Kaposi's Sarcoma and Transplantation

Julio C Mendez and **Carlos V Paya**, Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA.

HUMAN HERPESVIRUS 8 (HHV-8) DNA HAS BEEN DETECTED IN DIFFERENT TYPES OF KAPOSI'S SARCOMA, SUGGESTING AN ESSENTIAL ROLE OF HHV-8 IN ITS PATHOGENESIS. THE IMMUNOSUPPRESSIVE DRUG THERAPY USED IN TRANSPLANT RECIPIENTS FAVOURS THE DEVELOPMENT OF KAPOSI'S SARCOMA, AND ITS INCIDENCE IN THE TRANSPLANT POPULATION IS 400–500 TIMES GREATER THAN THAT IN THE GENERAL POPULATION

KEY WORDS

KAPOSI'S SARCOMA ▮ *ORGAN TRANSPLANTATION* ▮ *HUMAN HERPESVIRUS 8 (HHV-8)* ▮ *KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS (KSHV)* ▮ *IMMUNOSUPPRESSIVE THERAPY* ▮ *EPIDEMIOLOGY* ▮ *PATHOGENESIS*

SUMMARY

Kaposi's sarcoma is a tumour of multicentric origin, composed of endothelium-lined vascular spaces and spindle-shaped cells. The incidence of Kaposi's sarcoma in transplant recipients is 400–500 times greater than that in the general population, and is rising within the transplant population, currently comprising more than 5% of all *de novo* neoplasms in this group. The exact pathogenesis is still unknown but DNA sequences from human herpesvirus 8 (HHV-8) are present in the different clinical variants of Kaposi's sarcoma. Risk factors associated with development of these tumours post-transplantation include the geographical origin of the patient, HSV-8 infection before and after transplantation, and the immunosuppressive regimen used, but the importance of each factor remains to be determined. Apart from conventional treatment with surgical excision, radiotherapy or chemotherapy, cessation, reduction or modification of immunosuppressive therapy has been shown to be effective in a significant number of patients. This article reviews recent advances in our understanding of Kaposi's sarcoma after transplantation.

Introduction

FIRST DESCRIBED AS an 'idiopathic multiple pigmented sarcoma of the skin' by Moritz Kaposi in 1872,[1] Kaposi's sarcoma (Figure 1) was a rare medical curiosity in Europe and USA prior to the AIDS epidemic, which was officially recognized in 1981.[2] With the advent of immunosuppressive drug therapies and transplantation, more cases were reported.

Kaposi's sarcoma is now categorized according to four different epidemiological manifestations:[3]

- Classic, in which the skin lesions have little or no visceral involvement. This type is commonly found in older men who are of Mediterranean origin;
- African endemic, which can show systemic involvement and progress rapidly, and is found in southern equatorial Africa;
- AIDS-associated, which manifests both as cutaneous and visceral lesions, and is the most aggressive form of the disease;
- Iatrogenic immunosuppression-related, which develops as a result of immunnosuppressive medications in transplant recipients.

The first case of post-transplantation Kaposi's sarcoma was described in 1969 in a renal transplant recipient.[4] Additional cases were subsequently reported, emphasizing the relationship between immunosuppressive therapy and Kaposi's sarcoma.[5] The first case following the use of cyclosporin was reported from Saudi Arabia in 1983.[6] With the increased use of cyclosporin and newer immunosuppressive drugs such as tacrolimus and mycophenolate mofetil, more transplant-related Kaposi's sarcoma cases continue to appear.

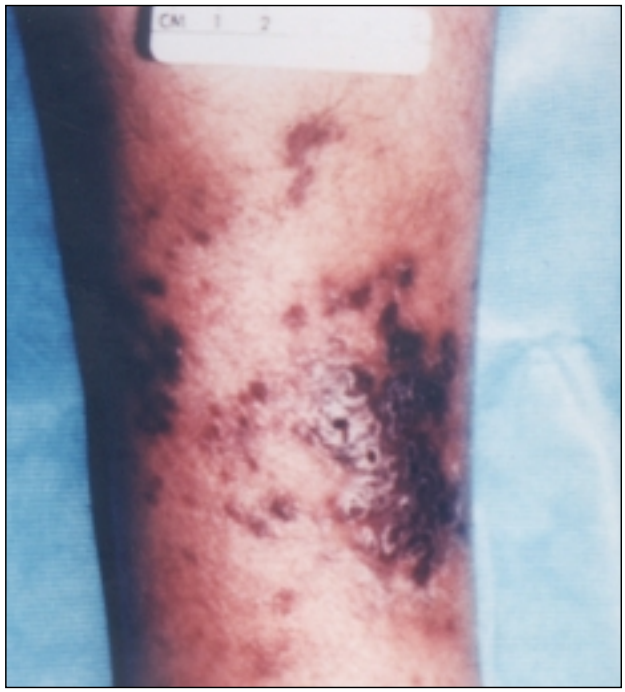

Figure 1:
The characteristic reddish purple lesions of Kaposi's sarcoma.

Aetiology

The aetiology of Kaposi's sarcoma was unknown for many years, although an infectious agent was believed to be the most likely cause, based on certain epidemiological and clinical observations (Table 1). Some investigators, however, have regarded Kaposi's sarcoma not as a malignancy but as a benign reversible hyperplasia.[7]

Among the viruses with which a link with Kaposi's sarcoma has been proposed are herpes simplex virus, cytomegalovirus, human herpesvirus 6, human papilloma virus, hepatitis B virus, human immunodeficiency virus and others.[8,9] Of these, cytomegalovirus was considered the most likely agent but stringent studies failed to show any connection.[10]

More recently, a new gamma herpesvirus, HHV-8, originally termed Kaposi's sarcoma-associated herpesvirus (KSHV), was identified from the majority of patients with all the clinical variants of Kaposi's sarcoma.[11] The detection of HHV-8 DNA in the different types of Kaposi's sarcoma is a strong indicator for an essential role of this virus in the pathogenesis of Kaposi's sarcoma.[12]

There is now more evidence to indicate that HHV-8 is a potent oncogenic herpesvirus and the most likely

Table 1: Epidemiological and clinical observations implicating an infectious agent in the aetiology of Kaposi's sarcoma[21,24]

- Clustering of this tumour in certain populations and geographical areas
- Rapid appearance following the induction of immunosuppressive therapy
- Frequent history of relapses and remissions of individual Kaposi's sarcoma lesions
- Occasional history of apparently spontaneous cures in classic and AIDS-related Kaposi's sarcoma
- Regression of Kaposi's sarcoma following reduction or discontinuation of immunosuppressive drugs in some transplant recipients
- Some transplant recipients with Kaposi's sarcoma received organs from the same donor, suggesting transmission of an infective agent from donor organs

infectious cause of Kaposi's sarcoma. Based on epidemiological studies, detection of this virus in lesions from all forms of Kaposi's sarcoma by molecular techniques and isolation *in vitro* with immortalized B-cell lines derived from a secondary malignancy is associated with HHV-8 body cavity-based lymphomas (BCBLs).[13] The virus itself has been studied in detail and its genome and nucleotide sequence has largely been determined.[14] Serological data is now accumulating, indicating that HHV-8 seropositivity is associated with an increased risk for Kaposi's sarcoma in patients with HIV.[15]

Incidence and Age and Gender Distribution of Transplant-related Kaposi's sarcoma

The incidence of Kaposi's sarcoma in transplant recipients is higher than that in the general population. Kaposi's sarcoma is estimated to occur in 0.4–0.6% of solid organ transplant recipients, in whom its frequency is 150–200 times greater than that in the general population (0.01–0.06%).[16] An epidemiological study showed a 400–500-fold increase in the incidence of Kaposi's sarcoma in renal transplant recipients compared with control populations of the same ethnic origin.[17]

According to the Cincinnati Transplant Tumor Registry (CTTR), when non-melanoma skin cancers and *in situ* carcinomas of the uterine cervix were excluded (omitted from most surveys of cancer statistics), Kaposi's sarcoma comprised 5.7% of the neoplasms reported. In addition, the total number of cases of Kaposi's sarcoma reported to the Registry exceeded the totals for two tumours that are common in the general population, namely carcinomas of the colon and breast.[18]

Kaposi's sarcoma is found in a higher proportion of transplant recipients who are of Mediterranean and Middle Eastern origin. For example, in one series, the overall incidence among transplant patients was 0.78% but up to 4% among those of Jewish or Mediterranean origin.[17] In series from Saudi Arabia, Kaposi's sarcoma was the most common tumour in renal transplant recipients,[19,20] representing, according to one report, 76% of all the *de novo* malignancies developing after transplantation, with an incidence of 4.7%, whereas in the general population of Saudi Arabia, the incidence of Kaposi's sarcoma was 0.38%.[21]

The average age of presentation of Kaposi's sarcoma in 356 transplant recipients reported to the CTTR was 43 years (range 4.5–67 years). The male:female ratio, according to the same registry, was nearly 3:1.[8,10,22] Few cases of Kaposi's sarcoma post-transplantation have been reported in the paediatric population. These cases have been seen more commonly after renal transplantation.[21] According to the CTTR, paediatric cases comprised only 3% of the patients with Kaposi's sarcoma.[8,10,22] Kaposi's sarcoma is observed mainly in kidney transplant recipients, with a much smaller incidence in recipients of other organs such as livers and hearts.[10,22,23]

The incidence, age and sex distribution for Kaposi's sarcoma according to the CTTR is summarized in Table 2.[24] These data have been corroborated by studies from other countries, Kaposi's sarcoma being seen in 1.6% of 820 Italian renal transplant recipients, for example.[16] In a study from France involving 7923 transplant recipients, the overall prevalence of Kaposi's sarcoma was 0.52% but, in contrast with other studies, the tumour was more common in liver transplant recipients (1.24%) than in recipients of kidneys (0.45%) or hearts (0.41%).[25]

Kaposi's Sarcoma and Other Malignancies

Kaposi's sarcoma has been associated with other tumours. In a study by Penn,[24] 6% of patients with Kaposi's sarcoma also had other malignancies. The association of Kaposi's sarcoma with lymphomas such as BCBL or primary effusion lymphoma (PEL) and others has been reported in transplant recipients (Figure 2).[26] Similarly, HHV-8 has also been associated with multicentric Castleman's disease, predominantly in patients with acquired immunodeficiency syndrome but also in HIV-negative patients.[27,28] According to the CTTR, eight of 356 transplant patients with Kaposi's sarcoma also had lymphomas.[24] Whether this reflects a more significant level of immunosuppression in these patients or a feature unique to HHV-8 infection is not known.

Kaposi's Sarcoma and Immunosuppressive Therapy

Several reports have confirmed the association of Kaposi's sarcoma with immunosuppressive drug therapy.[8,29] Cyclosporin-based therapy appears to favour development of Kaposi's sarcoma over azathioprine-based

Table 2: Incidence, age and sex distribution of transplant-related Kaposi's sarcoma according to reports from the Cincinnati Transplant Tumor Registry[24]

Total number of patients	356
Average age of presentation	43 years
Male:female ratio	3:1
Kaposi's sarcoma in paediatric patients	3% of the total number of patients with Kaposi's sarcoma
Frequency of Kaposi's sarcoma by transplanted organ	Kidney >heart >liver >lung
Average post-transplant time for development of Kaposi's sarcoma	21 months
Kaposi's sarcoma developing within 1 year after transplantation	46%
Incidence by racial or ethnic background	Majority were Arabic, Italian, Jewish, Greek or African

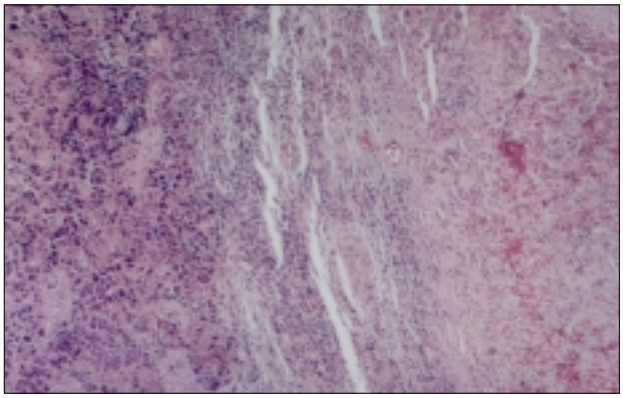

Figure 2:
Microscopic appearance of Kaposi's sarcoma and lymphoma.

regimens.[16] Although the overall incidence reported by the CTTR was 6%, that in patients on azathioprine and prednisolone was 3%, but for those on cyclosporin and prednisolone it was 10%.[30]

Another study suggests that cyclosporin-related Kaposi's sarcoma was more severe and seen at an earlier stage than that related to azathioprine.[25] What effect the new immunosuppressives, such as mycophenolate mofetil and rapamycin, will have on Kaposi's sarcoma remains to be seen.

A period of latency between the initiation of immunosuppressive therapy and development of Kaposi's sarcoma has been described[21,31] and is summarized in Table 3. Altogether, this information supports the concept that more effective immunosuppression will ultimately favour the expansion of HHV-8-infected transformed cells, as is seen with another herpesvirus, Epstein-Barr virus (EBV), which is responsible for EBV-induced post-transplant lymphoproliferative disease (EBV-PTLD). For a detailed discussion of PTLD, readers are referred to the article by J Christian Barrett on pages 4–8 of this issue.

Risk Factors for Transplant-related Kaposi's sarcoma

Risk factors for transplant-related Kaposi's sarcoma include patients originating from Africa and the Middle East, HHV-8 infection before and after transplantation, and initial use of polyclonal antilymphocyte antibodies.

A recent study by Farge *et al.*[31] has provided additional information on independent risk factors predisposing to Kaposi's sarcoma after transplantation. HHV-8 infection, determined by antibody testing, was detected in 68% of patients who developed Kaposi's sarcoma, compared with 3% of seronegative recipients. The presence of HHV-8 antibodies is, therefore, highly predictive of the emergence of post-transplantation Kaposi's sarcoma and confers a 28-fold increased risk.

In addition, HHV-8 DNA was detected from the peripheral blood mononuclear cells (PBMCs) in seven of nine patients with Kaposi's sarcoma, and in six of six Kaposi's sarcoma lesions. Importantly, HHV-8 DNA in PBMCs became undetectable in three of five patients concomitantly with tumour regression. These results suggest that detection of HHV-8 DNA within PBMCs and Kaposi's sarcoma lesions is related to tumour burden and evolution. They also indicate that careful virological monitoring, particularly in those from HHV-8 endemic regions, could help to identify individuals at high risk for post-transplantation Kaposi's sarcoma.

Pathogenesis

Although HHV-8 is widely acknowledged to be the aetiological agent of Kaposi's sarcoma, the identity of the oncogenic mechanisms triggered by this virus remains unclear.[9,32] One of theories put forward to explain the occurrence of Kaposi's sarcoma in transplant recipients suggests a chronic immunological process involving antigenically altered lymphoid cells and normal lymphocytes. During the graft versus host response, an angiogenesis factor is released, causing significant proliferation of mesenchymal and endothelial cells. At the same time, it is suggested, HHV-8 could be transferred to or induced in the cells responsive to the angiogenesis factor, causing their malignant transformation.[32]

Kaposi's sarcoma arises from endothelial cells that are known to have an important role in lymphocyte traffic and immune response, acting as antigen-presenting cells. It is possible that prolonged exposure to foreign histocompatibility antigens from a transplanted organ or repeated infections caused by different organisms (virus, bacteria, fungi) could stimulate lymphocytes and macrophages to release cytokines and growth factors, causing endothelial cell proliferation and leading to Kaposi's sarcoma development.[9] The fact that only a small proportion of patients at risk develop Kaposi's sarcoma suggests that factors additional to HHV-8 play a role. In this regard, some authors have reported high frequencies of some human leukocyte antigen (HLA) phenotypes.[33]

Examination of HLA phenotype and ethnicity was performed in 188 patients from the CTTR. HLA-A and B typing was available for 135 patients and HLA-DR for 67. The most relevant characteristic was the ethnic background (Table 2).[10] The donor–recipient HLA match was evaluated in 106 patients: 22% had four or more mismatches and 59% had at least two antigen matched. These results argue against poor donor-recipient matching as a risk factor.[34] Farge *et al.*[31] also reviewed the issue of genetic predisposition as a risk factor, but failed to find any association with HLA haplotypes.

Human herpesvirus 8 encodes cellular homologies to complement-binding proteins and cytokines, as well as interferon regulatory factors, IL-8 receptor and other proteins. More recently, HHV-8 has been shown to encode a viral homologue of the human cytokine IL-6 (vIL-6), which shares about 50% nucleic acid homology and functional properties with endogenous human IL-6. HHV-8 is a transforming virus, and the vIL-6 encoded by HHV-8 could prevent apoptosis in IL-6-dependent cell lines.[35]

The pattern of viral gene expression suggests that most cells in Kaposi's sarcoma lesions are latently infected with HHV-8, with lytic replication probably restricted to a smaller subpopulation of cells.[36] According to a study based on AIDS-related Kaposi's sarcoma, it has been postulated that a transforming agent such as a virus could cause alterations in the phenotypic and functional characteristics of mesenchymal progenitor cells, predisposing to the development of Kaposi's sarcoma.[37] A possible feature in this transformation process could be the modulation of oncostatin M or IL-6 receptors. During

Table 3: Latency period between the initiation of immunosuppressive therapy and development of Kaposi's sarcoma[18,40]

Type of patients	Immunosuppressive drugs	Latency period
Non-transplant patients	Prednisolone	61 months
Transplant patients	Azathioprine and prednisolone	24 months
	Cyclosporin and prednisolone	10 months
	Cyclosporin, azathioprine and prednisolone	9 months

periods of immunosuppression, such as after transplantation, and through the release of cytokines such as IL-1, TNF, oncostatin M, and IL-6, mitogenesis takes place in the progenitor mesenchymal cells.

Progression of the process and, possibly, opportunistic infections could lead to additional increases in cytokines and growth factors such as IL-1, IL-6, tumour necrosis factor, granulocyte–macrophage colony-stimulating factor, platelet-derived growth factor, basic fibroblast growth factor and vascular endothelial growth factor, resulting in a rapid increase in the growth rate of Kaposi's sarcoma lesions.[38] These lesions are characterized by proliferation of spindle-shaped cells, mixed with fibroblasts and inflammatory cells, with evidence of neoangiogenesis and oedema (Figure 3).[9] These cytokines may provide autocrine and paracrine growth stimulation of Kaposi's sarcoma cells, attracting other cells such as fibroblasts and smooth muscle cells into the lesions.[39]

Clinical Presentation and Staging

A staging procedure has been described and found to be helpful in designing treatment protocols and assessing prognosis and response to treatment as summarized in Table 4.[21]

Table 4. Staging procedure used in designing treatment protocols and assessing prognosis in patients with transplant-related Kaposi's sarcoma[21]

Stage	
I	Localized skin lesions involving one limb only
II	Widespread skin lesions involving more than one limb
III	Kaposi's sarcoma involving the viscera and/or lymph nodes
IV	Generalized Kaposi's sarcoma involving the skin, viscera and/or lymph nodes
Substage	
A	No associated malignancy or life-threatening infection
B	Associated malignancy or life-threatening infection

CUTANEOUS MANIFESTATIONS

The skin is the organ most commonly affected by Kaposi's sarcoma. Lesions present as multiple reddish blue to violet nodules or plaques (Figure 1).[1] The overlying skin is usually smooth but may be thickened or ulcerated.

In transplant-related Kaposi's sarcoma, the skin lesions may have a variable course, possibly related to the degree of immunosuppression. They may present with a benign appearance and no associated visceral involvement or may take a more aggressive form with a malignant appearance, which becomes widely disseminated and is usually associated with visceral involvement.

GASTROINTESTINAL MANIFESTATIONS

Gastrointestinal Kaposi's sarcoma has been reported frequently in transplant recipients.[4] It is usually not associated with any symptoms but may sometimes present with a variety of manifestations including non-specific upper gastrointestinal symptoms, gastrointestinal bleeding and, more rarely, as a perforation, intestinal obstruction, or protein-losing enteropathy.[21] Diagnosis is best made using endoscopy, which reveals the lesions as maculopapular, polypoid, and volcano or umbilicated nodular lesions. Gastrointestinal Kaposi's sarcoma tends to regress with regression of the skin lesions.[40]

PULMONARY MANIFESTATIONS

Pulmonary Kaposi's sarcoma has been documented in transplant recipients,[41] and can be diagnosed radiologically. It presents as reticulonodular infiltrates with hilar adenopathies with or without pleural effusions (Figure 4). The presenting symptoms may be dry cough, low-grade fever, non-specific chest pain, and haemoptysis. Pulmonary function tests reveal a restrictive pattern and patients may or may not present with associated skin lesions.

Bronchoscopy is sometimes a useful adjunct to diagnosis, revealing violaceous endobronchial lesions, as is transbronchial biopsy with subsequent histological evaluation (Figure 5).[42]

Mortality is usually high and is secondary to respiratory failure.

LYMPH NODE INVOLVEMENT

Lymphadenopathy is a common finding in patients with transplant-related Kaposi's sarcoma. Diagnosis is made by clinical examination and/or CT scan of the abdomen and chest. The most common location is the neck and, less frequently, the axillary area. Detection of a large lymph node around the mediastinum is quite common.

The lymph nodes are usually large, fleshy and dark blue. Histologically, the normal architecture is replaced by Kaposi's sarcoma tissue. The lymph node enlargement tends to regress with regression of Kaposi's sarcoma elsewhere, upon reduction of the immunosuppression.

OTHER MANIFESTATIONS

Kaposi's sarcoma has also been found less frequently in other organs including the liver, genitals, nose, larynx and oropharynx.[21]

According to the CTTR, 60% of the patients had non-visceral Kaposi's sarcoma confined to the skin, conjunctiva or oropharyngeal mucosa, and 40% had visceral disease mainly involving the gastrointestinal tract, lungs and lymph nodes.[10] The majority (98%) of those with non-visceral disease had lesions of the skin and 2% had involvement of the mouth.

Diagnosis is not easy in patients without the typical skin manifestations. In fact, 27% of the patients with visceral

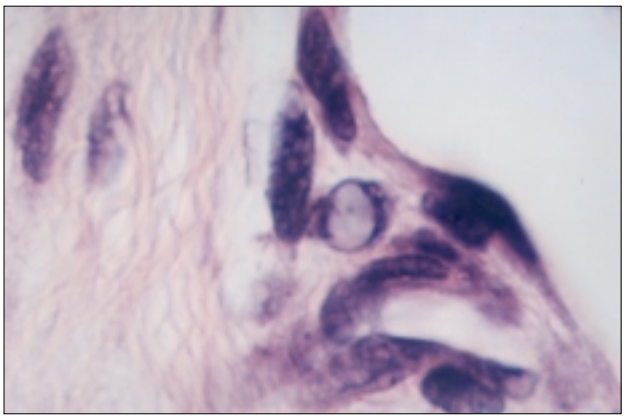

Figure 3:
Intranuclear inclusion in a Kaposi's sarcoma cell.

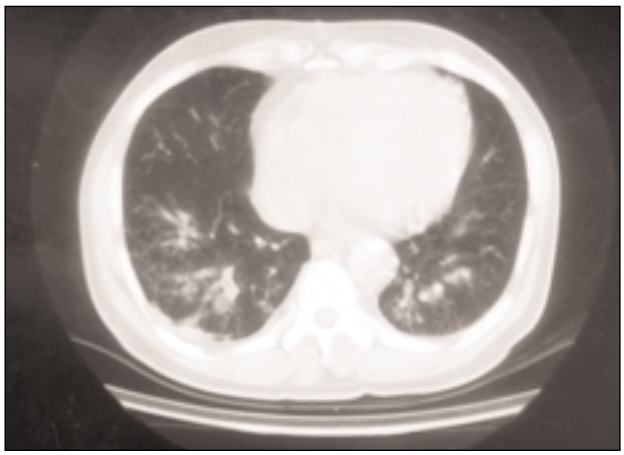

Figure 4:
Computerized tomography scan of pulmonary Kaposi's sarcoma in a heart transplant recipient.

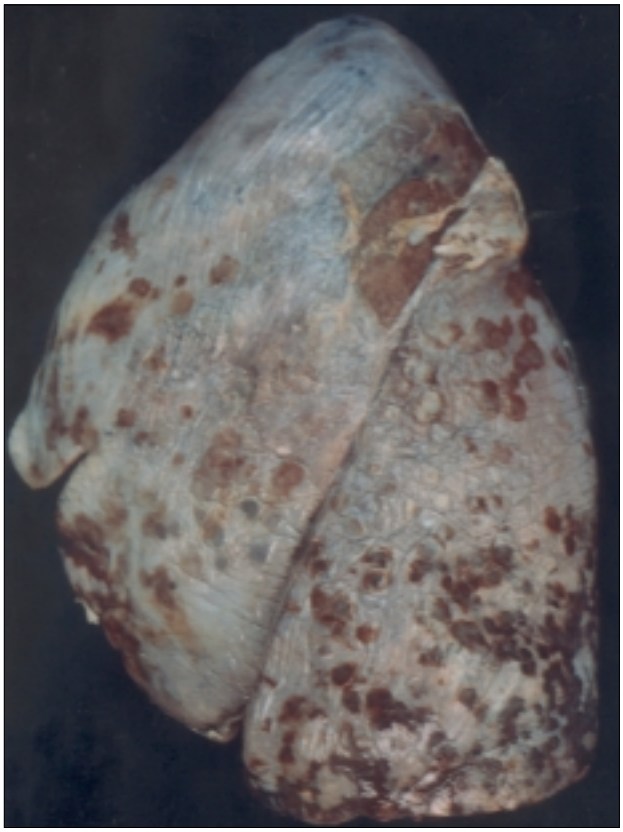

Figure 5:
Macroscopic appearance of pulmonary Kaposi's sarcoma in a heart transplant recipient.

disease had no skin manifestations but 3% did have oral lesions, providing easy access for biopsy and diagnosis.[10] The diagnosis of Kaposi's sarcoma should be suspected whenever a patient, particularly from the high-risk ethnic groups, presents with reddish blue macules or plaques in the skin or oropharyngeal mucosa, or apparently infected granulomas that fail to heal.[22] If the diagnosis is confirmed, a work-up including CT scans of the chest and abdomen and upper and lower gastrointestinal endoscopy will be needed to exclude any visceral involvement.

Treatment and Outcome

Different treatment modalities have been used including surgical excision, radiation therapy, chemotherapy, reduction of immunosuppressive therapy, or combinations of the various treatments.[17,22]

One of the main approaches is reduction or discontinuation of immunosuppressive drugs, which is usually associated with regression of lesions.[5] According to some studies and using the staging procedure previously described, a reduction of immunosuppression is usually sufficient to result in regression in the earliest stages (I and II). For the advanced stages (III and IV), a trial reduction of immunosuppression is always recommended first. If there is evidence of progression despite reduction of immunosuppression, however, discontinuation is recommended if it is feasible, e.g. kidney transplants. In cases of pulmonary Kaposi's sarcoma, discontinuation of treatment from the time of diagnosis is recommended because of the high associated mortality.[21]

Localized non-visceral Kaposi's sarcoma has resolved with surgical excision, radiation, intralesional injection of agents such as bleomycin, interferon-α, reduction of immunosuppression, systemic chemotherapy, or a combination of approaches.[43,44] Chemotherapy with agents such as vinblastine, vincristine, bleomycin, etoposide and mitoxantrone has been used successfully and is reserved for disseminated cases.[43,45] Some studies recommend the use of chemotherapy as an early treatment in cases of pulmonary Kaposi's sarcoma, because of the high associated mortality.[21]

Kaposi's sarcoma is a highly radiosensitive tumour and radiotherapy has been used to relieve painful lesions and limb oedema secondary to lymphatic obstruction, or to reduce the mass effect of the tumour.[46] Radiotherapy remains the treatment of choice for localized skin lesions.[19]

The role of antivirals such as aciclovir, ganciclovir, foscarnet and cidofovir is unclear but there has been some success when they have been used in combination with other treatments[47,48]

Variable results have been reported with the use of interferon-α.[49] Interferon is known to induce an immunologically mediated, steroid-resistant rejection, which limits its use.[50] Interferon may be indicated when, despite discontinuation of immunosuppression and loss of the graft, the tumour continues to progress.

According to the CTTR, 42% of the Kaposi's sarcoma patients experienced complete remission after various treatments including alterations of immunosuppressive regimens, chemotherapy and radiotherapy, and 38% of these remissions followed reduction or cessation of immunosuppression.[9] Patients with non-visceral disease had a higher remission rate (53%) than those with visceral disease (27%). Similar responses to reduction of immunosuppression have been noted by others,[17] but this approach of reducing the immunosuppression exacts a significant price: in one study, 59% of the renal transplant recipients successfully treated this way lost their allograft and 6% developed graft dysfunction.[10]

Immunosuppressive management is more difficult in non-renal transplant recipients such as heart, lung, or liver transplant patients, in whom the loss of the graft due to the reduction or discontinuation of immunosuppression could mean death unless re-transplantation is performed. According to a study of 11 liver transplant recipients with Kaposi's sarcoma in whom immunosuppression was drastically reduced, there was complete remission in two patients, stabilization of lesions in four, and progression in five – two of whom developed irreversible chronic rejection and died.[23]

Kaposi's sarcoma has been associated with significant mortality when it is not diagnosed or treated early. According to the CTTR, 57% of patients with visceral disease died, and 72% of these deaths were caused by Kaposi's sarcoma. In contrast, only 23% of patients with non-visceral Kaposi's sarcoma died, death being most commonly associated with infections or rejections.[10] The need for a higher and sustained immunosuppression in heart and liver transplant recipients most probably accounts for the higher mortality compared with kidney transplant recipients.[25]

A key question that the clinician faces is when to recommend another transplant and what type of immunosuppressives to use in patients who have had regression of Kaposi's sarcoma but in whom chronic allograft failure is present. The relationship between Kaposi's sarcoma and the immune system has been demonstrated in a study of renal transplant recipients:[51] seven patients with Kaposi's sarcoma were successfully treated by reduction or discontinuation of immunosuppressives, but the lesions recurred when the immunosuppression was resumed or when they underwent a second transplant. Kaposi's sarcoma regressed again when immunosuppression was reduced, but four of the patients lost their allograft to rejection. One of these patients had been successfully treated for Kaposi's sarcoma many years before transplantation and developed a recurrence 6 months after the transplant. Penn[8] recommends waiting for at least 2 years before re-transplantation for most malignancies, with the exception of those with a slow recurrence rate such as incidentally diagnosed renal cell carcinoma and *in situ* carcinoma of various organs.

Conclusions

Kaposi's sarcoma is an unusual neoplasm that is being seen more frequently in transplant recipients. The increasing number and indications for organ transplantation in the

population at risk, as well as the introduction of new and potent immunosuppressive agents may account, in part, for this increasing incidence.

Human herpesvirus 8 is considered the infectious agent most likely to be responsible for Kaposi's sarcoma, based on extensive epidemiological studies and detection of HHV-8 DNA in all types of Kaposi's sarcoma. The identification of HHV-8 has been crucial in improving our understanding of the complex pathogenesis and pathophysiology of Kaposi's sarcoma, and there have been rapid advances in the dissection of the complex mechanisms of virus–host interactions and the influences of immunosuppression and its induced factors in the genesis of this tumour.

Some risk factors predisposing to Kaposi's sarcoma have been described including geographical origin, HHV-8 infection before and after transplantation and initial use of polyclonal antilymphocyte antibodies. The significance of each of these factors, together with the identification of new ones, is currently under study.

The clinical diagnosis of Kaposi's sarcoma taking place after transplantation should be suspected in patients presenting with reddish blue macules or plaques in the skin or oropharyngeal mucosa. If the diagnosis is confirmed, any visceral involvement should be excluded. Mortality is significant when have taking place is not diagnosed or treated early, and is higher in cases of visceral involvement. The need for a higher and sustained immunosuppression in heart and liver transplant recipients may account for the higher mortality in this group compared with kidney transplant recipients.

Different therapeutic modalities including surgical excision, chemotherapy and radiotherapy have been described. One of the main approaches in the management of transplant-related Kaposi's sarcoma is reduction or discontinuation of immunosuppression, which is usually associated with regression of lesions. This approach may, however, be more difficult in non-renal transplant recipients (hearts, lungs, livers), in whom the loss of the graft due to reduction in immunosuppression could mean death unless re-transplantation is performed.

Our increasing understanding of this disease is contributing to the development of new molecular diagnostic assays and innovative technologies, improving the identification of individuals at risk for Kaposi's sarcoma, the determination of disease activity, and the monitoring of response to therapy. Some of these assays may, ultimately, be used to select patients who are more likely to respond to therapies targeting specific pathogenic pathways, and each component of the pathways could potentially serve as new therapeutic targets. Several therapeutic approaches to inhibit HHV-8 directly, the angiogenic process involved, or various cytokines or other factors are currently under investigation and include, among others, the use of cidofovir, lobucavir, retinoids, human chorionic gonadotropin, IL-4, thalidomide and human IL-12. Combinations of agents targeting different aspects of Kaposi's sarcoma pathogenesis may ultimately prove even more effective than any single intervention.

Address for correspondence:
Carlos V Paya, MD, PhD, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA.

E-mail: paya@mayo.edu

Received for publication: 14 October 1999
Accepted for publication: 16 November 1999

REFERENCES

1. Kaposi M. Idiopathic multiple pigmented sarcoma of the skin. *Arch Dermatol Syphilol* 1872;**4:**265–273. (English translation 1982;**32:**342–347.)
2. Center for Disease Control. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men – New York City and California. *MMWR Morb Mortal Wkly Rep* 1981;**30:**305–308.
3. Peterman TA, Jaffe HW, Friedman-Kien AE *et al.* The aetiology of Kaposi's sarcoma. *Cancer Surv* 1991;**10:**23–37.
4. Seigel JH, Janis R, Alper JC *et al.* Disseminated visceral Kaposi's sarcoma appearance after human renal homograft operation. *JAMA* 1969; **207:**1493–1496.
5. Myers BD, Kessler E, Levi J *et al.* Kaposi's sarcoma in kidney transplant recipients. *Arch Intern Med* 1974; **133:**307–311.
6. Little PJ, Al-Khader AA, Farthing CF *et al.* Kaposi's sarcoma in a patient after renal transplantation. *Postgrad Med J* 1983;**59:**325–326.
7. Brooks JJ. Kaposi's sarcoma: a reversible hyperplasia. *Lancet* 1986; **2:**1309–1311.
8. Penn I. Kaposi's sarcoma in immunosuppressed patients. *J Clin Lab Immunnol* 1983;**12:**1–10.
9. Ziegler JL, Dorfman RF. Overview of Kaposi's sarcoma: history, epidemiology, and biomedical features. In: *Kaposi's Sarcoma: Pathophysiology and Clinical Management* (Ziegler JL, Dorfman RF, eds). New York: Marcel Dekker 1988;pp1–22.
10. Penn I. Sarcomas in organ allograft recipients. *Transplantation* 1995; **60:**1485–1491.
11. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. *N Engl J Med* 1995;**332:**1181–1185.
12. Mendez JC, Procop GW, Espy MJ *et al.* Detection and semiquantitative analysis of human herpesvirus 8 DNA in specimens from patients with Kaposi's sarcoma. *J Clin Microbiol* 1998;**36:**2220–2222.
13. Chang Y, Moore PS. Kaposi's sarcoma (KS)-associated herpesvirus and its role in KS. *Infect Agents Dis* 1996; **5:**215–222.
14. Russo JJ, Bohenzky RA, Chien MC *et al.* Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). *Proc Natl Acad Sci USA* 1996;**93:**14862–14867.
15. Kedes DH, Operskalski E, Busch M *et al.* The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. *Nat Med* 1996;**2:**918–924.
16. Montagnino G, Bencini PL, Tarantino A *et al.* Clinical features and course of Kaposi's sarcoma in kidney transplant patients: report of 13 cases. *Am J Nephrol* 1994;**14:**121–126.
17. Harwood AR, Osaba D, Hofstader SL *et al.* Kaposi's sarcoma in recipients of renal transplants. *Am J Med* 1979; **67:**759–765.
18. Penn I. Malignancy. *Surg Clin North Am* 1994;**74:**1247–1257.
19. Al-Sulaiman MH, Al-Khader AA. Kaposi's sarcoma in renal transplant recipients. *Transplant Sci* 1994; **4:**46–60.
20. Qunibi W, Akhtar M, Sheth K *et al.* Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. *Am J Med* 1988; **84:**225.
21. Shaheen FA, Al-Sulaiman MH, Ramprasad KS, Al-Khader AA. Kaposi's sarcoma in renal transplant recipients. *Ann Transplant* 1997;**2:**49–58.
22. Penn I. Kaposi's sarcoma in organ transplant recipients: report of 20 cases. *Transplantation* 1979;**27:**8–11.
23. Bismuth H, Samuel D, Venancie PY *et al.* Development of Kaposi's sarcoma in liver transplant recipients: characteristics, management, and outcome. *Transplant Proc* 1991; **23:**1438–1439.
24. Penn I. Kaposi's sarcoma in transplant recipients. *Transplantation* 1997; **64:**669–673.
25. Farge D. Kaposi's sarcoma in organ transplant recipients: the collaborative transplantation research group of the Ile de France. *Eur J Med* 1993; **2:**339–343.
26. Jones D, Ballestas ME, Kaye KM *et al.* Primary-effusion lymphoma and Kaposi's sarcoma in a cardiac-transplant recipient. *N Engl J Med* 1998;**339:**444–449.
27. Parravicini C, Corbellino M, Paulli M *et al.* Expression of a virus derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. *Am J Pathol* 1997;**151:**1517–1522.
28. Oskenhendler E, Duarte M, Soulier J *et al.* Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996;**10:**61–67.
29. Penn I. First MR. Development and incidence of cancer following cyclosporine therapy. *Transplant Proc* 1986;**18:**210–215.
30. Penn I. Cancers in cyclosporine-treated vs azathioprine-treated patients. *Transplant Proc* 1996;**28:**876–878.
31. Farge D, Lebbe C, Marjanovic Z *et al.* Human herpes virus-8 and other risk factors for Kaposi's sarcoma in kidney transplant recipients. *Transplantation* 1999;**67:**1236–1242.
32. Warner TF, O'Loughlin S. Kaposi's sarcoma: a byproduct of tumor rejection. *Lancet* 1975;**2:**687–689.
33. Pollack MS, Safai B, Myskowski PL *et al.* Frequencies of HLA and Gm immunogenetic markers in Kaposi's sarcoma. *Tissue Antigens* 1983;**21:**1–8.
34. Brunson ME, Balakrishnan K, Penn I. HLA and Kaposi's sarcoma in solid organ transplantation. *Hum Immunol* 1990;**29:**56–63.
35. Nicholas J, Ruvolo VR, Burns WH *et al.* Kaposi's sarcoma-associated human herpesvirus 8 encodes homologues of macrophage inflammatory protein-1 and interleukin-6. *Nat Med* 1997; **3:**287–292.
36. Zhong W, Wang H, Herndier B, Ganem D. Restricted expression of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genes in Kaposi sarcoma. *Proc Natl Acad Sci USA* 1996;**93:**6641–6646.
37. Miles SA. Pathogenesis of human immunodeficiency virus-related Kaposi's sarcoma. *Curr Opin Oncol* 1992;**4:**875.
38. Samaniego F, Markham PD, Gendelman R *et al.* Vascular endothelial growth factor and basic fibroblast growth factor present in Kaposi's sarcoma (KS) are induced by inflammatory cytokines and synergize to promote vascular permeability and KS lesion development. *Am J Pathol* 1998;**152:**1433–1443.
39. Stürzl M, Roth WK, Brockmeyer NH *et al.* Expression of platelet-derived growth factor and its receptor in AIDS-related Kaposi sarcoma *in vivo* suggests paracrine and autocrine mechanisms of tumor maintenance. *Proc Natl Acad Sci USA* 1992; **89:**7046.
40. Bernal A, del Junco GW, Gibson SR. Endoscopic and pathologic features of gastrointestinal Kaposi's sarcoma: a report of four cases in patients with the acquired immune deficiency syndrome. *Gastrointest Endosc* 1985;**31:**74–77.
41. Mendez JC, Procop GW, Espy MJ *et al.* Relationship of HHV8 replication and Kaposi's sarcoma after solid organ transplantation. *Transplantation* 1999;**67:**1200–1201.
42. Pitchenik AE, Fischl MA, Saldoma MJ. Kaposi's sarcoma of the tracheobronchial tree: clinical, bronchoscopic, and pathologic features. *Chest* 1985;**87:**122–124.
43. Shepherd FA, Maher E, Cardella C *et al.* Treatment of Kaposi's Sarcoma after solid organ transplantation. *J Clin Oncol* 1997;**15:**2371-2377.
44. Abrams DI, Volberding PA. Alpha interferon therapy of AIDS-associated Kaposi's sarcoma. *Semin Oncol* 1986; **13:**43–47.
45. Dollinger M, Foye L. Kaposi's sarcoma and coexistent giant follicular lymphoblastoma. *Yale J Biol Med* 1966;**38:**449–455.
46. Holecek MJ, Harwood AR. Radiotherapy of Kaposi's sarcoma. *Cancer* 1978;**41:**1733–1738.
47. Hammoud Z, Parenti DM, Simon GL. Abatement of cutaneous Kaposi's sarcoma associated with cidofovir treatment. *Clin Infect Dis* 1998;**26:**1233.
48. Badiaga S, Parola P, Zandotti C *et al.* Successful treatment of Kaposi's sarcoma with a combination of antiviral drug therapy and chemotherapy: two case reports (Letter). *Clin Infect Dis* 1998;**27:**1558–1559.
49. Fournet JC, Peuchmaur NI, Eckart P *et al.* Multicentric Kaposi's sarcoma in a 5-year-old human immunodeficiency virus-negative and renal allograft recipient. *Hum Pathol* 1992;**23:**956–960.
50. Kramer P, Ten Kate FW, Bijnen AB *et al.* Recombinant leucocyte interferon A induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. *Lancet* 1984;**i:**989–990.
51. Doutrelepont JM, De Pauw L, Gruber SA *et al.* Renal transplantation exposes patients with previous Kaposi's sarcoma to a high risk of recurrence. *Transplantation* 1996;**62:**463–466.