesviruses are well known to be involved in the pathogenesis of several tumors, particularly lymphomas in humans and animals. Molecular epidemiologic data suggest that KSHV may be an ancient pathogen of humans that has spread very slowly in the population [28]. The 165-kb KSHV genome was sequenced within 2 years after its discovery [29] and provided important clues about the way in which this virus might induce uncontrolled cellular proliferation. Unlike most other viruses, KSHV incorporated several recognizable host-cell genes during its evolution. This molecular piracy facilitates studies of KSHV, as the viral genes can be readily compared with their cellular counterparts.

KSHV and molecular oncogenesis

Kaposi's sarcoma-associated herpesvirus encodes proteins that are homologous to human oncoproteins, including a cyclin that inhibits Rb and controls the progression to the S phase of the cell cycle [30], and a Bcl-2–like protein that prevents apoptosis [31]. Other regulatory KSHV proteins include a G-protein–coupled receptor [32], an inhibitor of apoptosis mediated by the Fas-associated death domain-like interleukin-1b-converting enzyme (FLICE) pathway [33], a constitutively active immunoreceptor [34], and an inhibitor of the interferon signaling pathway [35], all of which may disrupt the control of cellular proliferation and thus be responsible of the virus oncogenic activity. KSHV also encodes an interleukin-6 and three functional chemokines that can be secreted by infected cells, affecting the replication and migration of uninfected cells [36]. The viral interleukin-6 induces B-cell proliferation, whereas the chemokines may activate angiogenesis and inhibit the Th1 immune responses [37]. Friborg *et al.* demonstrated that the major latency-associated nuclear antigen (LANA) can interact with p53 and inhibit transcriptional activity mediated by p53 [38].

Although KSHV encodes several genes with the molecular potential to induce cellular proliferation and prevent apoptosis, the current research is oriented towards discovering which genes are active in specific human tumors. Preliminary studies on different KSHV proteins suggest that their expression is cell-specific. The viral LANA is expressed in all cells infected by KSHV, whereas viral interleukin-6 is only found in KSHV-infected B cells.

Recently a particular interest has been focused on the viral G protein-coupled receptor (vGPCR) expressed by KSHV-infected cells. This viral protein is a member of the CXC chemokine G-protein-linked receptors family [39], with significant homology with CXCR1 and CXCR2. However, this receptor exhibits significant ligand-independent activities. An increasing body of evidence suggests that vGPCR may play a pivotal role in KSHV oncogenesis [39]. In a mouse model of endothelial-specific retroviral transduction, vGPCR produced vascular tumors, strikingly similar to human KS lesions [40]. In addition to their histological and ultrastructural similarity to human lesions, vGPCR-induced tumors had a unique predilection for the dermis-like human KS, suggesting that dermal endothelial cells may be particularly vulnerable to vGPCR-induced sarcomagenesis. This observation might explain why systemic KSHV infection often manifests only with dermal KS lesions.

Different intracellular signaling molecules have been shown to be activated by vGPCR, including MAPK, p38, and JNK [32,41], which in turn may control the expression of growth-promoting genes. It has been recently suggested that vGPCR can promote the phosphorylation and subsequent activation of Akt. Sodhi *et al.* [42] demonstrated that this event is followed by phosphorylation of tuberin, one of the component of the tuberous sclerosis complex (TSC). The TSC, formed by hamartin (TSC1) and tuberin (TSC2), functions as a negative regulator for Rheb, a Ras-related small GTP binding protein that promotes the activation of mTOR. Phosphorylation of the tumor suppressor TSC2 by Akt in vGPCR-transfected

cells resulted in the inactivation of Rheb, thereby promoting mammalian target of rapamycin (mTOR) activation. Interestingly, the inhibition of this signaling pathway by rapamycin completely abolished the vGPCR-induced sarcomagenesis *in vivo* [42]. On the other hand, the consistutive activation of mTOR in TSC2 +/− mice induced the development of dermal vascular sarcomas similar to human KS [42].

Solid organ transplants and Kaposi's sarcoma

Transplant recipients receive long-term immunosuppressive therapy, trading off the reduced morbidity and mortality on account of the preservation of transplanted organs for the risks of infection and cancer [43]. Beside lymphoproliferative disorders [44], skin cancers are the most common neoplasia in transplant recipients and account for a substantial increase in post-transplant morbidity [45]. Squamous-cell and basal cell carcinomas account for more than 90% of all skin cancers in solid organ transplant patients [46] and their incidence is significantly associated with the duration of immunosuppressive therapy, ultimately affecting more than 50% of the White transplant recipients [46].

Kaposi's sarcoma incidence increases up to 500-fold in solid organ transplant recipients and up to 20 000-fold in male homosexual AIDS patients suggesting a strong correlation between a reduction in the immune defense and the development of the disease [47]. The clinical presentation of KS in transplant patients is often limited to the skin, although visceral KS has been described in several cases. The mortality associated with KS is related to the form of presentation and the extension of the lesions. The development of KS is also significantly influenced by the level of immunosuppression, as suggested by the observation that few cases of this sarcoma were reported before 1980 in transplant patients, whereas the frequency markedly increased with the introduction of novel and more potent immunosuppressive medications. The observation that KS lesions regress on discontinuation of cyclosporine (CsA) therapy and recur after drug reintroduction, pointed to this calcineurin inhibitor as one of the most critical agent in the development of the disease after transplantation [48]. CsA lowers host immune response favoring reactivation of latent KSHV infection and induces the expression of several growth factors, including transforming growth factor beta (TGF-β) and VEGF, which are important in the proliferative phase of KS development [49–51].

Recently, it has been shown that the development of KS lesions involves initial KSHV latent infection of normal vascular endothelial cells followed by a proliferative phase requiring expression of vGPCR protein [40,52]. This viral oncoprotein increases secretion of VEGF and upregulates the VEGF receptor (KDR) in endothelial cells [40]. The activation of the VEGF/KDR autocrine loop, together with the paracrine effects on neighboring spindle cells that are only latently infected, plays a key role in the development and progression of the final proliferative phase of KS. These findings support the hypothesis that in a state of generalized reduced host immune surveillance, such as in organ transplantation, chronic CsA administration contributes to KS development and progression by sustaining pro-cancerogenic pathways involving TGF-β, VEGF and its receptor. Not all transplant patients on CsA, however, develop KS, implying that the level of overall immunosuppression and/or the degree of exposure to CsA might be critical for the risk of developing the disease.

Treatment options for Kaposi's sarcoma in transplant recipients

Several therapeutic approaches have been suggested for the management of transplant-associated KS although for none of them we have data from any controlled trial [52]. Various reports have observed that a marked reduction or even discontinuation of immunosuppressive therapy leads to a complete regression of KS [52]. However, according to the original report from the Cincinnati Transplant Tumor registry, only 30% of the patients in whom immunosuppression was reduced/withdrawn, presented a complete remission of KS [52]. On the other hand, Montagnino *et al.*, in their case series, reported a complete remission in 9/11 patients [18]. This approach, however, is associated in most of the reports with a significant increase in graft loss [52], although Duman *et al.* in their experience observed only a 20% of failing graft for chronic rejection [48]. In a case report, Hussein *et al.* [53] suggested that withdrawing cyclosporine and adding mycophenolate to the immunosuppressive therapy may be effective and safe, although their observation was not confirmed by other reports on a larger-sized population of patients. A second line approach, particularly in patients with visceral involvement, is chemotherapy. Shepherd *et al.* suggested that doxorubicin alone or in combination with vincristine and/or bleomycin represents a safe and effective treatment [13]. Finally, based on the literature on AIDS-associated KS, Wu *et al.* reported the successful use of paclitaxel in a case report [54].

The cellular and clinical effects of Sirolimus on KS in renal transplanted patients

Sirolimus (SRL), an immunosuppressive drug recently introduced in the immunosuppressive therapy of kidney

transplantation, has been suggested to exert anti-neoplastic effects. The immunosuppressive and anti-neoplastic effects of SRL may share a common mechanism of action. SRL inhibits mTOR, which links mitogen stimulation to protein synthesis and cell cycle progression through the activation of p70S6 kinase (k), a key enzyme in the regulation of the translation machinery [55]. Thus, inhibition of mTOR prevents acute graft rejection inhibiting IL-2-induced T cell clonal expansion and could block tumorigenesis and metastatic progression directly inhibiting tumor cell proliferation. Indeed, SRL potently inhibits the growth of many tumor cell lines *in vitro* and has been demonstrated to have anti-tumor activity in both xenograft and syngeneic murine tumor models [56]. In addition, the molecular data from Sodhi *et al.* strongly supported the role of SRL as a potential therapeutic approach for KS treatment [42]. Beyond this direct effect, SRL has been shown to dramatically affect tumor angiogenesis. Indeed, Guba *et al.* [57] demonstrated in a mouse model that SRL inhibits tumor progression through anti-angiogenic activity related to impaired VEGF production and limited proliferative response of endothelial cells to VEGF stimulation.

The anti-angiogenic properties demonstrated by Guba *et al.* [57] in an animal model of neoplastic disease prompted the use of SRL in the clinical arena in the attempt to reduce the progression of post-transplant neoplasia. KS, because of its histological features, was the first and easier target for this therapeutic approach. Campistol *et al.* reported two cases of KS that completely regressed after conversion from a CsA-based to a SRL-based immunosuppressive therapy [58].

At the same time, we studied 15 recipients of a cadaveric kidney transplant who had biopsy-proven KS. When KS was diagnosed, CsA and mycophenolate mofetil were stopped and SRL was started. One month after withdrawal of CsA and switch-over to SRL, the cutaneous lesions gradually disappeared. After 3 months, no cutaneous KS lesions could be identified in any of our patients [59]. In addition, our *in vivo* study demonstrated the anti-angiogenic activity of SRL related to VEGF expression (Fig. 1).

The main limitation of our study to prove a direct effect of SRL on KS regression was represented by the abrupt withdrawal of CsA. Thus, we could not definitively prove whether it was the SRL introduction or the withdrawal of CsA, which played the major role. To answer this question, Gutierrez-Dalmau *et al.* reported a series of seven cases in which they first reduced CsA administration and then withdrawn the calcineurin inhibitor to introduce SRL [60]. They could demonstrate that only SRL introduction was able to induce the regression of the neoplasia.

On the other hand, Lebbè *et al.* reported a series of cases in which the conversion from a calcineurin-based to a SRL-based immunosuppressive therapy was not equally successful [61]. They observed complete and/or partial regression in 50% of the patients. However, their patients' population included only KS with extensive skin lesions, multiple visceral involvements and a long history of previously unsuccessful therapies. In this perspective, the observation

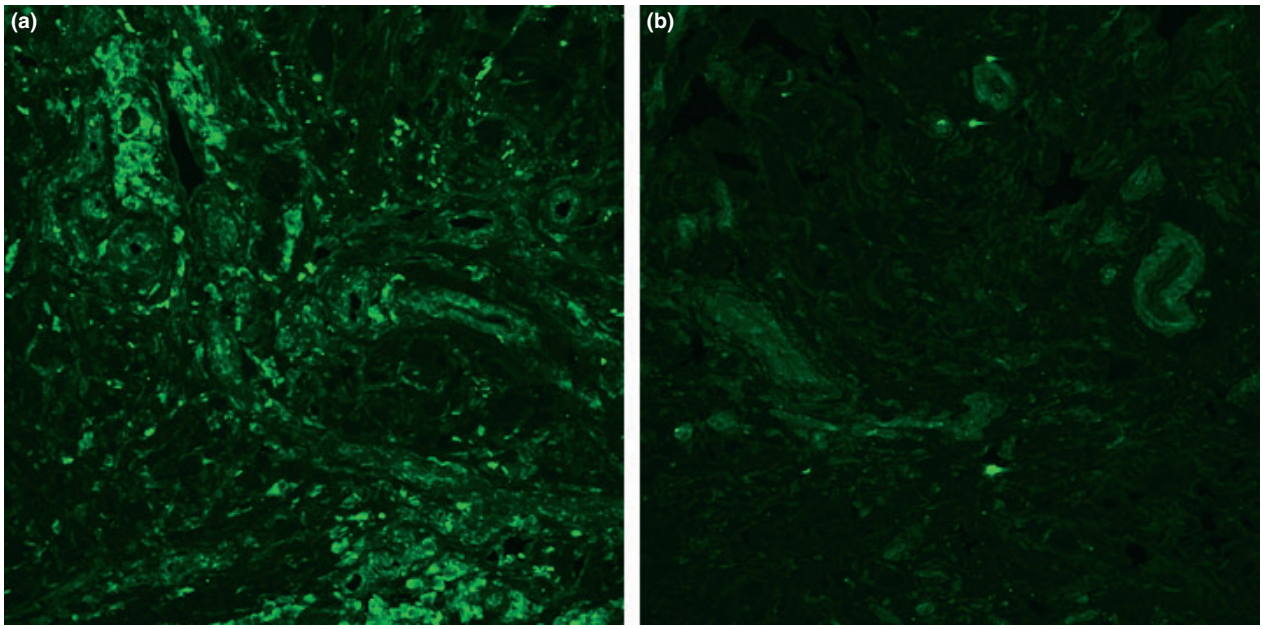

Figure 1 Vascular endothelial growth factor protein expression in KS biopsies at the time of diagnosis (a), and 6 months after conversion to SRL (b).

reported by Boratyńska *et al.*, is interesting, which is to the effect that SRL level may significantly influence the ability of the drug to control the growth of KS lesions. Indeed, in their experience, KS recurrence was associated with high blood levels of SRL and that dose reduction was sufficient to induce a complete remission [62].

Finally, it should be underlined that a beneficial effect on KS progression is not limited to SRL, as Campistol *et al.* recently reported also few cases of KS successfully treated with everolimus [63].

Conclusion

The increasing knowledge on the pathogenesis of KS has shed light on several molecular mechanisms potentially underlying its pathogenesis. This huge effort of basic science suggested several potential therapeutic targets. Among them, mTOR may represent a convenient one in transplant recipients, as its inhibition has been shown to protect solid organ transplant from rejection. On the basis of this observation, there are now several reports supporting the use of mTOR inhibitors in post-transplant KS, as this class of drug may reduce or even reverse KS progression, even as it preserved the graft function. In this perspective, we believe that the treatment of transplantation-associated KS may represent one of the best examples of bridging basic and clinical research to solve everyday clinical dilemmas.

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