Clinical Update

Kaposi’s sarcoma after renal transplantation

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Introduction

In 1872, a Viennese dermatologist, Moritz Kaposi, reported three adult males with multiple hyperpigmented cutaneous nodules on their legs which he termed ‘idiopathic multiple pigmented sarcoma of the skin’ [1]. This disease originally was considered to be a rare neoplasm with a protracted clinical course that affected older individuals. It is now eponymously designated Kaposi’s sarcoma (KS) although it is no longer considered neoplastic by many authors [2]. Kaposi described the sporadic or classic subtype. Other different main subtypes subsequently have been described: the endemic subtype observed in black Africans; the epidemic subtype in patients infected with human immunodeficiency virus (HIV); and the iatrogenic subtype in patients treated with immuno-suppressive therapy, especially organ transplant recipients.

Kaposi’s sarcoma or Kaposi’s disease?

Many observations suggest that KS is a benign, potentially controllable and reversible hyperplasia and not a malignant neoplasm. Clinically, KS lesions appear from the onset as multicentric outcroppings without metastases. Spontaneous regression occurs frequently, especially in the iatrogenic subtype and, very recently since the advent of efficacious tritherapy against HIV, in the epidemic subtype. As shown by immunohistology, various types of cells are involved in the KS cellular proliferation, including endothelial cells, myofibroblasts, macrophages and dendrocytes. Cultured KS cell phenotypes vary widely. KS-derived cells do not behave like transformed cells in terms of growth factor dependence, karyotype, lack of anchorage independence and stable tumour formation in nude mice [3]. The study of clonality using X-linked DNA polymorphism and especially the highly polymorphic human androgen receptor gene recently provided conflicting results [4,5]. All these observations would tend to favour the idea that KS sarcoma does not have all the characteristics of a true malignancy.

Epidemiology of KS after renal transplantation

The prevalence of KS after renal transplantation varies greatly depending on geography. Table 1 summarizes the main data from the literature [6–18]. In many countries, where the prevalence of KS in allograft recipients is low, most transplant recipients with KS come from abroad. Post-transplantation KS affects mainly patients originating from Mediterranean, black African or Caribbean countries. The same populations are also affected by sporadic or endemic KS. The magnitude of the increase of risk of KS conferred by transplantation was evaluated in several studies. It ranged from 25- to 400-fold in Toronto between 1979 and 1997 [7,19], and was estimated to be 224-fold in Italy [12].

<table>
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Kaposi’s sarcoma after renal transplantation

No genetic predisposition to KS has been identified to date; the predominance of HLA-DR5—initially found in sporadic KS—is no longer considered universally valid, and this includes KS after organ transplantation [20]. The male predominance—well-known in sporadic, endemic and epidemic KS—is also found in KS of transplant recipients, the male/female ratio varying from 2 to 40 in different studies [7,9]. The patient’s age at onset of KS depends essentially on the age at the time of organ transplantation; ~40 years in most cases. However, paediatric cases have been reported [21]. The average interval between organ transplantation and the onset of KS is 20 months, ranging from a few weeks to 18 years. This average time interval is less, ~12 months, in recipients treated with cyclosporin A [22].

Clinical and pathological features

Skin lesions are seen in >90% of all cases with KS. Lesions have a dark blue or purplish colour on white skin (Figure 1) and often appear pigmented on black skin (Figure 2). Initially, they may be macular and may coalesce to form large plaques. They subsequently are infiltrated and may form nodular and fungiform tumours. Although they are localized mainly on the legs, they may also appear on the trunk and the arms. Involvement of the face is less frequent than in epidemic KS. Köbner’s phenomenon, i.e. the appearance of the lesions in scars, occasionally is noted. This concerns especially the scar resulting from transplantation surgery (Figure 2). Leg oedema often pre-dates skin lesions on the legs by months. KS is difficult to diagnose in the initially oedematous stage when skin lesions are absent. In this situation, serological tests for human herpes virus-8 (HHV-8) may be useful to make an early diagnosis of KS. Oral lesions consist predominantly of purple stains on the palate (Figure 3). Gingival hyperplasia may occur and has to be differentiated from hyperplasia induced by cyclosporin. As in epidemic KS, oral lesions frequently are associated with involvement of the gastrointestinal tract. Involvement of genital mucosa or conjunctiva is less frequent. Usually these dermatological lesions cause moderate aesthetic or functional discomfort. Superinfection may occur when lesions are ulcerated.

Extracutaneous KS most frequently involves the lymph nodes, the gastrointestinal tract and the lungs. Enlarged lymph nodes should be biopsied to exclude the possibility of associated lymphoma which is found in 2% of cases according to Penn’s series of 356 patients [23]. Although lesions of KS can be found throughout the entire gastrointestinal tract, the most common localizations are stomach and duodenum. The lesions rarely cause clinical symptoms, e.g. nausea, major bleeding, perforation or obstruction, but usually are detected as more or less infiltrated red spots during endoscopic examination of asymptomatic patients. Pulmonary involvement appears at a more advanced stage of the disease; it may cause dyspnea, hypoxaemia and hypocapnia with diffuse interstitial infiltrates, pulmonary nodules and/or pleural infusions. Many other localizations have been reported, especially hepatosplenic involvement.

Regardless of the localization, the diagnosis of KS can be confirmed on the basis of its histological features. Early patch-like lesions exhibit only irregular capillaries sprouting out from normal capillaries. As the lesions develop, a network of spindle-shaped cells is seen as well as large vascular spaces surrounded by an endothelial cell layer. The predominant features of the tumour stage are interweaving bands of spindle cells embedded in a reticulin network; these lesions consistently are associated with the vascular spaces above. Extravasated erythrocytes may be seen. Around the cellular clusters, hemosiderin-laden macrophages are found as well as a moderate inflammatory infiltrate.

Staging

The disease is usually classified according to the four-stage classification described by Al-Khader et al. in 1988 [24]. Stage 1: localized skin lesions involving only one limb. Stage 2: involvement of the skin only, but widespread skin lesions involving more than one limb. Stage 3: involvement of one or more viscera or lymph

Fig. 1. Purplish papules, nodules and plaques of KS on the legs.
nodes. Stage 4: any of the above categories plus either life-threatening infection or another neoplasia.

This classification is simple and widely used. It indicates the extension of KS, but does not take into account information which is essential for therapeutic decisions, e.g. functional disability, rate of development of KS lesions and vital risk.

**Human herpes virus 8 (HHV-8) infection and co-infection with other microorganisms**

HHV-8 has been detected in AIDS-associated KS [25] and is now clearly associated with all epidemiological forms of KS. HHV-8 may be sexually transmitted [26]. Other possibilities of transmission of HHV-8 remain unknown. HHV-8 sequences have been detected in almost all KS tissue samples irrespective of the subtype of KS. They may also be found in mononuclear cells of peripheral blood. Whether quantitation of HHV-8 DNA in blood cells or tissues provides clinically useful information is unknown and will have to be evaluated in prospective studies. Epidemiological data suggest that a high prevalence of anti-HHV-8 antibodies in the general population is correlated with a higher frequency of KS after renal transplantation. Seroprevalence is very high in some African countries (> 50%), moderate in Italy and lower in other Western countries [27]. Most transplant recipients have anti-HHV-8 antibodies in their sera before immunosuppression is started, suggesting that subsequent KS results from reactivation of the virus [28]. Potential transmission of HHV-8 from the donor allograft to the recipient has been documented recently in one case [28]. Such transmission could explain rare, but intriguing, cases where KS appeared simultaneously in two recipients receiving allografts from the same donor [29].
possibility is substantiated by further observations, every donor will have to undergo anti-HHV-8 serological testing in the future. HHV-8 encodes genes [30, 31] that may cause KS via stimulating angiogenesis, e.g. through cytokine homologues such as interleukin-6, G-protein receptor, etc.

Viral, bacterial, fungal or parasitic infections are probably a factor aggravating KS and should, therefore, be treated promptly. They have been reported in many anecdotal observations, but controlled prospective information on their prevalence in post-transplantation KS is not available [32].

**Treatment**

Treatment of KS in renal transplant recipients varies greatly between different institutions, and this makes analysis of the data reported in the literature difficult. There is consensus that immunosuppressive drugs must be tapered to the lowest level which is consistent with allograft function. The degree to which immunosuppressive drugs can be reduced depends on the rate of development of the lesions, functional disability and vital risk posed by KS. Associated infections must be treated whenever feasible; we observed one patient with extensive cutaneous KS which disappeared without any modification of the immunosuppressive regimen once tuberculosis had been treated. In many cases, lowering the dose of immunosuppressive drugs may be sufficient to cause disappearance of the KS lesions. In the Cincinnati registry, KS disappeared after immunosuppression had been reduced in 17% of 213 patients with mucocutaneous involvement and 16% of 143 patients with single or multiple visceral involvement [23]. These figures presumably are underestimated, since regression of lesions was already underway in some patients at the time when their KS lesions were treated. Lesions may regress in a few weeks after immunosuppression has been tapered. In our experience, however, regression is often slower and can take several months. Regression can be monitored by assessing the size of mucocutaneous lesions. Whilst the development of cutaneous and visceral lesions does not occur consistently in parallel, they usually regress simultaneously. Regression of KS lesions is not an aim to be pursued at any price. For instance, some patients prefer maintaining good graft function, even if this means that a few skin lesions of KS persist.

Very specific therapies are available when lesions of KS (i) spread, (ii) cause functional or aesthetic discomfort or (iii) pose life-threatening risks. Cryotherapy, cryosurgery, laser or surgical removal yield aesthetically acceptable results and can be recommended when a limited number of cutaneous or mucosal lesions are present. Intralesional chemotherapy has also been recommended, but it is less popular because it is painful. Lesions regress more rapidly after radiotherapy, but this modality poses the long-term risk of cutaneous carcinomas. Various chemotherapeutic agents, singly or in combination, have been proposed. None has proven to be superior. The most commonly used chemotherapeutic agents for monotherapy are vinblastine (0.1 mg/kg/week for 5–10 weeks) and bleomycin (7.5 mg/week or 15 mg every 2 weeks). When multivisceral involvement progresses rapidly, many authors advise combination of chemotherapy, e.g. adriamycin or doxorubicin, bleomycin, and vinblastine or vincristine (ABV), or etoposide and cisplatin. Combination chemotherapy is able to control KS, but at the price of increasing immunosuppression. KS may recur several months or years after remission [7]. Interferon-α is used widely in endemic KS. After renal
transplantation, it cannot be recommended because it often triggers rejection [33]. Although several antiviral molecules (cidofovir, foscavir, ganciclovir) inhibit HHV-8 replication in vitro, they have not been proven to be effective on KS in transplant recipients. Whether HHV-8 can be eradicated at all is doubtful, since HHV-8, like other herpes viruses, is integrated into the genome and remains in the body in a latent state. In critical cases, these antiviral drugs can nevertheless be tried.

**Prognosis**

Mortality differs widely between different series. In a French study, 21% of 28 patients with KS died [9]; all had visceral involvement. In contrast, in another series [7], mortality was not increased in patients with visceral involvement. The proportion of patients returning to dialysis ranges from 21 to 58% [7,23].

**Risk of recurrence**

If patients had sporadic or post-transplantation KS, even if they had been free of lesions for several years, the risk of recurrence of KS proved to be very high when they then received a kidney allograft [34,35]. The risk of de novo development of KS after transplantation in patients who had anti-HHV-8 antibodies is unknown.

**Conclusion**

Today, KS in the allograft recipient is no longer a complication which is necessarily life-threatening. Substantial reduction of immunosuppression usually causes disappearance of KS, albeit at the risk of graft loss from rejection. The challenge in the future will be to prevent and treat KS while preserving renal function.

**References**

22. Penn I, Brunson ME. Cancers after cyclosporin therapy. Causes disappearance of KS, albeit at the risk of graft loss from rejection. The challenge in the future will be to prevent and treat KS while preserving renal function.